ATTACHMENT C

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SPECIAL ARTICLE

Health and Economic Implications of HPV Vaccination in the United States

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ABSTRACT

BACKGROUND

The cost-effectiveness of prophylactic vaccination against human papillomavirus types 16 (HPV-16) and 18 (HPV-18) is an important consideration for guidelines for immunization in the United States.

METHODS

We synthesized epidemiologic and demographic data using models of HPV-16 and HPV-18 transmission and cervical carcinogenesis to compare the health and economic outcomes of vaccinating preadolescent girls (at 12 years of age) and vaccinating older girls and women in catch-up programs (to 18, 21, or 26 years of age). We examined the health benefits of averting other HPV-16–related and HPV-18–related cancers, the prevention of HPV-6–related and HPV-11–related genital warts and juvenile-onset recurrent respiratory papillomatosis by means of the quadrivalent vaccine, the duration of immunity, and future screening practices.

RESULTS

On the assumption that the vaccine provided lifelong immunity, the cost-effectiveness ratio of vaccination of 12-year-old girls was $43,600 per quality-adjusted life-year (QALY) gained, as compared with the current screening practice. Under baseline assumptions, the cost-effectiveness ratio for extending a temporary catch-up program for girls to 18 years of age was $97,300 per QALY; the cost of extending vaccination of girls and women to the age of 21 years was $120,400 per QALY, and the cost for extension to the age of 26 years was $152,700 per QALY. The results were sensitive to the duration of vaccine-induced immunity; if immunity waned after 10 years, the cost of vaccination of preadolescent girls exceeded $140,000 per QALY, and catch-up strategies were less cost-effective than screening alone. The cost-effectiveness ratios for vaccination strategies were more favorable if the benefits of averting other health conditions were included or if screening was delayed and performed at less frequent intervals and with more sensitive tests; they were less favorable if vaccinated girls were preferentially screened more frequently in adulthood.

CONCLUSIONS

The cost-effectiveness of HPV vaccination will depend on the duration of vaccine immunity and will be optimized by achieving high coverage in preadolescent girls, targeting initial catch-up efforts to women up to 18 or 21 years of age, and revising screening policies.

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IN THE UNITED STATES, CERVICAL CANCER developed in an estimated 11,150 women and caused death in 3600 women in 2007.[1] Infection with high-risk "oncogenic" types of human papillomavirus (HPV) is the cause of 100% of cervical cancers, 90% of anal cancers, 40% of vulvar and vaginal cancers, at least 12% of oropharyngeal cancers, and 3% of oral cancers.[2] Worldwide, HPV types 16 (HPV-16) and 18 (HPV-18) cause approximately 70% of cases of cervical cancer.[3,4]

Vaccines against HPV-16 and HPV-18 appear to be highly efficacious in preventing HPV-16 and HPV-18 infections and cervical lesions in girls and women who have not previously been infected with these types.[5-9] The vaccine currently licensed in the United States also prevents HPV types 6 and 11 (HPV-6 and HPV-11), which are responsible for most genital warts and juvenile-onset recurrent respiratory papillomatosis.[10]

There are important questions regarding the appropriate target population for prophylactic vaccination against HPV-16 and HPV-18. Since the vaccine is most efficacious before the onset of sexual activity, most investigators agree that the target population for routine immunization should be adolescents who are approximately 12 years of age.[11,12] Recommended temporary catch-up programs to provide vaccine coverage to girls and women 13 years of age and older range from an upper age limit of 18 to 26 years.[11,12]

The impact of HPV vaccination on the rate of cervical cancer will not be observable for decades; thus, decisions regarding a vaccination policy will inevitably rely on studies reporting intermediate outcomes. Estimating the magnitude of the benefit of vaccination is further complicated when one considers the extensive secondary-prevention program in the United States. This program, which involves the use of cytology-based screening, is recommended annually or biennially, starting 3 years after the first sexual intercourse and no later than 21 years of age.[13-15] HPV DNA testing is recommended as a triage test for equivocal results of cytologic analysis and in combination with cytologic tests for primary screening in women 30 years of age or older.[16]

Before long-term data become available, mathematical models used in a decision-analytic framework that synthesize the best available data while ensuring consistency with epidemiologic observations can project outcomes beyond those reported in clinical trials, provide insight into key drivers of cost-effectiveness, and be revised as new information emerges. Extending previous studies of HPV vaccination,[17-22] we evaluated the cost-effectiveness of vaccinating 12-year-old girls and of temporary catch-up programs. We considered the dynamics of HPV transmission, the duration of vaccine efficacy, the potential benefits of preventing noncervical HPV-related conditions, the anticipated changes in screening practice, and potential disparities in access to care.

METHODS

ANALYTIC OVERVIEW

Synthesizing epidemiologic, clinical, and demographic data from the United States, we used empirically calibrated simulation models to estimate the lifetime costs and benefits of vaccinating 12-year-old girls (herein referred to as the vaccination of preadolescent girls), as well as catch-up programs in girls and women up to 18, 21, or 26 years of age, in the context of current cytology-based screening in the United States. The base-case analysis was intended to be relevant to both the bivalent and quadrivalent HPV vaccines and therefore focused on the outcomes of cervical cancer. To examine the additional benefits of the vaccine for which empirical data were available, we also assessed the effect of the quadrivalent vaccine on HPV-6–associated and HPV-11–associated genital warts. Although the efficacy of the vaccine against noncervical HPV-16–associated and HPV-18–associated cancers and HPV-6–associated and HPV-11–associated juvenile-onset recurrent respiratory papillomatosis is more uncertain, we assessed the effect of their inclusion on our results. Although we assumed lifelong complete protection against the vaccine-targeted types of HPV in the base-case analysis, we evaluated the effect of waning vaccine-induced immunity (without and with a booster). Other uncertainties that we evaluated included cross-protection of the vaccine against high-risk types of HPV that did not include HPV-16 and HPV-18, the increased incidence of high-risk types of HPV that did not include HPV-16 and HPV-18, disparities in vaccination and screening coverage, and revisions in screening practices.

We adopted a societal perspective, discounted costs and benefits by 3% annually, and expressed benefits as quality-adjusted life-years (QALYs) gained. After eliminating strategies that were more costly and less effective or less costly and less cost-effective than an alternative strategy, incremental cost-effectiveness ratios were calculated as the

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additional cost divided by the additional health benefit associated with one strategy as compared with the next-less-costly strategy. Although there is no consensus on a cutoff point for good value for resources, we interpreted our results in terms of a commonly cited threshold of $50,000 per QALY gained, as well as an upper-bound threshold of $100,000 per QALY gained.[23]

MODELS

We used a flexible modeling approach that included a dynamic model to simulate the sexual transmission of HPV-16 and HPV-18 infections between men and women and an individual-based stochastic model to simulate the cervical carcinogenesis associated with all types of HPV. Both models have been described previously.[24,25] Briefly, the dynamic model is an open-cohort, age-structured compartmental model in which women and men form sexual partnerships over time. Women and men enter the susceptible pool on sexual initiation starting at 10 years of age, and with each partnership, HPV-16 or HPV-18 may be transmitted, depending on the number of new partners, the prevalence of HPV among the opposite sex, and the probabilities of transmission of HPV-16 and HPV-18 from an infected partner. After the first HPV infection and clearance, partial type-specific natural immunity develops, effectively reducing a person's susceptibility to future infections of the same type. Grade 1 cervical intraepithelial neoplasia (CIN 1) or grade 2 or 3 CIN (CIN 2/3) can develop in women with HPV-16 or HPV-18 infection, and invasive cancer may develop in women with CIN 2/3.

The individual-based stochastic model has a similar structure. However, all types of HPV (categorized as HPV-16, HPV-18, other high-risk types of HPV, and low-risk types of HPV) are included, the incidence of HPV is a function of age and individual-level characteristics, it keeps track of each person's history (e.g., vaccination, screening, treatment, and past abnormalities), and it can accommodate complex screening strategies.[25,26] The dynamic model was used to estimate reductions in the age-specific incidence of HPV-16 and HPV-18 with vaccination, reflecting the direct benefits to persons who were vaccinated, as well as indirect benefits, because of herd immunity, to those who were not vaccinated. The generated reductions in the incidence of HPV-16 and HPV-18 served as inputs to the stochastic model, which was used to compare multiple strategies for the prevention of cervical cancer. The specific features of the individual-based stochastic model allowed us to identify the synergies between vaccination and screening, study the implications of disparities in vaccination and screening coverage, assess the effect of cross-protection to other types of HPV, and explore the potential for an increase in the incidence of types of HPV that were not targeted by the vaccine.

The initial variables from the models were based on data from epidemiologic studies, cancer registries, and demographic statistics. The models were calibrated with the use of a likelihood-based approach to fit to empirical data, such as the age-specific prevalence of HPV, the age-specific incidence of cervical cancer, and the distribution of types of HPV observed among girls and women in the U.S. population.[3,4,27-31] These approaches have been described elsewhere,[24,25] and details relevant to the current analysis are provided in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

For noncervical cancer conditions, data included the incidence of other HPV-16–associated and HPV-18–associated cancers; the incidence of low-risk, HPV-associated genital warts and juvenile-onset recurrent respiratory papillomatosis; the proportion of each disease attributable to vaccine-targeted types of HPV; and the disease-specific quality of life, costs, and mortality[2,10,32-41] (Table 1). Costs (in 2006 U.S. dollars) included the direct medical costs associated with screening, diagnosis, and treatment (e.g., tests, procedures, and hospitalizations) and with vaccination (e.g., three doses of the vaccine at $120 per dose, wastage, supplies, and administration).[42-45] Direct nonmedical costs such as the patients' time and transportation were included for all strategies.

COST-EFFECTIVENESS ANALYSIS

To estimate the long-term outcomes associated with vaccination and screening, we projected the lifetime health and economic consequences for all birth cohorts of women in the first 10 years of the vaccine program. We included all birth cohorts, regardless of whether or not they received the vaccine, to capture the benefits of herd immunity in unvaccinated persons (see the Supplementary Appendix). The incremental costs and the health benefits of each vaccination strategy as compared with screening alone served as the basis for calculations of cost-effectiveness.

Strategies included HPV vaccination of 12-year-old girls and catch-up vaccination over a 5-year period for girls and women from 13 years of age

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Table 1. **Values for HPV-Related Health Conditions in the Model.***

Variable	Values	Reference
Cervical cancer		
Incidence (no./100,000 women)†	4.2–62.8	
Five-year survival (%)‡	16.5–92.0	National Cancer Institute[32]
Quality-of-life adjustment§	0.48–0.76	Myers et al.,[36] Gold et al.[39]
Cases attributable to HPV-16 and HPV-18 (%)	70.0	Parkin and Bray[2]
Cost per case ($)¶	26,540–45,540	Goldie et al.[33]
Vulvar cancer		
Incidence (no./100,000 women)	0.2–24.9	National Cancer Institute[32]
Five-year survival (%)	77.8	National Cancer Institute[32]
Quality-of-life adjustment§	0.68	Gold et al.[39]
Cases attributable to HPV-16 and HPV-18 (%)	32.0	Parkin and Bray[2]
Cost per case ($)¶	20,430	Hu and Goldie[38]
Vaginal cancer		
Incidence (no./100,000 women)	0.1–6.0	National Cancer Institute[32]
Five-year survival (%)	55.7	National Cancer Institute[32]
Quality-of-life adjustment§	0.68	Gold et al.[39]
Cases attributable to HPV-16 and HPV-18 (%)	32.0	Parkin and Bray[2]
Cost per case ($)¶	23,440	Hu and Goldie[38]
Anal cancer		
Incidence (no./100,000 women)	0.0–5.6	National Cancer Institute[32]
Five-year survival (%)	66.2	National Cancer Institute[32]
Quality-of-life adjustment§	0.68	Gold et al.[39]
Cases attributable to HPV-16 and HPV-18 (%)	82.8	Parkin and Bray[2]
Cost per case ($)¶	31,300	Hu and Goldie[38]
Oral cancer		
Incidence (no./100,000 women)	0.2–13.9	National Cancer Institute[32]
Five-year survival (%)	62.6	National Cancer Institute[32]
Quality-of-life adjustment§	0.68	
Cases attributable to HPV-16 and HPV-18 (%)	2.9	Parkin and Bray[2]
Cost per case ($)¶	37,370	Hu and Goldie[38]
Oropharyngeal cancer		
Incidence (no./100,000 women)	0.0–1.1	National Cancer Institute[32]
Five-year survival (%)	62.6	National Cancer Institute[32]
Quality-of-life adjustment§	0.68	
Cases attributable to HPV-16 and HPV-18 (%)	10.7	Parkin and Bray[2]
Cost per case ($)¶	37,370	Hu and Goldie[38]

to 18, 21, or 26 years of age. On the basis of rates of vaccinations among adolescents in the United States,[46] we assumed that approximately 75% of the target population was covered within the first 5 years after the beginning of the program, at a coverage rate of 25% per year (Fig. 1). The efficacy of the vaccine was assumed to be lifelong and 100% against the types of HPV targeted by the vaccine among girls and women without a previous history of those infections.

All strategies included routine screening for cervical cancer with conventional or liquid-based cytologic testing, beginning in women at an average age of 20 years, according to U.S. guide-

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Table 1. (Continued.)

Variable	Values	Reference
Genital warts		
Prevalence (no./1000 women)	0.07–6.20	Insinga et al.[35]
Quality-of-life adjustment§	0.91	Insinga et al.,[35] Myers et al.[36]
Cases attributable to HPV-6 and HPV-11 (%)	100	Lacey et al.[10]
Cost per case ($)¶	430	Hu and Goldie[38]
Juvenile-onset recurrent respiratory papillomatosis		
Incidence (no./100,000 children 0–14 yr old)	4.30	Derkay[37]
Quality-of-life adjustment§	0.69	Bishai et al.[40]
Cases attributable to HPV-6 and HPV-11 (%)	100	Lacey et al.[10]
Cost per case ($)¶	62,010	Hu and Goldie[38]

* Ranges represent age-specific values, and rates are annual rates unless otherwise noted. HPV denotes human papillomavirus.
† Incidence rates for cervical cancer were generated by the calibrated stochastic model in the absence of screening or vaccination (i.e., natural history).
‡ The 5-year survival for cervical cancer varied according to the stage (i.e., 92.0% for local, 55.7% for regional, and 16.5% for distant disease).
§ The quality-of-life adjustment assumed a health-state utility weight of 0 (death) to 1 (perfect health). The health-state utility weight for cervical cancer varied according to the stage: 0.76 for local cancer, 0.67 for regional cancer for a period of 5 years, and 0.48 for distant cancer over the lifetime with disease. For noncervical cancers, we assumed an average health-state utility weight of 0.68 over the lifetime with disease in order to reflect a weighted average of stage-specific utility weights and distribution of disease according to stage. For genital warts, we assumed a health-state utility weight of 0.91 over 3 months. All disease-specific utility weights were multiplied to baseline age-specific utility weights in order to estimate the overall utility weight (data are from Fryback et al.[41]).
¶ The cost per case is expressed in 2006 U.S. dollars and represents the average discounted lifetime costs of a new case of disease, including direct medical costs (i.e., the cost of procedures, hospitalizations, and office visits). The costs of treatment of cervical cancer varied according to stage (e.g., $26,540 for local, $28,430 for regional, and $45,540 for distant disease) and included direct nonmedical costs such as the patients' time and transportation.

lines that recommend that screening should start 3 years after the first sexual intercourse.[13,47] Abnormal results of cytologic tests were managed according to standard clinical guidelines.[48] On the basis of reported patterns of cervical-cancer screening in women in the United States,[49-51] we assumed that 53% of women were screened annually, 17% every 2 years, 11% every 3 years, and 14% every 5 years and that 5% were never screened. We considered scenarios in which girls who were unlikely to be vaccinated were also unlikely to be screened. We also assessed the implications of screening less frequently (every 3 or 5 years), delaying the initiation of screening (until 25 years of age), and the use of HPV DNA testing.[52]

To gauge the benefits of the quadrivalent vaccine against HPV-6 and HPV-11 in women, we modeled the age-specific incidence and duration of genital warts,[35] including their effect on quality of life and treatment costs,[36,38] and we estimated the quality-adjusted life expectancy gained and costs averted with vaccination. Similarly, we estimated the number of cases of juvenile-onset recurrent respiratory papillomatosis averted per vaccinated woman using data on the number of births per woman,[53] annual incidence rates of juvenile-onset recurrent respiratory papillomatosis per live child,[37] costs per case, and effects on quality of life.[38,40] For both vaccines, we modeled age-specific incidence rates of HPV-16–associated and HPV-18–associated noncervical cancer among women,[32] taking into account cancer-specific mortality and health-state utility weights (i.e., values from 0 to 1 indicating the quality of a person's state of health, with 0 indicating death and 1 indicating perfect health),[32,39] to estimate quality-adjusted life expectancy gained and costs averted (Table 1). Vaccination was assumed to reduce the proportion of cases attributable to vaccine-targeted types of HPV, and we varied the efficacy on these conditions from 50% to 100% (see the Supplementary Appendix for additional details on noncervical conditions).

RESULTS

COST-EFFECTIVENESS OF VACCINATION

The routine vaccination of 12-year-old girls, in the context of current screening and assuming lifelong vaccine-induced immunity, had an incremen-

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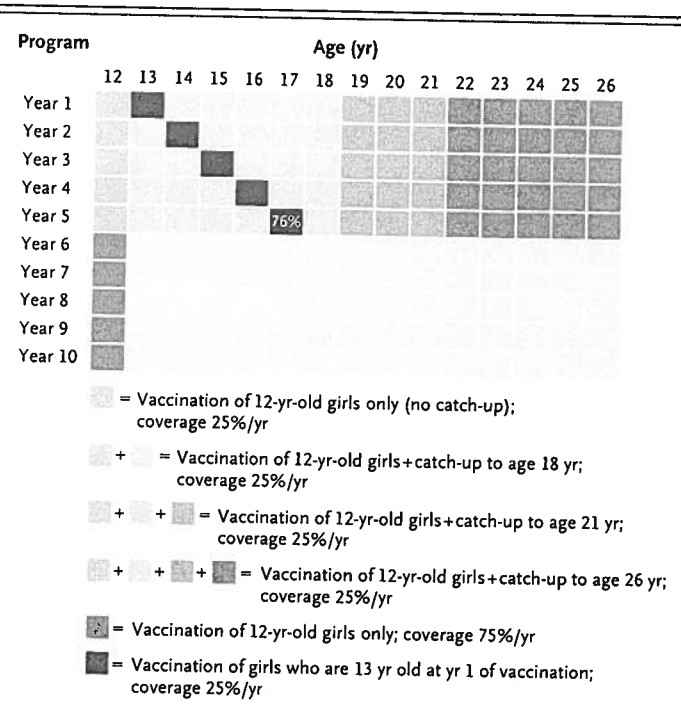

Figure 1. Vaccination Coverage.

Pink boxes indicate vaccination of preadolescent 12-year-old girls at a coverage rate of 25% per year for the first 5 years of the vaccination program; purple boxes indicate a coverage rate of 75% in years 6 to 10 of the vaccination program. Without a catch-up program, each birth cohort of 12-year-olds had no future opportunities for vaccination beyond a single year. Yellow, light-orange, and dark-orange boxes indicate catch-up vaccination of girls and women from age 13 up to 18, 21, or 26 years of age, which occurred over a 5-year period at 25% coverage per year. Therefore, an additional 25% of the initial cohort of 12-year-old girls who were not vaccinated in the first year had another opportunity to receive the vaccine in the second year of the program, when they were 13 years old; such opportunities continued through program year 5. Brown boxes show catch-up vaccination in the initial cohort of 13-year-old girls. In year 1 of the vaccination program, 25% of the 13-year-old girls were assumed to be covered; in year 2, among the 75% of 13-year-olds who were not vaccinated in year 1, 25% would be covered when they were 14 years old. At the end of year 5, 76% of the original cohort of 13-year-olds was covered. The number of opportunities for vaccination depended on the specific catch-up strategy; for example, a 16-year-old in the first year of the program would have only three chances of receiving the vaccine in a catch-up program up to 18 years of age, since she would be older than 18 years of age in program year 4.

tal cost-effectiveness ratio of $43,600 per QALY gained, as compared with screening alone (Table 2). The addition of a 5-year catch-up program for girls between the ages of 13 and 18 years cost $97,300 per QALY, and extension to 21 years of age cost $120,400 per QALY. The extension of the catch-up program to 26 years of age cost $152,700 per QALY, as compared with the catch-up program to 21 years of age.

Inclusion of protection against HPV-6–related and HPV-11–related genital warts reduced the cost per QALY for vaccination of preadolescent girls by 20% to $34,900, for catch-up to 18 years of age by 17% to $81,000, and for catch-up to 21 years of age by 16% to $101,300. The cost per QALY for catch-up to 26 years of age was reduced by only 13%, to $133,600.

INCLUSION OF OTHER HPV-ASSOCIATED CONDITIONS

When the potential benefits associated with preventing noncervical HPV-16–related and HPV-18–related cancers and HPV-6–related and HPV-11–related juvenile-onset recurrent respiratory papillomatosis were included, cost-effectiveness ratios were reduced. The magnitude of these reductions depended on the specific outcomes that were included and on assumptions about the efficacy of the vaccine (Fig. 2). In all scenarios, the cost of vaccination of preadolescent girls remained below $50,000 per QALY, and catch-up vaccination of girls to 18 years of age remained between $50,000 and $100,000 per QALY.

EFFECT OF WANING IMMUNITY, VACCINE CROSS-PROTECTION, AND TYPE REPLACEMENT

If vaccine-induced immunity lasted only 10 years, the vaccination of preadolescent girls provided only 2% marginal improvement in the reduction in the risk of cervical cancer as compared with screening alone, and it cost $144,100 per QALY, whereas catch-up programs were more costly and less effective than screening alone (Table 3). With a completely efficacious vaccine booster at 10 years, the cost of vaccination of preadolescent girls was $83,300 per QALY, although catch-up strategies exceeded $125,000 per QALY. There were marginal improvements in cost-effectiveness when cross-protective effects were included against other high-risk types of HPV.[8] Furthermore, in a separate analysis, with a 5% increase in the baseline risk of infection with high-risk types of HPV other than HPV-16 and HPV-18, the cost per QALY of vaccination of preadolescent girls increased from $43,600 to $53,000.

EFFECT OF PATTERNS OF VACCINATION AND SCREENING COVERAGE

If 5% of women in the United States were neither screened nor vaccinated, all strategies that involved a catch-up program exceeded $100,000 per QALY;

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Table 2. Cost-Effectiveness of Vaccination of Preadolescent Girls and Temporary Catch-Up Programs.*

Strategy†	Base Case‡	With Outcomes Related to HPV-6 and HPV-11 Genital Warts§
	$/QALY	
Screening only¶	—	—
Vaccination (age 12 yr)	43,600	34,900
Vaccination (age 12 yr) plus catch-up vaccination (age 13–18 yr)	97,300	81,000
Vaccination (age 12 yr) plus catch-up vaccination (age 13–21 yr)	120,400	101,300
Vaccination (age 12 yr) plus catch-up vaccination (age 13–26 yr)	152,700	133,600

* The values represent incremental cost-effectiveness ratios (i.e., the additional cost divided by the additional health benefit compared with the next-less-costly strategy) expressed as cost per quality-adjusted life-year ($/QALY). All costs are expressed in 2006 U.S. dollars. HPV denotes human papillomavirus.
† All strategies included current cytologic screening (see the Methods section).
‡ The base-case analysis reflected the outcomes related to cervical cancer only.
§ The analysis included outcomes related to cervical cancer and HPV-6–associated and HPV-11–associated genital warts in girls and women.
¶ Since screening only is the baseline strategy, it is not associated with an incremental cost-effectiveness ratio.

catch-up to 26 years of age exceeded $200,000 per QALY (Table 4). The ratios became even less attractive when we assumed that girls who were vaccinated were preferentially screened more frequently in adulthood.

Even if all women were equally likely to be screened, the cost-effectiveness of vaccination was influenced by the frequency of screening and test protocols. With annual and biennial screening, the cost of vaccination of preadolescent girls increased to $118,200 and $45,800 per QALY, respectively; the negative effect on the cost-effectiveness of catch-up programs was greater, with catch-up vaccination of girls and women up to 26 years of age increasing to more than $300,000 and approximately $190,000 per QALY, respectively. The cost-effectiveness ratio for the vaccination of preadolescent girls associated with initiating screening later (e.g., at 25 years of age) with the use of cytologic tests with HPV triage every 3 years, followed by combined HPV DNA testing and cytologic tests for primary screening after 35 years of age, was similar to the base case, although catch-up vaccination programs for women up to 21 and 26 years of age were associated with higher cost-effectiveness ratios (see additional results in the Supplementary Appendix).

DISCUSSION

Vaccination against HPV-16 and HPV-18 is expected to be economically attractive (i.e., <$50,000 per QALY) if high coverage can be achieved in the primary target group of 12-year-old girls and if vaccine-induced immunity is lifelong. Under these conditions, if we are willing to pay $100,000 per QALY, a catch-up program for girls between 13 and 18 years of age appears to be reasonable, especially when we include the benefits of averting genital warts (with the use of the quadrivalent vaccine) or the benefits of cross-protection against other high-risk types of HPV not including HPV-16 and HPV-18 (as reported with the bivalent vaccine). Extending the catch-up program to 21 years of age is less cost-effective, but it also becomes more favorable when the potential benefits of preventing noncervical HPV-16–associated and HPV-18–associated cancers in women are included.

Extending vaccine coverage to women up to 26 years of age generally exceeds $130,000 per QALY. This result is not unexpected, since nearly 90% of women in the United States have had vaginal intercourse by 24 years of age[47] and up to 30% of women may be exposed to HPV in the first year of intercourse.[54] The cost of extending a catch-up program to women up to 26 years of age is less than $100,000 per QALY only in the context of 100% lifelong efficacy against other outcomes associated with HPV-16, HPV-18, HPV-6, and HPV-11 in women; these outcomes include cervical cancer, warts, other cancers, and juvenile-onset recurrent respiratory papillomatosis. The cost of extending this program is more than $200,000 per QALY when a booster is required to maintain lifelong

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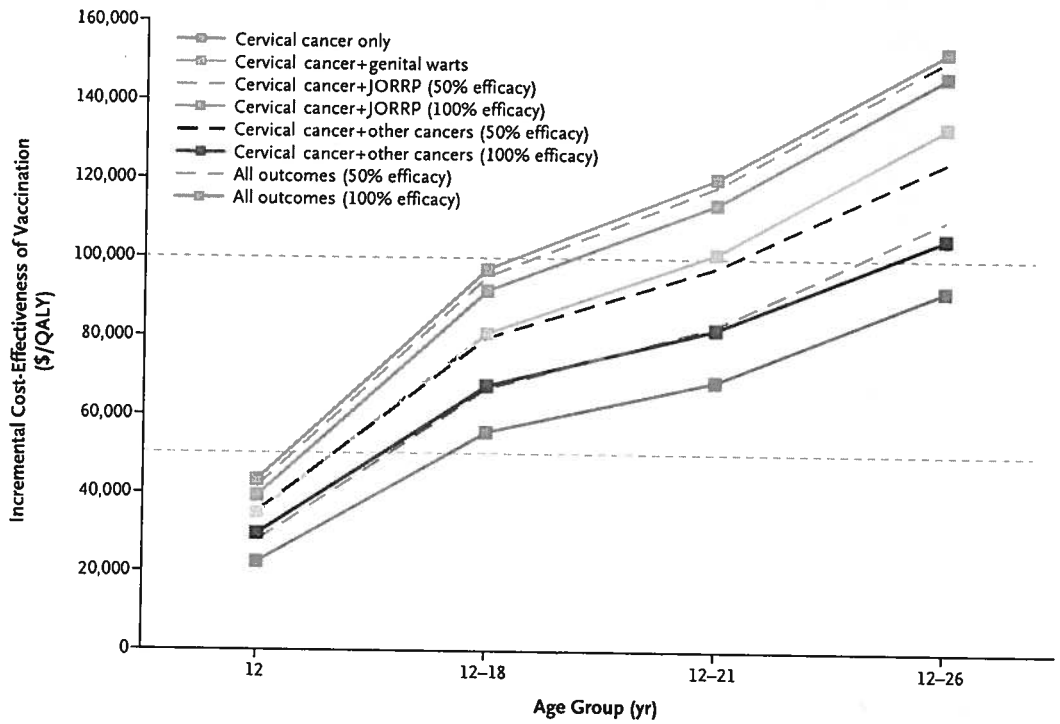

Figure 2. Effect of Inclusion of Other Health Conditions on the Cost-Effectiveness of Vaccination Strategies. The solid lines represent analyses in which the efficacy of the vaccine against human papillomavirus (HPV) was assumed to be 100% among girls and women without a previous history of type-specific infection (for all conditions). The dashed lines represent analyses in which the efficacy of the vaccine was assumed to be 50% (only for cancers other than cervical cancer and juvenile-onset recurrent respiratory papillomatosis [JORRP]; the efficacy remained 100% for cervical cancer and genital warts) among girls and women without a previous history of type-specific infection. In all analyses, the efficacy of the vaccine was assumed to be 0% among persons with a previous type-specific infection or infections. Including the potential benefits of the vaccine against noncervical HPV-16–related and HPV-18–related cancers, HPV-6–related and HPV-11–related JORRP, or both reduced the cost-effectiveness ratios, but the magnitude of the reduction depended on the specific outcomes included and the assumptions about efficacy. For instance, including other cancers reduced the cost-effectiveness ratios from 18% to 30% depending on the efficacy of the vaccine, whereas including JORRP had less of an effect. Under all assumptions, the cost of vaccination of preadolescent girls (i.e., 12-year-old girls) remained below $50,000 per quality-adjusted life-year (QALY), and the cost of catch-up vaccination of girls to 18 years of age was between $50,000 and $100,000 per QALY. The cost of catch-up vaccination of girls and women to 21 years of age decreased below $100,000 per QALY when other cancers or all outcomes were included, and the cost of catch-up vaccination to 26 years of age exceeded $100,000 per QALY, unless all outcomes were included with a vaccine efficacy of 100% for all conditions.

immunity, when there are disparities in screening and vaccination coverage, and when vaccinated girls undergo frequent screening in adulthood. The benefits of vaccine in most HPV-16 and HPV-18 noncervical cancers and HPV-6 and HPV-11 juvenile-onset recurrent respiratory papillomatosis have not been shown in clinical studies.

Our results were sensitive to the duration of vaccine-induced immunity; if immunity lasted 10 years, the vaccination of preadolescent girls exceeded $140,000 per QALY, and all catch-up strategies were less cost-effective than screening alone. Although immunologic data have provided support for a strong initial immune response with antibody levels persisting at a level higher than the level after natural infection,[9,55,56] observations in published reports are limited to 5 years after vaccination. With partial natural immunity to type-specific infection, if a vaccinated girl loses vaccine-induced protection and becomes susceptible at a

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Table 3. Effect of Uncertain Vaccine Properties on Cost-Effectiveness.*

Strategy†	Base Case‡	Waning Immunity at 10 Yr§	Booster at 10 Yr¶	Inclusion of Cross-Protection against Other High-Risk Types of HPV‖
			$/QALY	
Screening only**	—	—	—	—
Vaccination (age 12 yr)	43,600	144,100	83,300	33,700
Vaccination (age 12 yr) plus catch-up vaccination (age 13–18 yr)	97,300	Not cost-effective	140,700	79,300
Vaccination (age 12 yr) plus catch-up vaccination (age 13–21 yr)	120,400	Not cost-effective	185,400	102,200
Vaccination (age 12 yr) plus catch-up vaccination (age 13–26 yr)	152,700	Not cost-effective	233,500	129,500

* The values represent incremental cost-effectiveness ratios (i.e., the additional cost divided by the additional health benefit compared with the next-less-costly strategy) expressed as cost per quality-adjusted life-year ($/QALY). A strategy that is not cost-effective is more costly and less effective than another strategy. All costs are expressed in 2006 U.S. dollars. HPV denotes human papillomavirus.

† All strategies included current cytologic screening (see the Methods section).

‡ The base-case analysis reflected the outcomes related to cervical cancer only.

§ The analysis assumed full vaccine-induced protection up to 10 years, after which protection waned completely.

¶ The analysis assumed a vaccine booster was administered to all previously vaccinated persons 10 years after initial vaccination and provided lifelong protection. The booster was assumed to cost $250 per vaccinated person (including the cost of the vaccine dose, supplies, wastage, administration, and patients' time and transportation, as well as an additional cost for the booster campaign and outreach efforts).

‖ The efficacy of the vaccine against other high-risk types of HPV (i.e., other than HPV-16 and HPV-18) was assumed to be 27.1%; data are from Paavonen et al.[8]

** Since screening only is the baseline strategy, it is not associated with an incremental cost-effectiveness ratio.

later age when the risk of cancer may be higher, an increased risk of cervical cancer is plausible. There are no empirical data to show whether reinfection or reactivation of a previous infection predominates in older women; as previously described,[17] which one of these predominates will influence the implications of waning vaccine protection. There are other important uncertainties. Although HPV infections may be independent from one another,[56] our exploratory analysis showed that replacement of the vaccine-targeted types of HPV with other high-risk types could be influential. Vaccination against HPV may also alter sexual behavior in the population or lead to a misperception that screening is no longer necessary. These uncertainties highlight the priorities for surveillance of epidemiologic characteristics and behaviors after vaccination against HPV.

Our results of vaccinating preadolescent girls were consistent with those of other studies.[17-22,57,58] Elbasha et al.[21] reported that the cost of a catch-up program in women up to 24 years of age was less than $5,000 per QALY; none of our strategies had a cost-effectiveness ratio this low, and the cost of a catch-up program in women up to 26 years of age generally exceeded $100,000 per QALY. Differences in assumptions have been summarized in several review articles.[59-61] Our findings, which were consistent with those of others,[20,22] were that high vaccination coverage warranted modification of screening protocols and that the cost-effectiveness of vaccination was enhanced with less frequent screening with more sensitive tests and beginning at later ages.

Our analysis has important limitations. Data on sexual behavior were primarily based on population averages from large surveys, and there were limited data on type-specific HPV transmission according to age and sex. By means of a model-fitting process, we estimated probabilities of transmission that were higher than those of some other analyses[62,63]; as better data become available, the estimation of these variables may be refined. Other limitations of the data included the incidence, mortality, and quality of life associated with noncervical HPV-related cancers, the long-term ef-

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Table 4. **Effect of Disparities in Vaccination and Screening Coverage and Revised Cervical-Cancer Screening Policies on Cost-Effectiveness.***

Strategy	Base Case†	Vaccine Coverage		Screening Policy		
		Only Women Who Will Be Screened‡	Only Women Who Will Be Screened Frequently§	Cytologic Screening (1 yr)¶	Cytologic Screening (2 yr)¶	Revised Screening (3 yr)‖
				$/QALY		
Screening only**	—	—	—	—	—	—
Vaccination (age 12 yr)	43,600	47,900	106,000	118,200	45,800	40,900
Vaccination (age 12 yr) plus catch-up vaccination (13–18 yr)	97,300	121,900	136,300	186,700	102,400	103,500
Vaccination (age 12 yr) plus catch-up vaccination (13–21 yr)	120,400	153,300	172,400	250,600	120,600	128,700
Vaccination (age 12 yr) plus catch-up vaccination (13–26 yr)	152,700	204,700	231,000	324,200	189,700	185,400

* The values represent incremental cost-effectiveness ratios (i.e., the additional cost divided by the additional health benefit compared with the next-less-costly strategy), expressed as the cost per quality-adjusted life-year ($/QALY). All analyses reflect outcomes related to cervical cancer only. All costs are expressed in 2006 U.S. dollars. HPV denotes human papillomavirus.

† The base-case analysis included current cytologic screening (see the Methods section).

‡ The analysis assumed that women who were never screened were also not vaccinated.

§ The analysis assumed that women who were screened less frequently (i.e., every 5 years or never) were also not vaccinated.

¶ The analysis assumed the base-case screening test and age for initiation of screening, but the screening interval was changed to every 1 or 2 years, which is consistent with current screening guidelines.

‖ The analysis assumed cytologic screening with HPV DNA testing as triage for equivocal results starting at 25 years of age, with a switch to combined cytologic and HPV DNA testing starting at 35 years of age.

** Since screening only is the baseline strategy, it is not associated with an incremental cost-effectiveness ratio.

ficacy of the vaccine against cervical lesions and warts, and the efficacy of the vaccine against noncervical cancers. As with all model-based analyses, there are trade-offs with regard to the choice of model structure; we used two different modeling techniques to try to best capture the features of HPV infection and cervical carcinogenesis that were most relevant to the key policy questions. The complexities that are introduced with the use of multiple models should be explored further.[24]

A decision-analytic approach allows for acknowledgment of uncertainty while informing decisions that need to be made now. Accordingly, we emphasized broad qualitative themes that we found to be consistent throughout a range of assumptions. The cost-effectiveness of HPV vaccination in the United States will likely be optimized by achieving universal coverage in young adolescent girls and targeting initial catch-up efforts to girls and women younger than 21 years of age. Optimal synergies between vaccination and screening will involve revisions to current screening practice. Priorities for empirical data collection include surveillance to understand the HPV type-specific epidemiologic factors and screening behavior in vaccinated populations, the duration of vaccine-induced protection, and the long-term impact on other HPV-related conditions.

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REFERENCES

1. American Cancer Society. Cancer facts and figures 2007. (Accessed July 28, 2008, at http://www.cancer.org/downloads/STT/CAFF2007PWSecured.pdf.)

2. Parkin DM, Bray F. Chapter 2: the burden of HPV-related cancers. Vaccine 2006; 24:Suppl 3:S11-S25.

3. Clifford G, Franceschi S, Diaz M, Muñoz N, Villa LL. Chapter 3: HPV type-distribution in women with and without cervical neoplastic diseases. Vaccine 2006;24: Suppl 3:S26-S34.

4. Clifford GM, Smith JS, Plummer M, Muñoz N, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. Br J Cancer 2003;88:63-73.

5. The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915-27.

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6. Ault KA. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. Lancet 2007;369:1861-8.
7. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007;356:1928-43.
8. Paavonen J, Jenkins D, Bosch FX, et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. Lancet 2007;369:2161-70. [Erratum, Lancet 2007;370:1414.]
9. Harper DM, Franco EL, Wheeler CM, et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet 2006;367:1247-55.
10. Lacey CJ, Lowndes CM, Shah KV. Chapter 4: burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. Vaccine 2006;24:Suppl 3:S35-S41.
11. Saslow D, Castle PE, Cox JT, et al. American Cancer Society guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. CA Cancer J Clin 2007;57:7-28.
12. Markowitz LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER. Quadrivalent human papillomavirus vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2007;56:RR-2:1-24.
13. Saslow D, Runowicz CD, Solomon D, et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. CA Cancer J Clin 2002;52:342-62.
14. American College of Obstetricians and Gynecologists. ACOG practice bulletin: cervical cytology screening. Int J Gynaecol Obstet 2003;83:237-47.
15. Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. JAMA 2002;287:2120-9.
16. Wright TC Jr, Schiffman M, Solomon D, et al. Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. Obstet Gynecol 2004;103:304-9.
17. Goldie SJ, Kohli M, Grima D, et al. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. J Natl Cancer Inst 2004;96:604-15.
18. Sanders GD, Taira AV. Cost-effectiveness of a potential vaccine for human papillomavirus. Emerg Infect Dis 2003;9:37-48.
19. Taira AV, Neukermans CP, Sanders GD. Evaluating human papillomavirus vaccination programs. Emerg Infect Dis 2004;10:1915-23.
20. Kulasingam SL, Myers ER. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. JAMA 2003;290:781-9.
21. Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. Emerg Infect Dis 2007;13:28-41.
22. Goldhaber-Fiebert JD, Stout NK, Salomon JA, Kuntz KM, Goldie SJ. Cost-effectiveness of cervical cancer screening with human papillomavirus (HPV) DNA testing and HPV-16,18 vaccination. J Natl Cancer Inst 2008;100:308-20.
23. Eichler HG, Kong SX, Gerth WC, Mavros P, Jönsson B. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? Value Health 2004;7:518-28.
24. Kim JJ, Andres-Beck B, Goldie SJ. The value of including boys in an HPV vaccination programme: a cost-effectiveness analysis in a low-resource setting. Br J Cancer 2007;97:1322-8.
25. Kim JJ, Kuntz KM, Stout NK, et al. Multiparameter calibration of a natural history model of cervical cancer. Am J Epidemiol 2007;166:137-50.
26. Goldie SJ, Kim JJ, Kobus K, et al. Cost-effectiveness of HPV 16, 18 vaccination in Brazil. Vaccine 2007;25:6257-70.
27. Dunne EF, Unger ER, Sternberg M, et al. Prevalence of HPV infection among females in the United States. JAMA 2007;297:813-9.
28. Clifford GM, Gallus S, Herrero R, et al. Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. Lancet 2005;366:991-8.
29. Clifford GM, Smith JS, Aguado T, Franceschi S. Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: a meta-analysis. Br J Cancer 2003;89:101-5.
30. International Union against Cancer. Cancer incidence in five continents. Vol. New York: Springer-Verlag; 1966.
31. Franceschi S, Castellsagué X, Dal-Maso L, et al. Prevalence and determinants of human papillomavirus genital infection in men. Br J Cancer 2002;86:705-11.
32. Surveillance, Epidemiology, End Results (SEER) cancer statistics review, 1975-2001. National Cancer Institute, 2005. (Accessed July 28, 2008, at http://seer.cancer.gov/csr/1975_2001/.)
33. Goldie SJ, Kim JJ, Wright TC. Cost-effectiveness of human papillomavirus DNA testing for cervical cancer screening in women aged 30 years or more. Obstet Gynecol 2004;103:619-31.
34. Insinga RP, Dasbach EJ, Elbasha EH. Assessing the annual economic burden of preventing and treating anogenital human papillomavirus-related disease in the US: analytic framework and review of the literature. Pharmacoeconomics 2005;23:1107-22.
35. Insinga RP, Dasbach EJ, Myers ER. The health and economic burden of genital warts in a set of private health plans in the United States. Clin Infect Dis 2003;36:1397-403.
36. Myers ER, Green S, Lipkus I. Patient preferences for health states related to HPV infection: visual analogue scales versus time trade-off elicitation. In: Proceedings of the 21st International Papillomavirus Conference, Mexico City, February 20–26, 2004. abstract.
37. Derkay CS. Task force on recurrent respiratory papillomas: a preliminary report. Arch Otolaryngol Head Neck Surg 1995;121:1386-91.
38. Hu D, Goldie S. The economic burden of noncervical human papillomavirus disease in the United States. Am J Obstet Gynecol 2008;198(5):500.e1-500.e7.
39. Gold MR, Franks P, McCoy KI, Fryback DG. Toward consistency in cost-utility analyses: using national measures to create condition-specific values. Med Care 1998;36:778-92.
40. Bishai D, Kashima H, Shah K. The cost of juvenile-onset recurrent respiratory papillomatosis. Arch Otolaryngol Head Neck Surg 2000;126:935-9.
41. Fryback DG, Dasbach EJ, Klein R, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. Med Decis Making 1993;13:89-102.
42. HPV vaccine questions and answers. Atlanta: Centers for Disease Control and Prevention, 2006. (Accessed July 28, 2008, at http://www.cdc.gov/std/hpv/STDFact-HPV-vaccine.htm#hpvvac4.)
43. Wallace LA, Young D, Brown A, et al. Costs of running a universal adolescent hepatitis B vaccination programme. Vaccine 2005;23:5624-31.
44. Iskedjian M, Walker JH, Hemels ME. Economic evaluation of an extended acellular pertussis vaccine programme for adolescents in Ontario, Canada. Vaccine 2004;22:4215-27.
45. Revised guidelines for HIV counseling, testing, and referral. MMWR Recomm Rep 2001;50(RR-19):1-58. (Also available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5019a1.htm.)
46. National vaccination coverage among adolescents aged 13–17 years — United States, 2006. MMWR Morb Mortal Wkly Rep 2007;56:885-8.

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47. Mosher WD, Chandra A, Jones J. Sexual behavior and selected health measures: men and women 15-44 years of age, United States, 2002. Advance data from vital and health statistics. No. 362. Atlanta: Centers for Disease Control and Prevention, 2005:1-55.
48. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 Consensus guidelines for the management of women with abnormal cervical cancer screening tests. Am J Obstet Gynecol 2007;197:346-55.
49. Eltoum IA, Roberson J. Impact of HPV testing, HPV vaccine development, and changing screening frequency on national Pap test volume: projections from the National Health Interview Survey (NHIS). Cancer 2007;111:34-40.
50. Soni A. Use of the Pap test as a cancer screening tool among women age 18-64, U.S. noninstitutionalized population, 2005. Statistical brief no. 173. Rockville, MD: Agency for Healthcare Research and Quality, 2007.
51. Insinga RP, Glass AG, Rush BB. Pap screening in a U.S. health plan. Cancer Epidemiol Biomarkers Prev 2004;13:355-60.
52. Franco EL, Cuzick J, Hildesheim A, de Sanjosé S. Chapter 20: issues in planning cervical cancer screening in the era of HPV vaccination. Vaccine 2006;24:Suppl 3: S171-S177.
53. Hamilton BE, Martin JA, Ventura SJ. Births: preliminary data for 2006. Natl Vital Stat Rep 2007;55:1-18.
54. Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. Am J Epidemiol 2003;157: 218-26. [Erratum, Am J Epidemiol 2003; 157:858.]
55. Mao C, Koutsky LA, Ault KA, et al. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial. Obstet Gynecol 2006;107:18-27. [Erratum, Obstet Gynecol 2006;107:1425.]
56. Stanley M, Lowy DR, Frazer I. Chapter 12: prophylactic HPV vaccines: underlying mechanisms. Vaccine 2006;24:Suppl 3:S106-S113.
57. Brisson M, Van de Velde N, De Wals P, Boily MC. The potential cost-effectiveness of prophylactic human papillomavirus vaccines in Canada. Vaccine 2007;25:5399-408.
58. Boot HJ, Wallenburg I, de Melker HE, et al. Assessing the introduction of universal human papillomavirus vaccination for preadolescent girls in The Netherlands. Vaccine 2007;25:6245-56.
59. Newall AT, Beutels P, Wood JG, Edmunds WJ, MacIntyre CR. Cost-effectiveness analyses of human papillomavirus vaccination. Lancet Infect Dis 2007;7:289-96.
60. Dasbach EJ, Elbasha EH, Insinga RP. Mathematical models for predicting the epidemiologic and economic impact of vaccination against human papillomavirus infection and disease. Epidemiol Rev 2006;28:88-100.
61. Barnabas RV, Kulasingam SL. Economic evaluations of human papillomavirus vaccines. Expert Rev Pharmacoeconomics Outcomes Res 2007;7:1-17.
62. Barnabas RV, Laukkanen P, Koskela P, Kontula O, Lehtinen M, Garnett GP. Epidemiology of HPV 16 and cervical cancer in Finland and the potential impact of vaccination: mathematical modelling analyses. PLoS Med 2006;3(5):e138.
63. Hughes JP, Garnett GP, Koutsky L. The theoretical population-level impact of a prophylactic human papilloma virus vaccine. Epidemiology 2002;13:631-9.
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