Potential Health and Economic Impact of Adding a Human Papillomavirus Vaccine to Screening Programs

Shalini L. Kulasingam, PhD
Evan R. Myers, MD, MPH

Context Recently published results suggest that effective vaccines against cervical cancer—associated human papillomavirus (HPV) may become available within the next decade.

Objective To examine the potential health and economic effects of an HPV vaccine in a setting of existing screening.

Design, Setting, and Population A Markov model was used to estimate the lifetime (age 12-85 years) costs and life expectancy of a hypothetical cohort of women screened for cervical cancer in the United States. Three strategies were compared: (1) vaccination only; (2) conventional cytological screening only; and (3) vaccination followed by screening. Two of the strategies incorporated a vaccine targeted against a defined proportion of high-risk (oncogenic) HPV types. Screening intervals of 1, 2, 3, and 5 years and starting ages for screening of 18, 22, 24, 26, and 30 years were chosen for 2 of the strategies (conventional cytological screening only and vaccination followed by screening).

Main Outcome Measures Incremental cost per life-year gained.

Results Vaccination only or adding vaccination to screening conducted every 3 and 5 years was not cost-effective. However, at more frequent screening intervals, strategies combining vaccination and screening were preferred. Vaccination plus biennial screening delayed until age 24 years had the most attractive cost-effectiveness ratio ($44 889) compared with screening only beginning at age 18 years and conducted every 3 years. However, the strategy of vaccination with annual screening beginning at age 18 years had the largest overall reduction in cancer incidence and mortality at a cost of $236 250 per life-year gained compared with vaccination and annual screening beginning at age 22 years. The cost-effectiveness of vaccination plus delayed screening was highly sensitive to age of vaccination, duration of vaccine efficacy, and cost of vaccination.

Conclusions Vaccination for HPV in combination with screening can be a cost-effective health intervention, but it depends on maintaining effectiveness during the ages of peak oncogenic HPV incidence. Identifying the optimal age for vaccination should be a top research priority.

JAMA. 2003;290:781-789 www.jama.com

THE VAST MAJORITY OF CERVICAL cancer is caused by persistent infection with cancer-associated human papillomavirus (termed *oncogenic* or *high-risk HPV*).[1,2] By identifying and treating cervical intraepithelial neoplasia (CIN), the cervical cancer precursor lesion associated with HPV infection, screening programs based on cytology have reduced the incidence of invasive cervical cancer.[3]

Because the majority of invasive cervical cancer and cervical neoplasia can be attributed to infection with a subset of HPV types, including HPV 16, HPV 18, HPV 31, and HPV 45,[2] a prophylactic vaccine to prevent infection with 1 or more of these types has the potential to substantially reduce the incidence of cervical cancer and its precursor lesions. Recent results from a phase 2 trial of a vaccine targeted against HPV 16 showed 100% (95% confidence interval, 90%-100%) efficacy over a median follow-up of 17.4 months in preventing HPV 16–specific persistent infection or CIN.[4] Larger phase 3 trials of vaccines targeted against multiple oncogenic types are under way. Because clinical trials are limited in their ability to explore the impact of vaccination on long-term outcomes and results may not be available for some time, mathematical modeling can be used to identify those variables that may have the greatest impact on the cost and benefits associated with vaccination, as well as suggest potential strategies for incorporating an effective vaccine into existing screening programs.[5,6]

Several well-validated models of the natural history of cervical cancer have

Author Affiliation: Department of Obstetrics and Gynecology and Center for Clinical Health Policy Research, Duke University, Durham, NC.
Financial Disclosure: Dr Myers has served as a consultant to Merck on issues relating to the design and conduct of clinical trials of an HPV vaccine.
Corresponding Author and Reprints: Shalini Kulasingam, PhD, Center for Clinical Health Policy Research, First Union Tower, Suite 220, 2200 W Main St, Durham, NC 27705 (e-mail: kulas002@mc.duke.edu).

been developed and used to evaluate various screening strategies.[7-12] Consistent themes have emerged from the use of these models. First, as screening frequency increases, the cost-effectiveness ratios increase dramatically due to increased detection of transient cervical abnormalities and associated low-grade CIN lesions. These transient lesions are primarily observed in younger women, which explains the second consistent finding: delaying screening until the mid-30s is a more efficient strategy for reducing cancer mortality.[7,11,13] In addition, screening appears to be less effective against rapidly progressing cancers, with proportionately smaller reductions in cancer incidence in younger women compared with women in their 40s and 50s.[7,14] These findings suggest that the costs of HPV vaccination might be partly offset by savings achieved by delaying the age of beginning screening and by screening less frequently.

In this study, we used mathematical modeling to explore potential strategies for combining existing secondary prevention methods for cervical cancer with primary prevention using an effective HPV vaccine.

METHODS

Natural History Model

We used a previously described health state-transition Markov model to simulate the natural history of HPV infection and cervical cancer: relevant parameters were derived from a published systematic review and are described in detail elsewhere.[7,8,12,15] The model was revised to separately simulate high- and low-risk HPV infection.[16]

In these analyses, we simulated a cohort of girls beginning at age 12 years (and followed-up until age 85 years), who, at the start of the simulation, had never had sex and were disease-free. Each year, they faced an age-specific risk of acquiring high-risk or low-risk HPV infection that could either persist, progress (to CIN 1 or CIN 2-3), or resolve. Those who developed CIN 1 or CIN 2-3 could have their disease persist, regress, or progress. Women with cancer (International Federation of Gynecology and Obstetrics stages I, II, III, or IV) could have their disease detected if they presented for a gynecologic examination based on their symptoms. If not, they could either progress to the next stage or remain in the same stage. Each year, women faced age-specific risks of dying from other causes or of having a hysterectomy for indications unrelated to cervical neoplasia. Additional health states were defined to distinguish women who had prior treatment for CIN, were cancer survivors, or had died due to cervical cancer.

We made several simplifying base-case assumptions about the natural history of high-risk HPV infection, which were tested in sensitivity analyses. First, we assumed that HPV infection progression to CIN 1 and CIN 2-3 was not differentially affected by an HPV vaccine. Because there is some evidence that infection with oncogenic HPV types, particularly HPV 16, is more likely to progress directly to CIN 2-3 (referred to as *rapidly progressing infections*),[7,8,17,18] we tested 2 different implications of our base-case assumption: (1) all rapidly progressing infections that result in CIN 2-3 lesions would be eliminated as a result of vaccination or (2) none of the rapidly progressing infections would be affected by vaccination. Second, we assumed in the base case that the vaccine would be targeted at a proportion of high-risk HPV types rather than 1 or 2 high-risk types and that this proportion would be constant as the cohort aged. However, depending on the particular HPV type targeted (eg, HPV 16), the contribution to the overall age-specific incidence might vary as a function of age. We therefore tested this assumption by increasing or decreasing the proportion of high-risk types that the vaccine targets as a function of age.

Strategies

For the base case, we used the model to estimate the cost and life expectancy associated with 3 strategies, under the assumption that an effective vaccine targeted at a defined proportion of high-risk HPV types was available: (1) 1-time vaccination of 12-year-old girls only; (2) conventional cytology-based screening only; and (3) 1-time vaccination of 12-year-old girls followed by cytology-based screening. Screening was performed at intervals of 1, 2, 3, and 5 years. Because American Cancer Society guidelines[19] for the optimal age of onset of screening have been recently revised, we varied the age of screening onset from 18 to 22, 24, 26, and 30 years.

Females were chosen as the target group because of current trial design, in which initial regulatory approval for a vaccine is likely to be limited to females (E. Barr, oral communication, February 12, 2002). Because HPV is a common sexually transmitted infection, we assumed that vaccination would be most effective if targeted toward girls prior to the onset of sexual activity. Vaccination at age 12 years was chosen for the base case because data suggest that very little sexual activity has taken place by this age.[20]

Screening and Treatment

We made several base-case assumptions for screening and treatment, all of which were subsequently tested in sensitivity analyses (TABLE 1). First, we assumed, as have others, that compliance with primary screening,[9] follow-up, and treatment[10] was 100%. Second, conventional cytology was chosen because its test characteristics are better characterized than liquid cytology.[7] Based on published systematic reviews and primary screening studies, we assumed that conventional cytology had a sensitivity of 55.6% and specificity of 95.7% for detection of ≥CIN 2-3.[21-23] Although liquid cytology is commonly believed to have superior sensitivity to conventional cytology, recent studies suggest that improvements may be less than previously thought.[24-26] We varied the sensitivity and specificity of cytology to account for this uncertainty. Third, we did not use the recent revision to the Bethesda system because data on its performance in practice are not yet available,[27] and previous studies have concluded that new categorizations for atypical squamous cells of undeter-

mined significance (ASCUS) do not have substantial effects in terms of clinical outcomes.[9] Fourth, women with ASCUS were managed by repeat cytology in 6 months' time; women with abnormal results (ASCUS or more severe result) had colposcopy performed. Although baseline data from the Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study[28] suggest that use of HPV testing may be superior to repeat cytology in the detection of high-grade lesions, we did not specifically evaluate the use of currently available HPV tests because of a lack of data on how type-specific vaccination might affect the characteristics of HPV tests that do not identify specific types. Fifth, we assumed that colposcopy was performed for all cytological results of low-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion, or cancer. Sixth, we assumed that colposcopy had perfect sensitivity and specificity for detection of ≥CIN 2-3; this assumption was tested in sensitivity analysis. Seventh, we assumed that those with no underlying disease confirmed at colposcopy returned to routine screening. Eighth, we assumed that women with treated CIN received annual screening for the remainder of their lifetime, or until hysterectomy for other indications. Ninth, we assumed that women with invasive cancer had their cancer staged and received stage-appropriate treatment. Finally, Hughes et al[29] have suggested that successful, aggressive treatment of CIN detected during screening may reduce a treated woman's risk of cancer because nonlesional tissue that is susceptible to infection with HPV also is removed. In the model, for the base case, we assumed that women who were screened and successfully treated would have a 95% reduction in risk of developing CIN, but varied this assumption in sensitivity analyses.

Vaccination

As with screening and treatment, we made several initial assumptions that were tested in sensitivity analyses. First, we assumed that vaccination and therefore vaccine efficacy was limited to the cohort itself. Thus, reductions in cancer were assumed to be due to reduced susceptibility to infection rather than due to a reduction in sexual transmission of HPV. Second, we assumed that a vaccine to prevent HPV infection in a US population would be targeted at more than 1 type to have a significant impact (>50%) on cancer and allow for a change in current screening policies. As such, we assumed the vaccine would be targeted against 70% of oncogenic HPV types, including HPV 16 and HPV 18. Third, we assumed vaccine efficacy was 90%, representing the lower bound of the 95% confidence interval for the recently published HPV 16 vaccine trial.[4] Fourth, efficacy was modeled as a proportionate reduction in the age-specific incidence of high-risk HPV. Fifth, the duration of vaccine efficacy was constant over 10 years and then was assumed to decrease to zero efficacy for the base case. Sixth, there were no significant adverse ef-

Table 1. Model Variables: Baseline Values and Ranges Used in Sensitivity Analyses

Variable	Base Case	Plausible Range
Natural history, %		
Proportion of HPV infections that progress directly to CIN 2-3	10	0-10[7,8,17,18]
Cytology (ASCUS-positive cut point for ≥CIN 2-3), %[21-23]		
Sensitivity	55.6	51-95
Specificity	95.7	80-97
Colposcopy and biopsy for ≥CIN 2-3, %		
Sensitivity	100	50-100
Specificity	100	70-100
Compliance, %		
Screening	100	50-100
Follow-up/treatment	100	50-100
Vaccination		
Efficacy, %	90[4]	25-100
Duration of efficacy, y	10	2-30
Proportion of high-risk HPV types covered, %*	70	30-90
Age, y	12	12-19
Vaccination coverage, %	100	50-100
Proportion successfully vaccinated, %	100	50-100
Utilities for quality-adjusted survival[9,10]		
CIN 1	NA	0.97-1.00†
CIN 2-3	NA	0.93-1.00†
Cervical cancer stage		
I	NA	0.68-1.00
II/III	NA	0.56-1.00
IV	NA	0.48-1.00
Medical costs, in 2001 US $[7-10,30]		
Conventional cytology	45‡	61-75§
Vaccine	200	100-600
Booster	NA	200
Colposcopy and biopsy	436	426-627
CIN 1	2010	508-2645
CIN 2-3	3546	3013-8178
Cervical cancer stage		
I	20 524	15 932-22 504
II/III	31 485	24 461-33 834
IV	46 851	38 576-54 095

Abbreviations: ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; NA, not applicable.
*Modeled as decreasing or increasing linearly until age 24 years.
†Applied for 1 month only.
‡Includes direct medical costs only.
§Includes direct and indirect (time) costs.

fects due to vaccination. Seventh, the entire cohort of 12-year-old girls was vaccinated once (with a 3-series vaccine) and all girls were successfully immunized.

Costs

Base-case direct medical cost estimates for screening and diagnoses were derived from MEDSTAT, the National Ambulatory Medical Care Survey, and Medicare data.[7] We assumed that the vaccine would be administered within current health care visits so that there would be no programmatic costs. Vaccine costs ($200) were based on an Institute of Medicine report on future vaccine development[30] and were assumed to include all direct medical costs associated with a 3-vaccine series. Because the inclusion of indirect costs associated with screening might be expected to favor vaccination, we examined the inclusion of indirect costs for screening in sensitivity analyses only using estimates derived from the published literature.[9,10] The indirect costs for vaccination used in sensitivity analyses were estimated as the costs for parent time taken for 3 office visits. We also examined the impact of including the cost for 1 or more booster series to increase vaccine duration in sensitivity analyses. All costs were expressed in 2001 US dollars using the medical care component of the consumer price index from the Bureau of Labor statistics.

Health-Related Quality of Life

There are currently no published utilities that are applicable to all states associated with cervical cancer screening and prevention. Because assumptions about which states to include and the value of utilities for these states can have a substantial impact on cost-effectiveness ratios,[31] we did not include health-related quality of life in the base case. However, to provide comparability with other published results, quality-adjusted life expectancy was calculated in sensitivity analyses using utilities derived from the literature (Table 1).[9,10] The disutility of having CIN 1 or ≥CIN 2-3 detected through screening was conservatively assumed to last for 1 month. The utilities for cancer were assumed to apply during the first 5 years of follow-up. After 5 years, a cancer survivor was assumed to have a utility of 1, corresponding to perfect health.

Analytic Strategy and Sensitivity Analyses

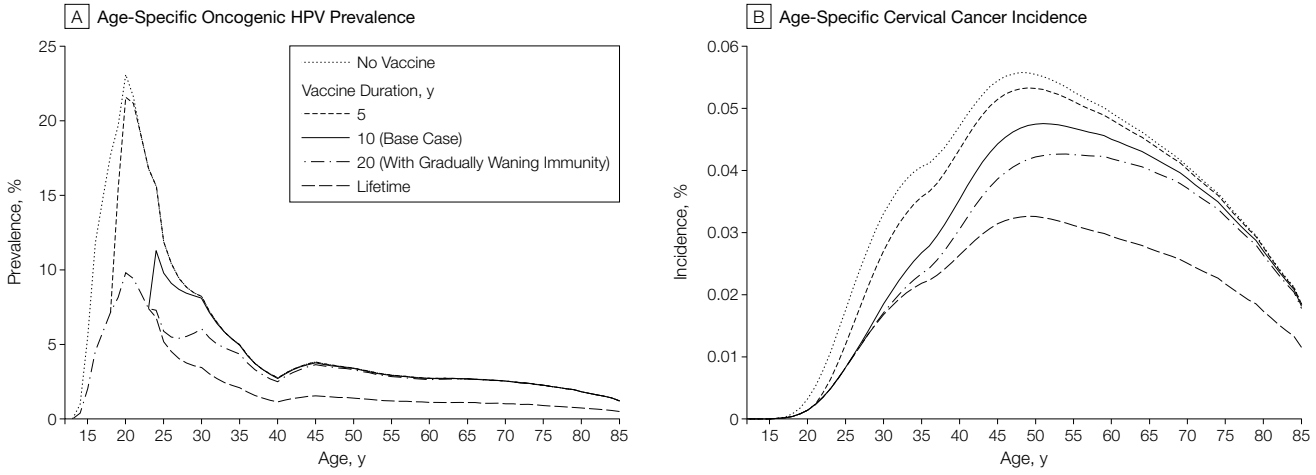
We calculated incremental cost-effectiveness ratios in which the additional costs of a strategy divided by the additional savings in life expectancy or quality-adjusted life expectancy were compared with the next, less costly strategy. Strategies were considered dominated if they were more costly and less effective (in terms of life expectancy) than an adjacent strategy or strategies. We also calculated the expected reductions in CIN, cancer incidence (all stages), and/or mortality for key sensitivity analyses. We adjusted future costs and life expectancy to current values by discounting them at 3% annually.[32] In the base case, we did not include nonmedical costs or quality-of-life measures. In sensitivity analyses, we used a broader societal perspective and included nonmedical costs and quality-of-life measures.

RESULTS

Validity of the Model

The face validity of our model has been previously confirmed by comparing the age-specific HPV, CIN, and cancer incidence curves with population-based data that were not used to create the model.[8] The age-specific high-risk HPV incidence curve has a peak within an age range and of similar magnitude to that reported in the literature.[33,34] The lifetime risk of 3.5% for incident cer-

Figure 1. Model-Predicted Age-Specific Prevalence of High-Risk (Oncogenic) Human Papillomavirus (HPV) and Cervical Cancer Incidence



Model-predicted age-specific prevalence of high-risk (oncogenic) human papillomavirus (HPV) and cervical cancer incidence in the absence of vaccination or screening, or after vaccination at age 12 years with vaccines of 90% efficacy against 70% of oncogenic HPV types, with durations of efficacy of 5, 10, or 20 years, or a lifetime.

vical cancer predicted by the model is similar to that reported in the literature.[9,10] In the absence of screening or vaccination, our model predicts mean discounted lifetime cost of $207 and life expectancy of 28.56 years for a cohort of 13-year-olds, which are similar to the $210 lifetime cost and life expectancy of 28.70 years reported by Kim et al.[9] The incremental cost-effectiveness ratios associated with different screening intervals for cytology only are of similar magnitude to those reported by Kim et al[9] and Mandelblatt et al[10] when run using similar parameters and assumptions.

Natural History of HPV and Cervical Cancer With and Without Vaccination

FIGURE 1A shows the predicted prevalence of oncogenic HPV (all types) with and without vaccination, using base-case assumptions, varying the duration of vaccine efficacy from 5 years to a lifetime, or assuming a gradual waning in vaccine efficacy. The model predicts a lowered prevalence of oncogenic HPV when a longer duration of vaccine efficacy is assumed or a gradual waning of efficacy is assumed instead of a blunt drop to 0. Figure 1B shows the projected impact of vaccination alone in terms of reducing cervical cancer incidence; results for cervical cancer mortality were similar (data not shown). For the base case, the model projects that vaccination will result in a reduction in cancer incidence (all stages) of 16.8% and a 17.7% reduction in cervical cancer deaths compared with no intervention.

Base-Case Analysis

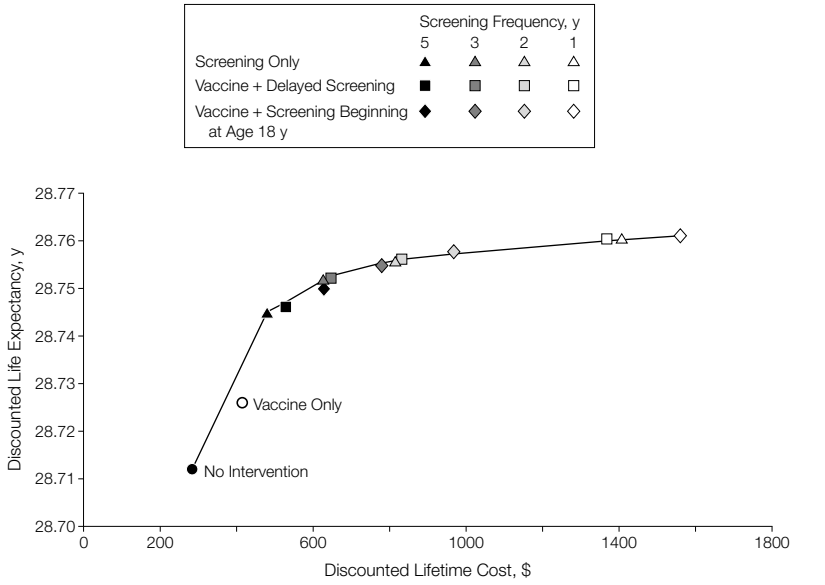
In initial analyses, we examined 40 strategies comparing screening only conducted every 1, 2, 3, and 5 years with a strategy of screening plus vaccination at identical intervals, varying the ages of screening onset (age 18 years, 22 years, 24 years, 26 years, and 30 years). Results from these initial analyses suggested that vaccination with screening would be cost-effective if the onset of screening for this combined strategy could be delayed relative to screening only. We assumed that implementation of a cost-effective policy including vaccination with a delayed age for screening onset would likely only be acceptable to policy makers, clinicians, and patients if it did not result in excess cancer mortality. As such, we defined a minimal acceptable efficacy for the strategy of vaccination and screening compared with screening alone by identifying an age for each screening interval beyond which a delay in the onset of screening would result in more cervical cancer deaths than a strategy of screening only. For simplification, we fixed the age of first screening for screening only to age 18 years. These delayed ages of first screening were 30 years for screening every 5 years, 26 years for screening every 3 years, 24 years for screening every 2 years, and 22 years for screening annually. For every interval, we theorized that this delayed age for first screening would result in a higher mean life expectancy at a reasonable cost for vaccination combined with delayed screening compared with screening only at age 18 years. First, our definition of a delayed age at first screening usually meant slightly fewer deaths (TABLE 2). Second, vaccination with delayed screening would result in fewer cancer deaths in younger women (5%

Table 2. Lifetime Costs, Life Expectancy, and Incremental Cost/Life-Year Saved of Strategies Under Base-Case Assumptions

Strategy (Age Started)	Reduction in Cancer, %		Mean*		Incremental Cost/ Life-Year Saved, $
	Incidence	Mortality	Lifetime Cost, $	Life Expectancy, y	
No intervention	NA	NA	284	28.712	NA
Vaccine only	16.8	17.7	417	28.7261	Not cost-effective
Screening every 5 y (30 y is delayed age)†					
Screening only (18 y)	59.3	71.2	483	28.745	6030
Vaccine + screening (30 y)	62.1	72.6	532	28.7461	Not cost-effective
Vaccine + screening (18 y)	65.5	75.7	632	28.7499	Dominated‡
Screening every 3 y (26 y is delayed age)†					
Screening only (18 y)	72.8	83.0	632	28.7518	21 912
Vaccine + screening (26 y)	74.3	83.5	650	28.7521	Not cost-effective
Vaccine + screening (18 y)	76.8	85.6	783	28.7548	Not cost-effective
Screening every 2 y (24 y is delayed age)†					
Screening only (18 y)	81.3	89.3	822	28.7558	Not cost-effective
Vaccine + screening (24 y)	82.6	89.8	834	28.7563	44 889
Vaccine + screening (18 y)	84.1	90.8	973	28.7578	92 667
Screening every year (22 y is delayed age)†					
Screening only (18 y)	92.1	96.0	1413	28.7604	Dominated‡
Vaccine + screening (22 y)	92.4	96.0	1374	28.7604	154 231
Vaccine + screening (18 y)	93.2	96.6	1563	28.7612	236 250

Abbreviation: NA, not applicable.
*Cost and life expectancy discounted at 3% annually.
†Delayed age of first screening for a given screening frequency is defined as the oldest age at which predicted cervical cancer deaths for a strategy of vaccination plus screening beginning at that age are equivalent or less than the predicted cervical cancer deaths for screening only at the same interval beginning at age 18 years.
‡Strategy has a lower life expectancy and higher cost than an adjacent strategy.

Figure 2. Efficiency Curve Comparing Vaccination Only, Screening Only, and Vaccination Plus Screening



fewer cancer deaths would occur in women aged ≤26 years when vaccination and delayed screening conducted every 2 years beginning at age 24 years was compared with screening alone conducted at the same interval beginning at age 18 years), which led to larger gains in mean life expectancy. Lastly, for the same comparison, 55% fewer CIN 1 lesions would be detected and treated among screened women aged 30 years or younger, thus avoiding the costs associated with detecting and treating lesions that were more likely to regress. As a result, from the initial 40 strategies, we focused our analyses on 12, including a strategy of vaccination and screening beginning at age 18 years.

FIGURE 2 depicts the discounted lifetime cost and life expectancy associated with the 12 strategies, as well as a strategy of vaccination only. The efficiency curve includes only strategies that dominate those to the right, either because they are more effective and less costly, or have a more attractive cost-effectiveness ratio compared with the next best strategy. As shown, a strategy of vaccination only would not be cost-effective. Focusing on those strategies on the efficiency curve, screening only was preferred at less frequent screening intervals (every 5 years and every 3 years). The strategy of screening only every 5 years beginning at age 18 years had an incremental cost-effectiveness ratio of $6030 per life-year gained compared with no intervention. The incremental cost-effectiveness ratio for the same strategy conducted every 3 years was $21 912. At more frequent screening intervals (every 2 years or annually), a combination of vaccination and screening was preferred with incremental cost-effectiveness ratios ranging from $44 889 (for vaccination and screening beginning at age 24 years and conducted every 2 years compared with screening only conducted every 3 years) to $236 250 (for vaccination and screening beginning at age 18 years and conducted every year compared with the same strategy and interval beginning at age 22 years). These results are also summarized in Table 2.

Sensitivity Analyses

Using $50 000 per life-year saved as a threshold,[35] vaccination plus biennial screening beginning at age 24 years appeared to be the most attractive strategy (Table 2). We therefore focused our sensitivity analyses around this screening interval to identify the assumptions and ranges for variables that had the largest impact on the cost-effectiveness ratio of this strategy compared with screening only every 2 years beginning at age 18 years.

Univariate analyses indicated that the age at which the cohort could receive vaccination could be delayed until age 15 years without compromising life-expectancy gains, given patterns of sexual activity and HPV acquisition. TABLE 3 shows the results of other univariate sensitivity analyses on key natural history, vaccination, screening, and treatment variables (base-case assumptions are presented in Table 1). Overall, values for parameters resulting in greater overall vaccine effectiveness (proportion of the population who receive vaccination and are successfully immunized, proportion of HPV types covered, vaccine efficacy, vaccine duration) resulted in more attractive cost-effectiveness ratios or dominance for vaccination plus delayed screening. If the same efficacy and duration of efficacy as that used in the base case could only be achieved using a booster (at age 17 years), the cost of vaccination with delayed screening would increase to more than $300 000 per life-year gained compared with screening only every 2 years beginning at age 18 years. Addition of a booster at age 22 years to extend duration an additional 10 years resulted in a cost of $77 000 per life-year gained for the delayed strategy compared with screening only.

Based on the results of the 1-way sensitivity analyses, we conducted a 2-way sensitivity analyses in which the total cost of the vaccine (assumed to include the costs for administration, a series of 3 shots, and any boosters needed to maintain efficacy over the duration modeled) was simultaneously varied with the duration of vaccine efficacy. These results indicated that at lower total costs for the vaccine and longer duration, the strategy of vaccinating all girls (at age 12 years) and delaying the onset of screening until age 24 years dominated a strategy of screening only beginning at age

18 years (FIGURE 3A). However, as the total cost for the vaccine increased, the incremental cost-effectiveness ratio associated with the delayed strategy increased. The area over which the delayed strategy dominated screening only increased if the age of vaccination was increased (until approximately age 15 years) or time costs for screening and vaccination, as well as utilities for cancer, CIN 1, and CIN 2-3 were included in the model (Figure 3B). If vaccination was delayed until a later age (≥16 years) or duration of vaccine efficacy was shorter than 9 years, the area over which the delayed strategy dominated decreased or disappeared.

Finally, for our main analysis we assumed that a proportion of HPV types would be targeted by the vaccine, rather than 1 or 2 specific HPV types. Because this choice may obscure the impact of a type-specific vaccine, we examined the impact of a vaccine targeted at HPV-16 only. For this analysis, we assumed that approximately 25% of CIN 1,[36] 50% of CIN 2-3, and 50% of cancers[2,37] were attributable to infection with HPV 16. Under base-case assumptions about vaccine efficacy and duration, an HPV-16 only vaccine reduced CIN 1, CIN 2-3, and cancer incidence by 7%, 11.4%, and 12.5%, respectively. Larger reductions were achieved when an HPV 16 vaccine was combined with screening or HPV 16 vaccination was assumed to provide lifelong immunity, suggesting that the relative cost-effectiveness of a type-specific vaccine will depend on the differential reductions achieved in CIN, and the impact this will ultimately have on reductions in cancer.

Table 3. One-Way Sensitivity Analyses

Parameters	Dominates or Is More Cost-effective: Screening Only Every 2 Years Beginning at Age 18 y	Dominates or Is More Cost-effective: Vaccination at Age 12 y + Biennial Screening Beginning at Age 24 y
Natural history		
Proportion of oncogenic HPV types covered, %	Decreases linearly	Increases linearly
Age 12 y	70	70
Age 24 y	30	90
Vaccine prevented rapidly progressing infections*	None	All
Vaccine		
Efficacy, %	<80	>92
Duration of efficacy, y	<7	>14
Cost, $	>240	<195
Nonresponders	More likely to develop cancer (CIN RR≥2 compared with responders)	Not more likely to develop cancer (CIN RR = 1 compared with responders)
Screening/treatment		
Participation in vaccination and/or screening, %		
Neither vaccinated nor screened	>20	NA
Vaccinated but not screened	NA	>10
Screened but not vaccinated	>10	NA
Papanicolaou test screening, %		
Sensitivity	≥72	No effect
Specificity	No change	≤94
Colposcopy, %		
Sensitivity	No effect	<80
Specificity	No effect	<95
Treatment of CIN lesions on risk of developing subsequent neoplasia	Base-case assumption (CIN RR = 0.05 compared with untreated women)	No effect (CIN RR = 1 compared with unteated women)

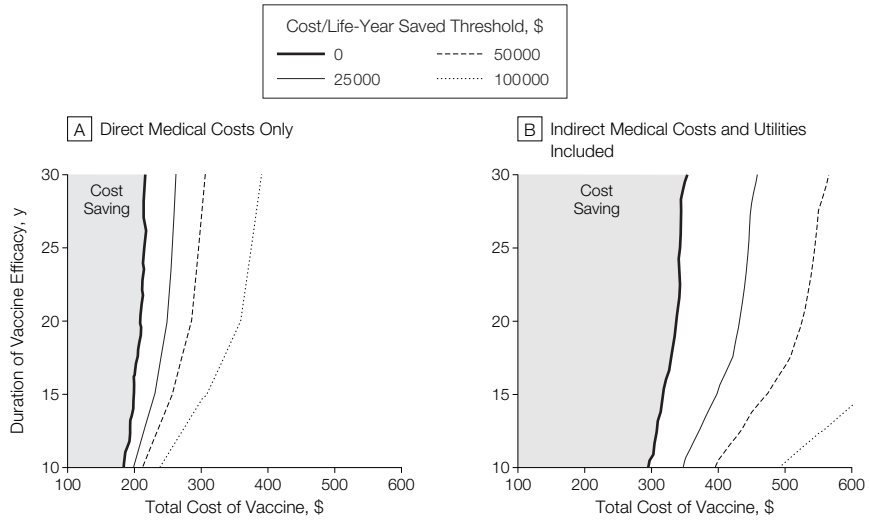
Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; NA, not applicable; RR, relative risk.
*Ten percent of HPV infections that are assumed to progress directly to CIN 2-3.

COMMENT

With the prospect of effective vaccines against high-risk HPV types becoming commercially available within the next 5 to 10 years,[4,38] and the limitations of trials to address all potential scenarios associated with a vaccine, we conducted an exploratory analysis to identify potentially cost-effective methods for adding vaccination to an existing screening program and to identify factors that would affect this decision. For more than a decade, published economic analyses of cervical cancer screening have consistently shown that annual screening results in exceptionally large costs with small gains in life expectancy compared with less frequent screening.[7-10,39-42] The introduction of more sensitive screening tests has made frequent screening even less economically attractive.[15] This is, in part, due to the fact that screening is most inefficient in younger women because the detection of transient lesions is greatest, and screening does not appear to be as effective against the relatively rare aggressive cancers that do occur in younger women.[7,11,13,14] Our findings suggest that a vaccine, which reduces the incidence of oncogenic HPV types during the peak ages of infection (generally the late teens and early 20s), can be economically attractive, especially if it allows for a delay in the onset of screening.

The key to overall vaccine effectiveness based on this analysis is adequate protection during the ages of peak oncogenic HPV incidence. Age of vaccination, HPV types covered, vaccine efficacy, and duration of efficacy are the specific components that determine this protection. The need for and cost of booster vaccines to extend duration have a direct impact on the cost-effectiveness of the vaccine in general. Because long-term (≥10 years) data on vaccine duration may not be available at the time of commercial availability, policies that allow for a delay in the onset of screening beyond the current sug-

Figure 3. Two-Way Sensitivity Analysis Varying Duration of Vaccine Efficacy and Total Cost of Vaccine



Biennial screening at age 18 years compared with vaccination at age 12 years followed up by biennial screening beginning at age 24 years. Shaded areas indicate combinations of vaccine duration and cost in which vaccination plus delayed screening is less costly and more effective than screening only beginning at age 18 years. Unshaded areas indicate combinations of vaccine duration and cost in which vaccination plus delayed screening is more costly and more effective than screening only beginning at age 18 years. Lines indicate specific incremental cost-effectiveness ratios associated with vaccination plus delayed screening.

gested upper limit of 21 years[19] after vaccination may not be able to be implemented for some time.

Because of the interaction between vaccine duration and age at vaccination in terms of overall vaccine effectiveness, research needs to be focused on the optimal time to offer vaccination, especially because the proportion of the female population who are vaccinated successfully also has cost-effectiveness implications. Although vaccinating young girls prior to the onset of sexual activity may be ideal in terms of an immunologically naive population, it is currently unclear whether parents will agree to have their children vaccinated against a sexually transmitted infection. An additional concern highlighted by our sensitivity analysis is that if women who are vaccinated perceive themselves to be at low risk for developing cancer and, as a result do not participate in screening as recommended, gains from vaccination may be offset.

Our analyses also showed that assumptions about the natural history of HPV infection and response to vaccine, such as the age-specific and lesion-specific distribution of high-risk types, the impact of treatment of cervical neoplasia on subsequent risk for neoplasia, the differential impact of a type-specific vaccine such as HPV 16 on CIN 1 compared with CIN 2-3 and cancer, and assumptions about women who do not respond to vaccination affect cost-effectiveness conclusions. In addition, it is unclear whether the vaccine will have an impact on cancers that occur in younger women, as predicted by the model. It is possible that the biological characteristics that lead to cancers in younger women are somehow related to response to the vaccine. If the vaccine is less effective against those HPV infections that occur in younger women, then we are overestimating the benefits of the vaccine. At the policy level, all of these parameters affect the net effectiveness of a vaccine—lower effectiveness makes a vaccine less attractive from both clinical and economic grounds. Refinement of models as further data become available will improve predictions of vaccine impact.

It should also be noted that, even with sensitivity analyses, we cannot entirely account for uncertainty in our results. For example, some of the strategies, which are clustered closely together near the efficiency curve depicted in Figure 2, might be considered reasonable alternatives if other noneconomic reasons existed for adopting them. Given the uncertainty in both the probability and cost estimates, it is also possible that even slightly different base-case estimates for some probabilities and costs might result in some strategies, which are dominated in the current base case but that lie close to the efficiency curve, becoming economically preferred.

We did not model HPV as an infectious disease, largely because of an almost complete lack of data on the sexual transmission dynamics of HPV. In addition, because current clinical trials are directed at vaccinating females, we did not directly consider the impact of vaccinating males. An effective vaccine, by reducing prevalence, will lead to further decreases in incidence through reduced transmission. If this is the case, then even partial coverage by a vaccine could result in even greater decreases in population incidence and prevalence than our analysis indicates.[43]

Our use of utilities for cancer and preinvasive lesions in sensitivity analyses should be interpreted with caution. There is a lack of data on cervical cancer-specific utilities, including those associated with screening. In addition, the appropriate method for measuring and including screening-associated utilities has yet to be determined. Screening using HPV tests or cytologic examinations can be associated with significant psychological distress as well as morbidity.[44,45] Additionally, the psychological and physical adverse effects that result from cervical cancer treatment are well documented.[46,47] Cost-effectiveness, as measured by quality-adjusted life expectancy, is quite sensitive to assumptions about the relative disutility of screening vs cancer, underscoring the need for studies that can provide appropriate measures for quality-of-life calculations.

Based on our results, the ability to change screening policies efficiently is dependent on maintaining adequate vaccine efficacy during the ages of peak on-

cogenic HPV incidence. Availability of a vaccine will not lead to overnight changes in screening policy: the majority of older women will not be eligible for a vaccine, and uncertainty about issues that impact overall effectiveness, such as vaccine duration and replacement, is unlikely to be resolved prior to commercial availability. Data on vaccine parameters, such as type-specific efficacy, duration, and impact on other HPV types will be collected as part of ongoing trials, as well as in other studies. Because the impact of these clinical and epidemiological variables on overall vaccine effectiveness is so dependent on the age at which vaccination is given, research into understanding the feasibility and acceptability of vaccination at different ages should be given high priority.

Author Contributions: *Study concept and design:* Kulasingam, Myers.
Acquisition of data: Kulasingam, Myers.
Analysis and interpretation of data: Kulasingam, Myers.
Drafting of the manuscript: Kulasingam, Myers.
Critical revision of the manuscript for important intellectual content: Kulasingam, Myers.
Statistical expertise: Kulasingam, Myers.
Obtained funding: Myers.
Administrative, technical, or material support: Myers.
Study supervision: Myers.
Funding/Support: This study was funded by a grant from Merck Research Laboratories.
Role of the Sponsor: Merck Research Laboratories had no role in the study design, data collection, analysis and interpretation, in the writing of the paper, or in the decision to submit this article for publication.

REFERENCES

1. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*. 1999;189:12-19.
2. Bosch FX, Manos MM, Munoz N, et al, for the International Biological Study on Cervical Cancer (IBSCC) Study Group. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. *J Natl Cancer Inst*. 1995;87:796-802.
3. National Cancer Institute. *Surveillance, Epidemiology and End-Results.* Washington, DC: Dept of Health and Human Services; 2000.
4. Koutsky LA, Ault KA, Wheeler CM, et al. A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med.* 2002;347:1645-1651.
5. Phelps CE, Mushlin AI. Focusing technology assessment using medical decision theory. *Med Decis Making*. 1988;8:279-289.
6. Hueston WJ, Mainous AG III, Brauer N. Predicting cost-benefits before programs are started: looking at a conjugate vaccine for invasive pneumococcal infections. *J Community Health*. 2000;25:23-33.
7. McCrory DC, Matchar DB, Bastian L, et al. *Evaluation of Cervical Cytology: Evidence Report/Technology Assessment No. 5.* Rockville, Md: Agency for Health Care Policy and Research; 1999. Publication No. 99-E010.
8. Myers ER, McCrory DC, Nanda K, Bastian L, Matchar DB. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. *Am J Epidemiol*. 2000;151:1158-1171.
9. Kim JJ, Wright TC, Goldie SJ. Cost effectiveness of alternative triage strategies for atypical squamous cells of undetermined significance. *JAMA*. 2002;287:2382-2390.
10. Mandelblatt JS, Lawrence WF, Womack SM, et al. Benefits and costs of using HPV testing to screen for cervical cancer. *JAMA.* 2002;287:2372-2381.
11. Sherlaw-Johnson C, Gallivan S, Jenkins D. Evaluating cervical cancer screening programmes for developing countries. *Int J Cancer*. 1997;72:210-216.
12. Maxwell GL, Carlson JW, Ochoa M, Krivak T, Rose GS, Myers ER. Costs and effectiveness of alternative strategies for cervical cancer screening in military beneficiaries. *Obstet Gynecol.* 2002;100:740-748.
13. Goldie SJ, Kuhn L, Denny L, Pollack A, Wright TC. Policy analysis of cervical cancer screening strategies in low-resource settings: clinical benefits and cost-effectiveness. *JAMA*. 2001;285:3107-3115.
14. Gustaffson L, Ponten J, Zack M, Adami H-O. International incidence of invasive cervical cancer after introduction of cytological screening. *Cancer Causes Control.* 1997;8:755-763.
15. Myers ER, McCrory DC, Subramanian S, et al. Setting the target for a better cervical screening test: characteristics of a cost-effective test for cervical neoplasia screening. *Obstet Gynecol.* 2000;96:645-652.
16. Jacobs MV, Walboomers JMM, Snijders PJF, et al. Distribution of 37 mucosotropic HPV types in women with cytologically normal cervical smears: the age-related patterns for high-risk and low-risk types. *Int J Cancer.* 2000;87:221-227.
17. Liaw KL, Glass AG, Manos MM, et al. Detection of human papillomavirus DNA in cytologically normal women and subsequent cervical squamous intraepithelial lesions. *J Natl Cancer Inst.* 1999;91:954-960.
18. Koutsky LA, Holmes KK, Critchlow CW, et al. A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. *N Engl J Med.* 1992;327:1272-1278.
19. Saslow D, Runowicz CD, Solomon D, et al. American Cancer Society guidelines for the early detection of cervical neoplasia and cancer. *CA Cancer J Clin.* 2002;52:342-362.
20. Leigh BC, Morrison DM, Trocki K, Temple MT. Sexual behavior of American adolescents: results from a US national survey. *J Adolesc Health.* 1994;15:117-125.
21. Cuzick J, Szarewski A, Terry G, et al. Human papillomavirus testing in primary cervical screening. *Lancet.* 1995;345:1533-1536.
22. Nanda K, McCrory DC, Myers ER, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. *Ann Intern Med.* 2000;132:810-819.
23. Ratnam S, Franco EL, Ferenczy A. Human papillomavirus testing for primary screening of cervical cancer precursors. *Cancer Epidemiol Biomarkers Prev.* 2000;9:945-951.
24. Kulasingam SL, Hughes JP, Kiviat NB, et al. Evaluation of human papillomavirus testing in primary screening for cervical abnormalities: comparison of sensitivity, specificity, and frequency of referral. *JAMA*. 2002;288:1749-1757.
25. Obwegeser JH, Brack S. Does liquid-based technology really improve detection of cervical neoplasia? a prospective, randomized trial comparing the ThinPrep Pap Test with the conventional Pap Test, including follow-up of HSIL cases. *Acta Cytol.* 2001;45:709-714.
26. Coste J, Cochand-Priollet B, de Cremoux P, et al, for the French Society of Clinical Cytology Study Group. Cross-sectional study of conventional cervical smear, monolayer cytology, and human papillomavirus DNA testing for cervical cancer screening. *BMJ.* 2003;326:733-738.
27. Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA.* 2002;287:2114-2119.
28. Solomon D, Schiffman M, Tarone R. Comparison of three management strategies for patients with atypical squamous cells of unknown significance: baseline results from a randomized trial. *J Natl Cancer Inst.* 2001;93:293-299.
29. Hughes JP, Garnett GP, Koutsky L. The theoretical population-level impact of a prophylactic human papillomavirus vaccine. *Epidemiology*. 2002;13:631-639.
30. Stratton KR, Durch JS, Lawrence RS, eds. *Vaccines for the 21st Century: A Tool for Decisionmaking.* Washington, DC: National Academy Press; 2001.
31. Kulasingam S, Harper DM, Tosteson AT, Myers ER. Impact of quality of life assumptions on cost-effectiveness of cervical cancer screening. Presented at: 20th International Papillomavirus Conference; October 5-9, 2002; Paris, France.
32. Gold MR, Siegel JE, Russel LB, Weinstein MC, eds. *Cost-effectiveness in Health and Medicine.* New York, NY: Oxford University Press Inc; 1996.
33. Thomas KK, Hughes JP, Kuypers JM, et al. Concurrent and sequential acquisition of different genital human papillomavirus types. *J Infect Dis.* 2000;182:1097-1102.
34. Ho GYF, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med.* 1998;338:423-428.
35. Winkelmayer WC, Weinstein WC, Mittleman MA, Glynn RJ, Pliskin JS. Health economic evaluations: the special case of end-stage renal disease treatment. *Med Decis Making.* 2002;22:417-430.
36. Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study (ALTS) Group. Human papillomavirus testing for triage of women with cytologic evidence of low-grade squamous intraepithelial lesions: baseline data from a randomized trial. *J Natl Cancer Inst*. 2000;92:397-402.
37. Munoz N, Bosch FX, de Sanjose S, et al, for the International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med.* 2003;348:518-527.
38. Crum CP. The beginning of the end for cervical cancer. *N Engl J Med.* 2002;347:1703-1705.
39. Eddy DM. Screening for cervical cancer. *Ann Intern Med.* 1990;113:214-226.
40. Brown AD, Garber AM. Cost-effectiveness of 3 methods to enhance the sensitivity of Papanicolau testing. *JAMA*. 1999;281:347-353.
41. Fahs MC, Plichta SB, Mandelblatt JS. Cost effective policies for cervical cancer screening: an international review. *Pharmacoeconomics.* 1996;9:211-230.
42. Fahs MC, Mandelblatt J, Schechter C, Muller C. Cost-effectiveness of cervical cancer screening for the elderly. *Ann Intern Med.* 1992;117:520-527.
43. Anderson RM, Swinton J, Garnett GP. Potential impact of low efficacy HIV-1 vaccine in populations with high rates of infection. *Proc R Soc Lond B Biol Sci.* 1995;261:147-151.
44. Conaglen HM, Hughes R, Conaglen JV, Morgan J. A prospective study of the psychological impact on patients of first diagnosis of human papillomavirus. *Int J STD AIDS.* 2001;12:651-658.
45. Jones MH, Singer A, Jenkins D. The mildly abnormal cervical smear: patient anxiety and choice of management. *J R Soc Med.* 1996;89:257-260.
46. Klee M, Thranov I, Machin D. Life after radiotherapy: the psychological and social effects experienced by women treated for advanced states of cervical cancer. *Gynecol Oncol.* 2000;76:5-13.
47. Li C, Samsioe G, Iosif G. Quality of life in long-term survivors of cervical cancer. *Maturitas*. 1999;32:95-102.