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New options in

# HPV Prevention

**Epidemiology and  
Natural History of HPV**

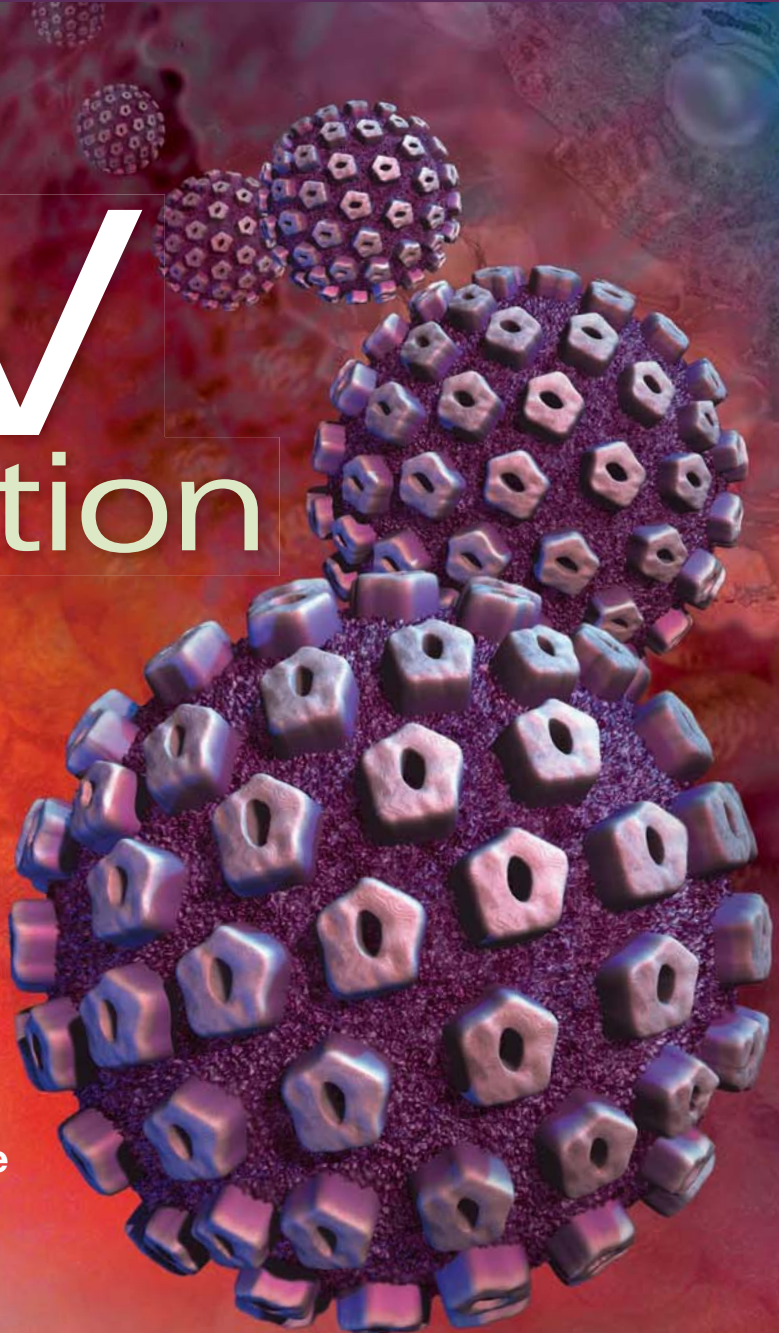
▶ J. Thomas Cox, MD

**Protecting Our Patients  
From HPV and HPV-Related  
Diseases: The Role of Vaccines**

▶ Martin C. Mahoney, MD, PhD, FAAFP

**Practical Implementation of  
HPV Vaccines in Clinical Practice**

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# New options in HPV Prevention

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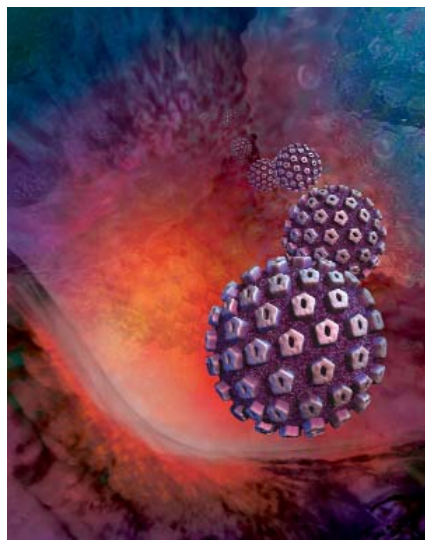


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**Release Date:** November 15, 2006

**Expiration Date:** November 15, 2007

**Estimated Time To Complete Activity:** 1.0 hour

### Target Audience

This activity has been designed to meet the educational needs of family physicians and other health care professionals interested in learning more about preventing cervical cancer and other HPV-related diseases.

### Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the relationship between HPV types 16 and 18 and cervical cancer
- Summarize the relationship between HPV types 6 and 11 and genital warts, recurrent respiratory papillomatosis, and abnormal cervical cytology
- Summarize the safety, efficacy, and immunogenicity of HPV vaccines in large clinical trials
- Identify practical strategies for implementing successful HPV vaccination programs in clinical practice

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#### J. Thomas Cox, MD

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**Evaluation Form:** See Evaluation Form on page 23.

# Epidemiology and Natural History of HPV

J. Thomas Cox, MD

## Abstract

Human papillomavirus (HPV) is a highly prevalent, sexually transmitted infection responsible for significant morbidity and mortality. High-risk HPV types are now known to be necessary in the etiology of cervical cancer and to lead to both high-grade and low-grade cervical lesions. They are also implicated in a substantial portion of anal, penile, and head and neck precancers and cancers. HPV 16 and 18 are the most common HPV types found in cervical cancer and are responsible for approximately 70% of these cancers. In contrast, low-risk HPV types, the most common of which are HPV 6 and 11, cause genital warts, low-grade cervical lesions, and recurrent respiratory papillomatosis, but they do not cause cervical or other HPV-related cancers. Infection is most common in young, sexually active populations, and an estimated three fourths of adults will be infected with HPV during their lifetime. Cervical screening programs exist in the United States and other developed countries to identify and treat precancerous cervical lesions, but they do not reach all women and are costly. Until recently, no highly effective primary prevention strategy to reduce the risk of HPV acquisition existed. However, a quadrivalent HPV vaccine, which protects against the most common high-risk and low-risk HPV infections (HPV 16, 18, 6, and 11), is now available. In addition, a bivalent HPV vaccine that protects against high-risk HPV types 16 and 18 is in the late stages of clinical development. If implemented widely, vaccination against HPV promises to dramatically reduce HPV-associated morbidity and mortality.

## Epidemiology of HPV Infection

Human papillomavirus (HPV) is the most common newly acquired sexually transmitted infection (STI) in the United States, with more than 6.2 million new HPV infections estimated to occur each year.<sup>1</sup> Seventy-five percent of sexually active Americans will be infected with HPV at some point in their lives.<sup>2</sup> HPV infection is most likely to occur in youth: 74% of new infections occur in individuals 15 to 24 years of age,<sup>1</sup> and the highest incidence of HPV is consistently found in sexually active women younger than 25.<sup>2</sup>

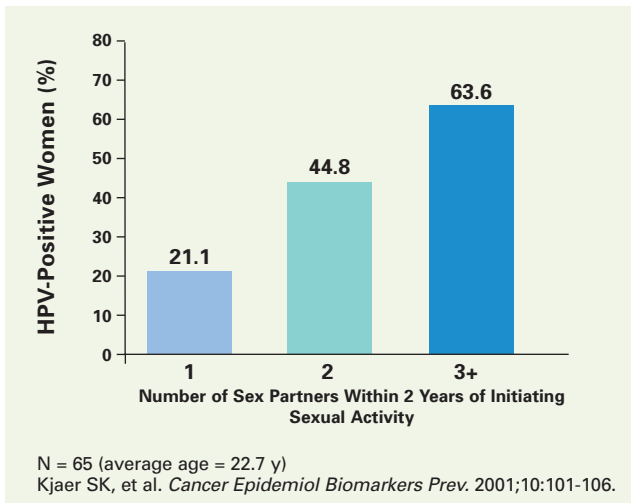
More than 100 types of HPV have been discovered and are generally classified as high-risk or low-risk types on the basis of their oncogenicity.<sup>3</sup> Among the high-risk types, HPV 16 and 18 account for approximately 70% of all cases of cervical cancer.<sup>4</sup> High-risk HPV types are also associated with the majority of cases of anal, penile, vaginal, and vulvar cancers,<sup>4,5</sup> as well as with a proportion of head and neck cancers.<sup>6-8</sup> HPV types 6 and 11 are the most common low-risk types and are associated with more than 90% of cases of genital warts.<sup>9</sup> HPV types 6 and 11 are also responsible for a small proportion of low-grade cervical cell abnormalities and for the vast majority of recurrent respiratory papillomatosis (RRP), a rare, yet potentially life-threatening condition.<sup>5,10</sup>

In a review of prevalence studies of adolescent and college-aged women repeatedly tested over time for HPV, as many as 90% tested positive for HPV at least 1 time.<sup>11</sup> Older women are also at risk: 34% of a sample of older, postmenopausal women (median age 56), most of whom had had only 1 sexual partner in their lifetime, were HPV-positive at some point during a 7-year follow-up, suggesting that the sexual history of the partner(s) may be a codeterminant of risk.<sup>12</sup>

Less is known about the prevalence and patterns of HPV infection in men. Studies have established the inci-

**FIGURE 1**

**HPV infection in young women following the initiation of sexual activity<sup>14</sup>**



dence of HPV infection in men at 4% to 45%, with low rates generally reflecting the absence of a sensitive HPV testing method for males. Higher rates of infection are generally found in studies with soldiers or visitors to STI clinics, or men in their twenties. Lower infection rates were found in the general population samples with a higher median age.<sup>13</sup> In the United States, the prevalence of HPV infection in men is estimated to be approximately 30%.<sup>13</sup> However, because HPV is a “shared” virus, it is most likely that HPV prevalence rates in men and women are identical and that differences likely reflect the difficulty in detecting the virus in men as compared with women.<sup>13</sup>

**Transmission of HPV**

HPV is spread primarily by sexual contact, the exception being RRP, which is most frequently spread perinatally from mother to child.<sup>10</sup> The incidence of HPV infection increases dramatically with the number of sexual partners (FIGURE 1).<sup>14</sup> Intromissive intercourse is not a prerequisite for HPV transmission, as women who remained virgins throughout a 2-year longitudinal study still had a 2-year cumulative HPV infection rate of 2.4%, and approximately 10% of virgins who engaged in nonpenetrative sexual contact (eg, finger-vulvar, penile-vulvar, oral-penile) were HPV-positive.<sup>15</sup>

Condoms do not completely prevent HPV transmission, although consistent condom use has been demon-

strated to reduce the risk of acquiring HPV by 70%.<sup>16</sup> In addition, condoms have been shown to reduce the risk of HPV-associated disease, including genital warts, cervical intraepithelial neoplasia (CIN) grade 2/3, and invasive cervical cancer,<sup>17</sup> as well as promote the regression of HPV-associated cervical disease and flat penile lesions and the clearance of HPV infection.<sup>16,18</sup>

**Risk Factors for HPV Infection and Associated Disease**

Risk factors for HPV infection in women include higher numbers of recent sexual partners, previous infection with herpes simplex and genital warts,<sup>19</sup> and younger age at initiation of sexual activity.<sup>20</sup> Additional risk factors for cervical neoplasia include cigarette smoking, use of oral contraceptives, increased parity, and previous exposure to other STIs, including chlamydia.<sup>21</sup> Like women, men increase their risk of HPV infection by having more lifetime sexual partners and more sexual partners in the past year; in addition, uncircumcised men are at a greater risk for infection and persistence.<sup>22</sup> Among men, risk factors for anal squamous intraepithelial neoplasia include HPV infection, as well as higher numbers of male partners for receptive anal intercourse in the previous 6 months, and the use of illegal drugs, such as alkyl nitrites and injection drugs. Risk factors for anal low-grade squamous intraepithelial lesion (LSIL) are similar, but also include older age at first receptive anal intercourse.<sup>23</sup>

Individuals who are immunocompromised, whether by human immunodeficiency virus (HIV) or by immunosuppression post-organ transplantation, are at an increased risk for HPV infection, are more likely to be infected with multiple HPV types, and are at an increased risk for developing HPV-associated disease.<sup>24</sup> In a group of HIV-positive women without acquired immune deficiency syndrome (AIDS) and HIV-negative women, the HIV-positive women were more likely to test positive for 1 or more high-risk HPV types (relative risk [RR], 1.8; 95% confidence interval [CI], 1.3-2.7), more likely to be infected with intermediate-risk HPV (RR, 2.1; 95% CI, 1.5-2.9), and more likely to be infected with low-risk HPV (RR, 2.7; 95% CI, 2.0-3.6).<sup>25</sup> HIV-positive women with CD4 counts less than or equal to 500/mcL were almost 3 times more likely than HIV-negative women to have squamous intraepithelial neoplasia.<sup>26</sup> This study is representative of findings in both men and women, with immunosuppression correlated with an increased incidence of HPV-associated disease in both genders.

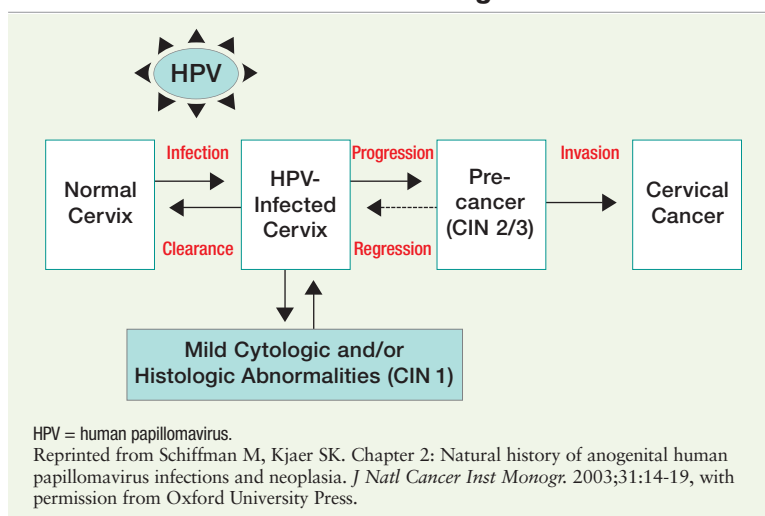
## Natural History of HPV Infection

HPV infects basal epithelial cells, where it exists for a variable period of time in a non-expressed, or latent, state. At some point the virus begins to replicate in dividing epithelial cells, most commonly causing low-grade cervical, vaginal, vulvar, and penile lesions, or genital warts.<sup>21</sup> Most of these low-grade cellular manifestations are so transient and minor that they are not known to be present. However, some cell changes may develop as monoclonal high-grade cancer precursor lesions, and these are far less likely to spontaneously regress. The squamous metaplasia of the cervical transformation zone is particularly vulnerable to HPV-induced oncogenic changes; this zone is even more susceptible during adolescence—a factor that is likely to be at least partially responsible for both the high incidence of low-grade lesions in HPV-infected adolescent women and the increased risk of cervical cancer with earlier sexual activity.<sup>21</sup> High-grade cervical precancer (CIN 2/3) may develop without a preceding low-grade lesion (CIN 1); when CIN 2/3 develops in the presence of CIN 1, it is not due to progression, but rather develops independently.<sup>27</sup> Low-grade lesions that are associated with high-risk HPV and that do not regress are at higher risk for CIN 2/3 development. CIN 3 that is not detected and treated is at high risk for eventual progression to invasive cancer (FIGURE 2).<sup>21</sup>

The cells in the region where the columnar epithelium of the rectum meets the squamous epithelium of the anus are structurally similar and likewise vulnerable to oncogenesis. As with cervical HPV infection, infection of the anal verge with high-risk HPV can result in the development of a high-grade anal cancer precursor lesion (anal intraepithelial neoplasia [AIN] 2/3), which, if not diagnosed and treated, may progress to anal cancer.<sup>28</sup>

Most individuals infected with HPV do not know that they are infected because they do not experience detectable HPV-associated disease. Among adolescent women, the average HPV infection lasts a median of 5.6 months, although high-risk HPV tends to be more persistent than low-risk HPV infection.<sup>29</sup> Most low-grade cervical lesions spontaneously regress, but approximately 10% to 13% will progress to a high-grade lesion, which will eventually put the individual at risk for invasive cervical cancer.<sup>30</sup> Approximately 70% to 91% of HPV infections will regress within 2 years, although as stated, high-

**FIGURE 2**  
 The natural history of HPV infection and cervical carcinogenesis



risk HPV infections are more persistent than low-risk HPV infections.<sup>31,32</sup> In a sample of high-risk HPV-positive women, more than half had no remaining HPV infection by 7.5 months, with those having higher baseline viral loads less likely to clear.<sup>33</sup> Age seemed to affect the rate of incident HPV infection only, as persistence was not shown to be more common in older women. The same study demonstrated that 35.5% of women with atypical squamous cells of undetermined significance (ASCUS) or LSIL cytology at baseline still had abnormal cytologic results at 12-month follow-up, and 47.4% had abnormal cytologic results at 24-month follow-up. The cumulative 18-month incidence of CIN 2/3 for women enrolled initially with an ASCUS or LSIL Pap result was 14%, whereas the incidence of CIN 2/3 for women persistently positive for high-risk HPV was 32%.<sup>33</sup> All cases of CIN 2/3 developed in women with a persistent HPV infection. No high-grade CIN developed in HPV-negative women or in those transiently HPV-positive. In another study, the cumulative incidence of genital warts in women exposed to HPV 6 or 11 was 64.2% (95% CI, 50.7-77.4) at 36 months.<sup>34</sup>

## Consequences of High-Risk HPV Infection

### Cervical Cancer and Precancerous Lesions

Cervical cancer is the second most common cancer in women worldwide, with an estimated 400,000 to 500,000 cases diagnosed each year,<sup>35</sup> with 80% of these

cases observed in developing countries.<sup>36</sup> Women in developing countries are at an increased disadvantage in that they lack access to both cervical cancer screening and treatment. However, even in countries where screening is widespread and treatment advanced, cervical cancer takes a heavy toll.<sup>35</sup> The American Cancer Society estimates that approximately 9710 new cases of cervical cancer and approximately 3700 deaths will occur in the United States in 2006.<sup>37</sup> This morbidity and mortality will occur despite the fact that more than 60 million Pap tests are performed each year.<sup>38</sup> Half the cases of cervical cancer will occur in women who have never been screened, and an additional 10% will occur in women not screened within the past 5 years.<sup>39</sup>

Young women, in whom HPV infection is most prevalent, experience high rates of low-grade precancerous lesions. As many as 37% of adolescent women have abnormal cervical cytology on at least 1 screening, but the majority of these cytologic changes will regress.<sup>29</sup> High-grade lesions, such as CIN 3, may occur within a short period of time from first intercourse, but the median age at which women develop CIN 3 (29 years) suggests that most high-grade lesions develop some years following exposure to 1 of the high-risk types of HPV.<sup>21</sup>

Current American College of Obstetrics and Gynecology cervical screening guidelines recommend that cancer screening be initiated after the woman has been sexually active for 3 years, but no later than age 21. This 3-year delay between risk of exposure to HPV and screening for the consequences of HPV infection is recommended because of the almost zero risk that the woman will develop cervical cancer before age 21. Screening should occur annually thereafter, although women with conditions such as HIV infection or transplant-associated immunosuppression that put them at higher risk for cervical cancer may require more frequent screening. Women 30 years of age or older may extend their screening interval by 2 to 3 years if they have had 3 consecutive negative Pap tests, and women of this age who test negative for high-risk HPV and have a normal Pap test should have their next cervical screening in 3 years. Of course, extending cervical screening intervals to 3 years does not eliminate the need for annual preventive health care visits for all other medical conditions.

For women who receive diagnoses of ASCUS, reflex HPV testing for common high-risk HPV types may be useful.<sup>40</sup> HPV testing is not useful in the evaluation of established CIN 1 and CIN 2/3 lesions, except as a follow-up test in the expectant management of CIN 1, or as “test of cure” posttreatment of high-grade lesions because nearly

all CIN 1 and all CIN 2/3 lesions test positive for high-risk HPV types.<sup>40,41</sup> The most established use of HPV testing is to determine which women with ASCUS are most likely to be at risk for having CIN 2/3 (high-risk HPV-positive) and which women are not at risk (high-risk HPV-negative).<sup>40</sup>

Cervical cancer and the screening involved are a significant source of health care costs. Annual costs for cervical screening are approximately \$2.3 billion, false-positive Pap tests cost approximately \$350 million, and the direct medical costs of abnormal Pap test results total approximately \$4.6 billion per year.<sup>42</sup> Interventions that reduce the incidence of HPV infection would also reduce the incidence of abnormal Pap test results, thus reducing the costs and other burdens of HPV infection. Eventually, if the majority of women are immunized against the HPV types that cause most of the clinically significant abnormal Pap tests, high-grade cervical lesions, and cervical cancer, it may be possible for guidelines to safely recommend a decrease in the frequency of Pap testing, which would result in further health care savings. However, for the present time, cervical screening must continue according to current guidelines.

Abnormal Pap test results, in addition to being costly, can create significant psychosocial effects. Many women react to abnormal Pap test results with distress and anxiety.<sup>43</sup> In a sample of women evaluated 5 years after 2 consecutive Pap smears graded as CIN 1, 59% reported feelings of anxiety and worry, and 8% reported a negative influence of the test result on their sexuality.<sup>44</sup> Women also reported fears that they would develop cancer or that these abnormalities would interfere with their ability to have children.<sup>45</sup>

## Other Cancers

Anal cancer affected 2.04 men and 2.06 women per 100,000 between 1994 and 2000; incidence has increased since the 1970s, and current incidence may be even higher.<sup>46</sup> HPV is implicated in most anal cancers, and HPV 16 is found in 73% of anal cancers.<sup>47</sup> Anal HPV infections and cancer can occur in both men and women.<sup>48</sup> As with cervical cancer, high numbers of sexual partners and smoking are associated with an increased risk of disease. In addition, receptive anal intercourse increased the odds of anal cancer in both men and women; of note, receptive anal intercourse is not a prerequisite for anal cancer.<sup>49</sup>

Anal HPV infection and anal HPV-associated disease are particularly common among HIV-positive patients. In 1 study, 95% of a sample of HIV-positive

men who reported having sex with men were anal HPV-positive, and 81% had some sort of AIN.<sup>50</sup>

Currently, formal screening guidelines do not exist for anal precancer or cancer, but experts have recommended that the following groups receive anal screening: men who have sex with men, women with high-grade cervical and vulvar disease, immunocompromised individuals (including HIV-positive patients and transplant recipients), and individuals who have perianal condylomata. HIV-positive patients should be screened annually, while others should be screened every 2 to 3 years. Anal Pap tests can be performed in a manner similar to cervical Pap tests,<sup>51</sup> and management of anal lesions is similar to that recommended for cervical disease.<sup>28</sup>

Penile cancer affects approximately 1 in 100,000 men in the United States,<sup>50</sup> and HPV is implicated in 80% of these cancers.<sup>52</sup> As with anal cancer, HPV 16 is by far the greatest contributor to penile cancer and is implicated in 70% of penile tumors.<sup>53</sup> Additional risk factors for penile cancer include not being circumcised, phimosis, and smoking.<sup>53</sup>

Oral and oropharyngeal cancers affect approximately 30,000 Americans each year and have a high fatality rate; only 50% of patients survive 5 years postdiagnosis.<sup>54</sup> HPV is implicated in a substantial portion of oral and oropharyngeal squamous cell carcinomas. Nearly one quarter of oral/oropharyngeal squamous cell carcinomas are estimated to be positive for high-risk HPV types.<sup>55</sup> Among the cases that are HPV-positive, an estimated 87% are associated with HPV 16.<sup>55</sup>

## Consequences of Low-Risk HPV Infection

### Genital Warts

At any given time, approximately 1% of the US population has clinically visible genital warts, and the incidence of genital warts is increasing.<sup>2</sup> Genital warts usually have a cauliflower-like appearance, although they can also be flat, papular, or less commonly, frond-like, and appear on the vulva, vagina, cervix, penis, scrotum, male urethra, perineum, and anus.<sup>56</sup> HPV 6 and 11 are found in 97% of the cauliflower-like condylomata,<sup>9</sup> although the distribution may be different among immunosuppressed patients, who tend to have a wider variety of HPV types.<sup>9</sup>

If left untreated, genital warts may resolve, but they may also increase in size and number.<sup>57</sup> Most patients are distressed by genital warts and prefer to have them

treated. In 1 study of a group of women reporting to a genitourinary clinic with genital warts, most of whom were aware of their diagnosis, 94% reported that they were anxious or very anxious.<sup>56</sup> Diagnosis often results in feelings of anger, depression, disgust, and self-blame and may result in separation from, or antagonistic relations with, a relationship partner.<sup>58</sup> Treatments are painful for some patients, and as many as one third of patients undergoing treatment worry that they may never be cured.<sup>58</sup> This fear is not entirely unfounded, given the extreme resilience of genital warts and the inability of currently available treatments to always eradicate condylomata.<sup>59</sup>

Current treatment options include podofilox, imiquimod, cryotherapy, trichloroacetic and bichloroacetic acid, surgical removal, intralesional interferon, and laser surgery.<sup>57</sup> Recurrence is most likely in the first 3 months posttreatment, and many patients will require more than 1 treatment. If improvement is not seen after 3 to 6 treatments, a different treatment modality should be tried.<sup>57</sup> Each episode of genital warts requires an average of 3.1 physician visits for treatment.<sup>60</sup> Direct medical costs attributable to genital warts reach \$200 million a year in the United States, an average cost of \$530 per case.<sup>42</sup>

### Low-Grade Genital Lesions

Low-risk HPV infections from HPV 6 or 11 and other low-risk types also result in low-grade genital lesions, although these lesions do not progress to cancer; low-risk HPV is rarely, if ever, found in cancerous lesions.<sup>21</sup> Nonetheless, these lesions result in abnormal Pap test results, which cause considerable distress to patients and incur significant health care costs.

### Recurrent Respiratory Papillomatosis (RRP)

RRP is a potentially fatal juvenile disease affecting 7 of every 1000 children born to mothers having genital warts at the time of delivery and, although rare, has been seen in children born by cesarean section.<sup>10</sup> The same low-risk types of HPV (6 and 11) found in most condylomata are also implicated in RRP, which is thought to be a result of vertical transmission, from mother to child. Papillomas occur and reoccur in the respiratory tract and must be removed each time they reoccur, commonly requiring frequent surgical intervention. RRP becomes fatal when the growths obstruct the airway, become malignant, or spread into the lungs, causing pulmonary failure.<sup>10</sup>

## Conclusion

HPV has only recently become a preventable infection. At present, infection is widespread such that most sexually active individuals will be infected in their lifetime. The majority of new infections occur in young, sexually active people. If patients are not screened for HPV-associated disease, they may develop cervical, anal, penile, and head and neck cancers, precancerous lesions, and genital warts; women with genital warts at the time of childbirth may also transmit HPV to their children, which may result in RRP. The majority of the oncogenic sequelae are seen at midlife or later. However, low-grade lesions and genital warts, and some high-grade precancerous lesions, occur relatively soon after infection and therefore are common in the young. The quadrivalent HPV vaccine, which protects against the types of HPV responsible for 70% of all cervical cancers (HPV types 16 and 18) and more than 90% of all genital warts (HPV types 6 and 11), is available and should dramatically reduce the burden of HPV-associated disease. In addition, a bivalent HPV vaccine protecting against HPV types 16 and 18 is currently in phase 3 trials. Vaccination against the most common disease-causing types of HPV is expected to dramatically reduce the burden of illness associated with HPV. ■

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# Protecting Our Patients From HPV and HPV-Related Diseases: The Role of Vaccines

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## Abstract

The clinical burden of disease resulting from human papillomavirus (HPV) infection is substantial and extends from genital warts to cytologic abnormalities to cervical, vaginal, and vulvar cancers and their associated precursor lesions. In addition, HPV is implicated in anal, penile, and head and neck cancers. Thus, HPV-related disease constitutes a significant burden for both men and women.

Large phase 2 and 3 clinical trials with a quadrivalent preventive HPV vaccine (HPV 6/11/16/18) and phase 2 trials with a bivalent preventive HPV vaccine (HPV 16/18) have demonstrated that both products are highly efficacious in preventing type-specific HPV infections and HPV-related disease and are well tolerated. Nearly all recipients demonstrate a robust immunologic response that currently appears to be durable for 4 or more years. Immunogenicity data among girls 9 to 15 years of age were used to “bridge” efficacy data from quadrivalent HPV vaccine trials completed to date.

In June 2006, the US Food and Drug Administration approved the quadrivalent HPV vaccine for use among females 9 to 26 years of age. The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices has recommended the 3-dose series for girls 11 to 12 years of age, catch-up vaccination for girls and women 13 to 26 years of age, and permissive use as early as age 9.

Computer models projecting the impact of these preventive HPV vaccines predict that they will be cost-effective and beneficial to the population; the use of preventive HPV vaccines will complement continued cytologic screening programs. Trials are under way to evaluate the duration of immune response as well as efficacy among men and women 27 years of age and older. Girls and women within the targeted age ranges should be offered vaccination to achieve the disease prevention potential of these vaccines.

## Introduction

Infection with human papillomavirus (HPV) represents a high-prevalence condition, with estimates that 20 million people in the United States are currently infected.<sup>1</sup> In 2000, the direct medical costs of HPV infection among persons 15 to 24 years of age were estimated to total \$2.9 billion, thereby ranking HPV ahead of genital herpes, chlamydia, and gonorrhea; the bulk of these costs are derived from the management of abnormal Pap smears.<sup>2</sup>

Various population surveys have demonstrated that 75% of sexually active adults have been infected with HPV at some point in their lives.<sup>3</sup> This figure is based on a variety of sources, including seroprevalence data, Pap smear abnormalities, colposcopic findings, HPV DNA testing, and the clinical diagnosis of genital warts. The clinical burden of HPV infection runs the spectrum from genital warts to cervical cancer, as well as premalignant cervical changes manifesting as abnormal Pap smears and colposcopic abnormalities. In addition, persistent HPV infection is also responsible for vaginal intraepithelial neoplasia (VaIN), vulvar intraepithelial neoplasia (VIN), anal

**TABLE 1**

**Summary of study design for phase 2 and phase 3 studies of preventive HPV vaccines**

	Phase 2 Bivalent <sup>16</sup>	Phase 2 Quadrivalent <sup>17</sup>	Phase 3 Quadrivalent (FUTURE I trial) <sup>18</sup>	Phase 3 Quadrivalent (FUTURE II trial) <sup>19</sup>
<b>Design</b>	RCT	RCT	RCT	RCT
<b>Duration</b>	18 mo; follow-up to 4.5 y*	3 y; follow-up to 5 y <sup>†</sup>	2 y	2 y
<b>Study population</b>	n=560 vaccine n=553 placebo 30.5% non-Causasian	n=277 vaccine n=275 placebo 22% non-Caucasian	5455 women: 1:1 randomization	n=5736 vaccine n=5766 placebo
<b>Gender/age</b>	Females ages 15-25 years	Females ages 16-23 years	Females ages 16-23 years	Females ages 16-23 years
<b>Accrual sites</b>	Canada, Brazil, US	Europe, Brazil, US	Multinational	Multinational
<b>Follow-up</b>	Cytology and cervico-vaginal HPV swabs at baseline and months 6, 12, and 18; self-collected cervicovaginal swabs at baseline, month 6, then every 3 months; serology at baseline, and months 1, 6, 7, 12, and 18	Cytology and cervico-vaginal HPV swabs at baseline and months 7, 12, 24, and 36; serology at baseline and months 2, 3, 6, 7, 12, 18, 24, 30, and 36	Cytology and HPV swabs at baseline and months 7, 12, 24, 36, and 48; serology at baseline and months 2, 3, 6, 7, 12, 24, 36, and 48; algorithm for colposcopy/excisional biopsy; standard lab for histology and PCR	
<b>Vaccine type</b>	Bivalent L1 VLP vaccine, based on recombinant baculovirus technology (Cervarix™)	Quadrivalent L1 VLP vaccine based on recombinant yeast technology (Gardasil®)	Quadrivalent L1 VLP vaccine based on recombinant yeast technology (Gardasil®)	Quadrivalent L1 VLP vaccine based on recombinant yeast technology (Gardasil®)
<b>HPV antigens</b>	HPV-16 (20 mcg) HPV-18 (20 mcg)	HPV-6 (20 mcg) HPV-11 (40 mcg) HPV-16 (40 mcg) HPV-18 (20 mcg)	HPV-6 (20 mcg) HPV-11 (40 mcg) HPV-16 (40 mcg) HPV-18 (20 mcg)	HPV-6 (20 mcg) HPV-11 (40 mcg) HPV-16 (40 mcg) HPV-18 (20 mcg)
<b>Vaccine adjuvant</b>	Aluminum hydroxide and 3-deacylated monophosphoryl lipid A	Aluminum hydroxy-phosphate sulfate	Aluminum hydroxy-phosphate sulfate	Aluminum hydroxy-phosphate sulfate
<b>Placebo</b>	Aluminum hydroxide	Aluminum hydroxy-phosphate sulfate	Aluminum hydroxy-phosphate sulfate	Aluminum hydroxy-phosphate sulfate
<b>Schedule</b>	0, 1, and 6 months	0, 2, and 6 months	0, 2, and 6 months	0, 2, and 6 months

\*Harper DM, et al. (2006) extended cohort follow-up<sup>23</sup>

<sup>†</sup>Villa LL, et al. (2006) extended cohort follow-up<sup>22</sup>

FUTURE = Females United To Universally Reduce Endo-ectocervical Disease; HPV = human papillomavirus; PCR = polymerase chain reaction; RCT = randomized controlled trial; VLP = virus-like particle.

<sup>16</sup>Harper DM, et al. *Lancet*. 2004;364:1757-1765.

<sup>17</sup>Villa LL, et al. *Lancet Oncol*. 2005;6:271-278.

<sup>18</sup>Sattler C, FUTURE I Investigators. ICAAC; Dec 16-19, 2005.

<sup>19</sup>Skjeldestad FE, FUTURE II Steering Committee. IDSA; Oct 6-9, 2005.

cancers,<sup>4</sup> penile cancers,<sup>5</sup> and head and neck cancers.<sup>6</sup>

Although more than 100 types of HPV have been characterized, these subtypes can be categorized into those associated with either cutaneous or mucosal infection. The 30 to 40 mucosotrophic types can be subdivided

into high-risk and low-risk types based on their potential to result in malignancies. The subtype classification is based upon genetic sequences.<sup>7</sup> Low-risk HPV types include types 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, and 81.<sup>8</sup> Infections with low-risk HPV types most typi-

cally result in genital warts (ie, condylomata acuminata) or benign low-grade cervical changes; in rare cases, children born to women with low-risk HPV infections may develop recurrent respiratory papillomatosis. High-risk HPV types include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82; additional probable types include 26, 53, and 66.<sup>8</sup> Infections with high-risk HPV types typically manifest as low-grade cervical changes, high-grade cervical changes, and cervical cancers, in addition to anogenital and head and neck cancers.<sup>5,6,8,9</sup>

### Disease Burden From Selected HPV Types

Oncogenic HPV types 16 and 18 are generally considered to account for approximately 70% of all cervical cancers in high-grade cervical lesions (eg, cervical intraepithelial neoplasia grade 3 [CIN 3]),<sup>8</sup> and more than 90% of cervical adenocarcinomas.<sup>10</sup> These 2 HPV types are also thought to account for approximately 50% of CIN 2/3 cases, and close to 80% of VIN 2/3.<sup>3</sup> Low-risk HPV types, types 6 and 11, are thought to account for one third to one half of all low-grade cervical lesions (CIN 1) as well as low-grade vaginal and vulvar lesions (VaIN 1 and VIN 1).<sup>3</sup> HPV types 6 and 11 account for more than 90% of cases of genital warts.<sup>11</sup>

### HPV and Cervical Cancer Risk

Reanalysis of a large series of cervical cancer specimens using more sensitive polymerase chain reaction (PCR) techniques revealed that HPV DNA could be detected in nearly all specimens.<sup>8,12</sup> Based on these observations, the International Agency for Research on Cancer has identified HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 66 as being human carcinogens.<sup>13</sup> As a result, HPV can be considered as a necessary cause of cervical cancer. To put the magnitude of risk associated with high-risk HPV into perspective, it is widely accepted that the odds ratio for alcohol consumption and breast cancer ranges from 1.2 to 1.8, whereas the odds ratio for cigarette smoking and lung cancer is approximately 10.<sup>14</sup> In contrast, the odds ratio for exposure to high-risk HPV DNA in the development of cervical cancer is 158 (95% confidence interval, 113-221).<sup>8</sup>

### Vaccine Trials

During the last several years, a number of publications and presentations have summarized the development of candidate vaccines to protect against HPV infection. This work is based on population studies, which suggest that

type-specific immunity develops following HPV infection. The proof-of-principle trials were based on administration of virus-like particle (VLP) vaccines to seronegative, HPV DNA-negative participants.<sup>15</sup> These VLP vaccines were based on L1 outer capsid proteins, which were observed to induce an immunologic response. These VLPs assume the conformation of a viral capsid but contain no viral DNA and hence are noninfectious.<sup>15</sup>

The bulk of clinical trial data relating to the development of the preventive HPV vaccine is derived from phase 2 and phase 3 clinical trials of the US Food and Drug Administration (FDA)-approved quadrivalent HPV vaccine (Gardasil®, Merck & Co., Inc., Whitehouse Station, NJ), which protects against HPV 16, 18, 6, and 11, and phase 2 clinical trials of a bivalent HPV vaccine (expected to be marketed as Cervarix™, GlaxoSmithKline, London, UK), which protects against HPV 16 and 18. The phase 2 trials included both the bivalent vaccine<sup>16</sup> and the quadrivalent vaccine<sup>17</sup>; the phase 3 trials completed to date are based on the quadrivalent vaccine.<sup>18,19</sup> The enrollment criteria for all of the clinical trials were generally similar and enrolled women from their mid-teens to mid-twenties (see **TABLE 1**). Participants were required to have a limited number of prior sex partners, have no prior history of abnormal Pap smears or cervical pathology, and be seronegative and HPV DNA-negative for the relevant HPV types. Accrual was accomplished via participating sites in Canada, Brazil, Europe, and the United States. The protocols involved a rigorous screening process and follow-up schedule, which included serologic, cytologic, and PCR testing of cervicovaginal swabs and specimens.

### Efficacy

**TABLE 2** summarizes efficacy results from the phase 2 and 3 trials of the preventive quadrivalent HPV vaccine and from the phase 2 trials of the preventive bivalent HPV vaccine. Although the studies examined somewhat different end points, the clinical outcomes are overlapping. Also, the table summarizes the definitions for various analytic cohorts using either an according-to-protocol or an intention-to-treat approach. Results of these trials provide consistent evidence confirming high levels of efficacy against incident and persistent HPV infection, cytologic abnormalities, histologic changes, and HPV-related disease, including cancers and precursor lesions. Vaccine efficacy was generally within the range of 90% to 100% across studies and clinical outcomes.

**TABLE 2**

**Summary of efficacy results from phase 2 and phase 3 studies of preventive HPV vaccines**

End points	Phase 2 Bivalent <sup>16</sup>		Phase 2 Quadrivalent <sup>17</sup>		Phase 3 Quadrivalent (FUTURE I trial) <sup>18†</sup>		Phase 3 Quadrivalent (FUTURE II trial) <sup>19†</sup>	
	PP	ITT	PP	MITT	PP	MITT	PP	MITT
Incident and persistent HPV 16/18 infections; HPV-related cytologic abnormalities	3 vaccine doses, seronegative for HPV 16/18 at baseline and month 6, HPV DNA-negative to high-risk types		3 vaccine doses, seronegative and HPV DNA-negative at baseline through month 6, no protocol violations; end points tracked beginning in month 7		3 vaccine doses, no protocol violations, HPV-seronegative at baseline, HPV DNA-negative through month 7; end points tracked beginning at month 7		3 vaccine doses, no protocol violations, HPV-seronegative at baseline, HPV DNA-negative through month 7; end points tracked beginning at month 7	
PP analysis	≥1 vaccine dose(s), negative for high-risk HPV DNA at baseline, data available for outcome(s)		MITT: ≥1 vaccine dose(s), seronegative and HPV DNA-negative at baseline; end points tracked beginning at month 1		MITT: ≥1 vaccine dose(s), HPV-seronegative and HPV DNA-negative at baseline; end points tracked beginning at month 1		MITT: ≥1 vaccine dose(s), HPV-seronegative and HPV DNA-negative at baseline; end points tracked beginning at month 1	
ITT analysis	≥1 vaccine dose(s), negative for high-risk HPV DNA at baseline, data available for outcome(s)		MITT: ≥1 vaccine dose(s), seronegative and HPV DNA-negative at baseline; end points tracked beginning at month 1		MITT: ≥1 vaccine dose(s), HPV-seronegative and HPV DNA-negative at baseline; end points tracked beginning at month 1		MITT: ≥1 vaccine dose(s), HPV-seronegative and HPV DNA-negative at baseline; end points tracked beginning at month 1	
Outcome/analytic cohort	PP	ITT	PP	MITT	PP	MITT	PP	MITT
Persistent HPV infection*	0:7 cases	1:20 cases	4:35 cases	6:47 cases				
Vaccine efficacy (%)	100	95	89	88				
Incident HPV infection*	2:23 cases	7:42 cases						
Vaccine efficacy (%)	92	83						
ASCUS (bivalent) or any CIN (quadrivalent)*		3:27 cases	0:3 cases	0:7 cases				
Vaccine efficacy (%)		93	100	100				
HPV-related disease*			0:6 cases	0:10 cases	0:6 cases	0:10 cases		
Vaccine efficacy (%)			100	100	100	100		
CIN or worse*							0:37 cases	2:57 cases
Vaccine efficacy (%)							100	97
External genital lesions*							0:40 cases	3:59 cases
Vaccine efficacy (%)							100	95

\*Ratio of end point observations in vaccine group:placebo group.

†Analytic cohorts the same for FUTURE I and FUTURE II trials.

AIS = adenocarcinoma *in situ*; ASCUS = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; FUTURE = Females United To Universally Reduce Endo-ectocervical Disease; HPV = human papillomavirus; ITT = intention to treat; MITT = modified intention to treat; PP = per protocol; ValN = vaginal intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia.

<sup>16</sup>Harper DM, et al. *Lancet*. 2004;364:1757-1765.

<sup>17</sup>Villa LL, et al. *Lancet Oncol*. 2005;6:271-278.

<sup>18</sup>Sattler C, FUTURE I Investigators. ICAAC; Dec 16-19, 2005.

<sup>19</sup>Skjeldestad FE, FUTURE II Steering Committee. IDSA; Oct 6-9, 2005.

**TABLE 3**

**Summary of adverse events in phase 2 and phase 3 studies of preventive HPV vaccines**

Adverse Event Tracking Method	Phase 2 Bivalent <sup>16</sup>		Phase 2 Quadrivalent <sup>17</sup>		Phase 3 Quadrivalent (FUTURE I trial) <sup>18,24</sup>	Phase 3 Quadrivalent (FUTURE II trial) <sup>19,24</sup>
	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo
Diary cards for 7 d after vaccination; interview 30 d after vaccination					Diary cards for 7 d after vaccination; interview 30 d after vaccination	Diary cards for 14 d after vaccination
Overall adverse events (%)			92	88	89.9	85.5
Injection site (%)	94	87.7	86	77	83	73.4
Systemic (%)	86.3	85.9	69	69	59.2	60.4
Serious adverse events (%)	4	3.5	1	1	0.61	0.65
Withdrawal from study (%)	0.1	0.6	6.8	5.5	—	—

FUTURE = Females United To Universally Reduce Endo-ectocervical Disease.

<sup>16</sup>Harper DM, et al. *Lancet*. 2004;364:1757-1765.

<sup>17</sup>Villa LL, et al. *Lancet Oncol*. 2005;6:271-278.

<sup>18</sup>Sattler C, FUTURE I Investigators. ICAAC; Dec 16-19, 2005.

<sup>19</sup>Skjeldestad FE, FUTURE II Steering Committee. IDSA; Oct 6-9, 2005.

<sup>24</sup>Centers for Disease Control and Prevention. [www.cdc.gov/nip/acip/slides/jun06/hpv-2-barr.pdf](http://www.cdc.gov/nip/acip/slides/jun06/hpv-2-barr.pdf).

**Adverse Events**

TABLE 3 summarizes adverse events in the phase 2 and phase 3 trials. Adverse event tracking included the use of both diary cards and follow-up interviews after vaccine administration. Overall, the rate of any adverse events is slightly increased in the vaccine group compared with the placebo group. Not surprisingly, injection site reactions such as pain, swelling, and redness were common in both groups and were somewhat more frequent in the vaccine group. Pain severity was typically reported as mild to moderate and lasted for 1 to 2 days. Systemic symptoms such as fatigue, headache, rash, upset stomach, and temperature elevation were comparable between groups. The occurrence of serious adverse events was infrequent, and vaccine-related serious adverse events were extremely rare. Taken together, the data on adverse events from these trials suggest that the HPV preventive vaccines are well tolerated.<sup>16-19</sup>

**Immunogenicity**

Nearly all participants in clinical trials of HPV vaccines have demonstrated seroconversion to each of the compo-

nent HPV antigens; antibody levels are generally several-fold higher than those observed following natural infection.<sup>16-19</sup> However, minimal antibody levels considered to provide protection against each of the HPV subtypes have not yet been established. Moreover, antibody levels are HPV type-specific and assay-specific, and for these reasons, it is not possible to compare antibody levels across or within trials.

**Immunogenicity in Younger Subjects**

The concept of “immuno-bridging” is used to “bridge,” or to extend, efficacy data from the age groups studied in clinical trials of the quadrivalent HPV vaccine to other age categories. The rationale is that participants in the HPV vaccine clinical trials demonstrated measurable increases in type-specific HPV antibody levels, as well as reductions in HPV-related clinical disease. Thus, if the “extended” age groups show a comparable immunologic response, then similar clinical efficacy would be expected.

The immunogenicity of the quadrivalent HPV vaccine (HPV types 6, 11, 16, and 18) among boys and girls

10 to 15 years of age (n=510) was compared with the immunogenicity of the vaccine among young women 16 to 23 years of age (n=513). Following completion of a 3-dose series (0, 2, 6 months), nearly 100% of participants demonstrated seropositivity to each of the 4 HPV types. Geometric mean titers (GMTs) among subjects 10 to 15 years of age were noninferior to those produced by subjects 16 to 23 years of age, and titers in the 10- to 15-year-olds were in fact 1.7- to 2.7-fold higher.<sup>20</sup>

Reisinger and colleagues completed a randomized, placebo-controlled trial of the quadrivalent HPV vaccine in 1781 girls and boys 9 to 15 years of age that demonstrated HPV antibody levels exceeding those seen in adults; seroconversion rates of more than 99% were observed, with persistent seropositivity in 92% of subjects at month 18.<sup>21</sup>

Together, these immunogenicity studies of boys and girls provide evidence of an immunologic response to the quadrivalent HPV vaccine that is at least comparable to that observed among young women. Thus, these data can be used to “bridge” efficacy data from studies that included young women to other age groups not included in the efficacy trials completed to date.

### Long-Term Effectiveness

The quadrivalent HPV vaccine has demonstrated an ability to prevent HPV-related disease over the long term. Five-year follow-up data included a subset of subjects who participated in the earlier phase 2 trials of the quadrivalent HPV vaccine (n=241)<sup>17</sup> and established the lasting efficacy and immunogenicity of the vaccine. The quadrivalent vaccine was 96% effective in preventing persistent infection with HPV types 6, 11, 16, or 18 and 100% effective at preventing HPV 16- and 18-related CIN and HPV 6- and 11-related genital warts. GMTs for HPV 6, 11, 16, and 18 remained at or above levels induced by natural infection for the duration of the study.<sup>22</sup>

Extended follow-up data for the bivalent HPV vaccine (HPV 16/18) also provide information on long-term effectiveness, safety, and immunogenicity.<sup>23</sup> This extended follow-up study builds on the earlier phase 2 data of the bivalent HPV vaccine<sup>16</sup>; the median follow-up for this group was extended to nearly 48 months. More than 98% of vaccine recipients maintained seropositivity to HPV types 16 and 18 throughout the follow-up phase. Although some decline in GMT levels was noted, the values appeared to plateau beginning at month 18, with titer levels remaining 14- to 17-fold above levels observed for natural infection. The bivalent HPV vaccine continued to show high levels of clinical efficacy during the extended follow-up phase for protection against both incident HPV 16/18 infections and

persistent HPV 16/18 infections (94% to 100% vaccine efficacy). A combined analysis of the initial interval plus the extended follow-up demonstrated levels of efficacy ranging between 93% and 100% with regard to a variety of cytologic and histologic end points associated with HPV 16 and 18. In addition, preliminary data show efficacy against incident infections due to HPV types 45 and 31, which are not components of the bivalent vaccine. The observation of cross-protection against other high-risk HPV types with either vaccine will require validation in other data sets; however, in the absence of antibody data, it is uncertain whether these results represent true cross-protection. Finally, assessment of long-term adverse events revealed no differences in the proportion of participants reporting at least 1 adverse event, no differences in the onset of new chronic diseases, and no serious adverse events during the extended follow-up.<sup>23</sup>

### Pregnancy Outcomes

Using data from the 2 large, phase 3 Females United To Universally Reduce Endo-ectocervical Disease (FUTURE) I and II trials, pregnancy outcomes were summarized as part of a presentation to the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices (ACIP) in June 2006.<sup>24</sup> Although participants were counseled not to become pregnant during the trials, more than 1100 pregnancies were observed in each of the vaccine and placebo arms of the phase 3 studies (N≈20,000 participants). Analyses to date have not suggested any differences in pregnancy outcomes, and post-licensure tracking of fetal outcomes will continue.

### Indicated and Recommended Use of the HPV Quadrivalent Vaccine

On June 8, 2006, the FDA approved the quadrivalent HPV vaccine (Gardasil®, Merck & Co., Inc., Whitehouse Station, NJ). The labeled indication is for the prevention of clinical diseases caused by HPV types 6, 11, 16, and 18 among girls and women between the ages of 9 and 26 years, including cervical cancer and genital warts, as well as CIN grades 1-3, VaIN/VIN grades 2 and 3, and cervical adenocarcinoma *in situ*. These indications were based on efficacy studies that included females between the ages of 16 and 26 years, as well as safety and immunogenicity studies that included females 9 to 15 years of age.

At the June 29, 2006 meeting of the ACIP, provisional recommendations for use of the quadrivalent HPV vaccine were developed, including<sup>25</sup>:

1. Routine vaccination of females 11 to 12 years of age.
2. Use of the vaccination series as early as age 9 years, at the clinician's discretion.
3. Catch-up vaccination for females between the ages of 13 and 26 who have not been previously vaccinated.

The full vaccination series consists of 3 doses of vaccine, administered at 0, 2, and 6 months. These recommendations are considered to be provisional until published in an upcoming issue of *Morbidity and Mortality Weekly Report*, after which they become official policy.

Use of the quadrivalent HPV vaccine during pregnancy is not recommended. Completion or initiation of vaccination of women who have begun or wish to begin the series should be deferred until after completion of the pregnancy. The HPV vaccine may be administered to lactating women. Contraindications to use of the quadrivalent HPV vaccine include a history of hypersensitivity or allergy to yeast or any other vaccine component. Vaccination should be deferred in patients with moderate or severe acute illness. A resolution for the Vaccines for Children Program to include the quadrivalent HPV vaccine for females 9 to 18 years of age was adopted on June 29, 2006.<sup>26</sup>

Girls and women within the recommended target age ranges should be offered vaccination; testing for high-risk HPV DNA and serologic testing are not recommended prior to vaccination. It would be highly unlikely that patients offered HPV vaccination would have already been infected with all 4 HPV subtypes included in the vaccine. For individuals who are already infected with 1 or more HPV subtypes included in the vaccine, the vaccine will still provide protection against diseases caused by the other component antigens.

Although the existing clinical trials have not provided data on specific patient subgroups, the ACIP acknowledged special circumstances under which use of the quadrivalent HPV vaccine might be considered, including women with a history of equivocal or abnormal cytology smears, women known to be positive for the presence of high-risk HPV DNA, women with a history of genital warts, and women who are immunocompromised.<sup>25</sup>

### HPV Vaccine Among Females Older Than 26 Years of Age and Males

At present, there are no data that address vaccine efficacy among women 27 years of age and older, nor among males, although clinical trials focusing on these 2 subpopulations are ongoing. Interim analyses of these trials are planned.

### Population Benefits

Maximum benefit of this preventive vaccine will be realized among populations who have not yet initiated sexual activity. In a recent national survey of risk behaviors among high school students, 7.4% of respondents reported having initiated sexual intercourse before the age of 13; higher rates were observed among males and among blacks. The proportion of high school students who report that they are currently sexually active ranges from 22% of 9th grade students to 49% of 12th grade students; the proportion who report ever having had sexual intercourse ranges from 34% to 63% in these same grade levels.<sup>27</sup>

Markov models examining the use of a preventive HPV vaccine show the vaccine to be cost-effective and beneficial at the population level.<sup>28,29</sup> It is important to emphasize to patients that a preventive HPV vaccine will not replace cervical cancer screening. Rather, an HPV vaccine will complement an ongoing cervical cancer screening program. In addition, neither the bivalent nor the quadrivalent vaccine covers all high-risk HPV subtypes or other sexually transmitted infections; for this reason, ongoing gynecologic care and cervical cancer screening will remain important for early disease detection and prompt intervention.

At the level of the population, herd immunity is the reduced risk of infection that results from a subset of the population having acquired immunity. Whether the immunity results from natural infection or vaccination, the risk of disease transmission is reduced. In the case of the HPV vaccine, models suggest that achieving a high level of coverage among females may result in reduced transmission among males; however, the additional vaccination of males would further boost herd immunity and be invaluable where vaccine coverage is low.<sup>30</sup>

### Conclusion

Results from phase 2 and phase 3 clinical trials involving the FDA-approved quadrivalent HPV vaccine demonstrate dramatic efficacy in preventing HPV 6-, 11-, 16-, and 18-related infections and genital disease. In addition, phase 2 clinical trials of the bivalent HPV vaccine reveal that it is highly efficacious in preventing infections related to HPV 16 and 18 as well as genital disease. Moreover, safety data from both vaccines show the occurrence of vaccine-related symptoms (eg, arm pain, redness) without concern for systemic adverse events. Nearly all subjects demonstrate a robust immunologic response, which appears to be durable for 4 or more years, with surveil-

lance ongoing. In addition, both manufacturers have continued to build on these initial clinical trials and are including the enrollment of males as well as females older than the age of 26. Routine vaccination with the quadrivalent HPV vaccine has been recommended by the ACIP for girls 11 to 12 years of age, although the vaccine is approved for girls and women 9 to 26 years of age for the prevention of cervical cancer, genital warts, CIN grades 1-3, VaIN/VIN grades 2 and 3, and cervical adenocarcinoma *in situ*.

Vaccine adjuvants are used to boost the immunologic response, and these vaccines differ in the type of adjuvant used in each formulation. However, the clinical significance of the different adjuvants at present remains unclear as there is no established correlate of immunity. The duration of seroconversion to both the bivalent and quadrivalent vaccines has not been established.

At the present time, any differences between the bivalent and quadrivalent vaccines regarding their protection against HPV 16- and 18-related disease appear to be theoretical rather than proven. Both vaccines appear to induce a robust immunologic response and to demonstrate high levels of efficacy with regard to the HPV 16- and 18-related disease outcomes, and they are well tolerated. The quadrivalent HPV vaccine provides the additional benefit of protection against genital warts, low-grade cervical lesions, and recurrent respiratory papillomatosis associated with infection with HPV 6 and 11. Ongoing studies are evaluating the duration of immune response as well as efficacy in other population subgroups, including women older than 26 years of age and males. ■

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# Practical Implementation of HPV Vaccines in Clinical Practice

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## Abstract

Human papillomavirus (HPV) currently infects approximately 20 million people in the United States. An effective new vaccine has been approved for girls and young women aged 9 to 26 years that can decrease the spread of infection due to HPV and the future incidence of cervical cancer and genital warts. Family physicians should be aware of parental or patient attitudes and knowledge about HPV and concerns about HPV vaccination if they are to successfully implement HPV vaccination in their practices.

## Introduction

Approximately 20 million people in the United States are currently infected with human papillomavirus (HPV) and 6.2 million will get a new genital HPV infection each year.<sup>1</sup> The American Cancer Society cites approximately 9710 new cases of cervical cancer and 3700 deaths annually, all of which can be attributed to HPV infection.<sup>2</sup> The 2005 United States Youth Risk Behavior Survey found that 41% of Caucasian, 68% of African-American, and 51% of Hispanic high school students indicated that they had had sexual intercourse.<sup>3</sup> Against this background, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) has recommended that the quadrivalent HPV vaccine be routinely given to girls when they are 11 to 12 years of age.<sup>4,5</sup>

## ACIP Recommendations for HPV Vaccination

In June 2006, the ACIP voted to recommend that the first

licensed vaccine designed to protect against HPV (Gardasil®, Merck & Co., Inc., Whitehouse Station, NJ) be used for routine immunization of girls aged 11 to 12 years. The quadrivalent HPV vaccine is licensed for use in females aged 9 to 26 years. The ACIP recommended that the vaccine can be started as early as 9 years of age (at the discretion of the clinician) and be given to adolescent girls and young women aged 13 to 26 years who have not been previously vaccinated. The vaccine is recommended at routine adolescent immunization visits, especially before the age when sexual activity is likely to begin (TABLE 1).<sup>4,5</sup>

## Factors Influencing Parental or Patient Attitudes About HPV Vaccination

Factors influencing the attitudes of parents toward vaccinating their children against HPV are presented in TABLE 2.<sup>6,7</sup> Parents' decision-making process is influenced by their knowledge of HPV disease and its potential

TABLE 1

ACIP recommendations for HPV vaccination\* of girls and women

Age (y)	Recommendation
9-10	Vaccination at physician discretion
11-12	Vaccination recommended
13-26	Vaccination recommended for girls and women who have not previously been vaccinated

\*June 2006; recommendations refer to the quadrivalent HPV vaccine (Gardasil®). ACIP = Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention; HPV = human papillomavirus.

**TABLE 2**

**Factors affecting parental attitudes toward acceptance of HPV**

Factor	Consequence
Knowledge of HPV <ul style="list-style-type: none"> <li>• HPV can cause cervical cancer</li> <li>• HPV can cause genital warts</li> <li>• HPV can be asymptomatic</li> </ul>	Vaccine acceptance related to desire to protect child and concern about or personal experience with HPV <sup>6</sup>
Child's perceived risk for STIs and HPV <ul style="list-style-type: none"> <li>• Age sexual activity began (ie, sexually active vs not sexually active)</li> <li>• Practices responsible sexual behavior (eg, condom usage)</li> </ul>	Vaccine refusal related to perceived low risk for acquiring disease (child not sexually active) or lack of concern about disease characteristics and features <sup>6</sup>
Belief that vaccination would promote promiscuity	Vaccine refusal if belief that it encourages early and/or widespread sexual activity <sup>7</sup>
Influence of religious/cultural beliefs	May limit uptake among some ethnic or religious groups <sup>7</sup>
Concern about vaccine effectiveness	Belief in effectiveness of vaccine increases vaccine acceptance <sup>7</sup>
Concern about vaccine safety	Vaccine refusal if anxious about safety <sup>7</sup>
Belief or trust in authorities	Greater trust in authorities increases vaccine acceptance <sup>7</sup>

HPV = human papillomavirus; STIs = sexually transmitted infections.  
<sup>6</sup>Mays RM, et al. *Soc Sci Med*. 2004;58:1405-1413.  
<sup>7</sup>Brabin L, et al. *Vaccine*. 2006;24:3087-3094.

severity and future consequences along with the likelihood of their child acquiring the disease.<sup>6</sup> Parents who accept vaccination may be more likely to acknowledge that they cannot prevent all situations that put their child at risk for HPV infection, including those beyond the parents' or child's control, such as unwanted sexual contact or rape.<sup>6</sup> Parents who refuse vaccination may do so because they do not believe that their child is or will be sexually active or because they fear that giving the vaccine would be equivalent to giving their children permission to engage in sexual activity.<sup>6</sup>

**Knowledge and Awareness of HPV**

Several studies have demonstrated that college students in the United States have little knowledge of HPV.<sup>8,9</sup> In a Florida study of university students, only 37% of respondents had even heard of HPV, 59% did not know how HPV was transmitted, and 64% were unsure if HPV caused genital warts.<sup>8</sup> A New York study of college students' knowledge of sexually transmitted diseases found that only 45% of HPV questions were answered correct-

ly compared with 87% of non-HPV questions, which were about other sexually transmitted infections (STIs) such as human immunodeficiency virus. After an educational intervention, respondents answered 79% of HPV questions correctly.<sup>9</sup>

Among predominantly young, Caucasian, well-educated attendees of a "well-woman" clinic in the United Kingdom (UK), only 30% had heard of HPV and fewer than half of those who were aware of it knew about its association with cervical cancer.<sup>10</sup> Women who were older and those who had a past history of candida, genital warts, or an abnormal Pap smear had a greater awareness of HPV.<sup>10</sup> Only 30% of female employees of a university in the UK had also ever heard of HPV.<sup>11</sup> Of those who had heard of HPV, only 30% knew it was sexually transmitted, and only 11.3% linked it to cervical cancer.<sup>11</sup>

In another study from the United States, male university students did not perceive HPV to be a severe disease for themselves but did perceive it to be severe for their female partners.<sup>12</sup> Before participating in the study, 54.9% of the students had not heard of HPV, but upon completing the study, 89% knew that HPV is a cause of cervical cancer and that they could transmit HPV to their partner even if they themselves had no symptoms.<sup>12</sup> Most of the men indicated that if they were diagnosed with HPV, they would use condoms with new sex partners (95.1%) and/or reduce their number of new sex partners (53.7%).<sup>12</sup>

**Potential Parental or Patient Concerns About HPV Vaccination**

Multiple factors may influence parents and/or patients in their decision to consent to HPV vaccination. Vaccine recipients may mistakenly believe HPV vaccines protect them against other STIs or against HPV types other than those contained within the vaccine. Parents and patients may also assume that they will require less frequent or even no cytologic surveillance.<sup>13</sup> Some parents may be

uncomfortable discussing the rationale for vaccination with preadolescent or younger adolescent children or not wish to acknowledge that their child may already be or could become sexually active. Parents may also be concerned that vaccination of their children against HPV would condone or increase sexual risk-taking, lower the age of sexual initiation, increase the numbers of sex partners or level of sexual activity with partners, and decrease the use of condoms or other barrier protection methods by their children. It should be noted that no evidence has been found linking the concern about contracting either HPV or associated anogenital cancers with diminished sexual activity among adolescents. Adolescents seldom consider the future consequences of their actions, and it is unlikely that fear of HPV and cervical cancer would change their sexual behavior, especially when cervical cancer may take years to develop.

A study of female and male Midwestern university students found that factors favoring HPV vaccine acceptance included higher numbers of sexual partners, perceived higher risk of current or future HPV acquisition, belief that the vaccine is safe, and support of vaccination by parents, partners, and health care providers. University students consequently indicated they were willing to discuss sexual matters with parents as well as with health care providers.<sup>14</sup>

### Vaccine Safety Concerns

Approximately 93% of parents in the United States rate vaccines as safe, and this belief has been significantly associated with the vaccination status of preschool children.<sup>15</sup> However, a nationwide study found that parents may also have misconceptions about vaccines, for example, that children receive more immunizations than are good for them or that too many immunizations could weaken their child's immune system. This study also found that women, Caucasians, college graduates, and those with an orientation toward alternative medicine might be more likely to decline immunizations.<sup>16</sup>

Parental concerns about vaccine safety may consequently have a negative influence on vaccination rates.<sup>17</sup> For example, parental concerns about the alleged association of autism with the MMR (measles, mumps, rubella) vaccine has led to MMR uptake rates as low as 50% in some areas of the UK.<sup>18</sup> Lack of adequate information from health care professionals to parents about the vaccine may have also contributed to the low immunization rates.<sup>18,19</sup> In the US study cited

above, 84.2% of respondents indicated that they received their information about immunizations from their doctor.<sup>16</sup>

### Communicating Vaccine Information to Parents

The media are more likely to report events that are sensational, albeit uncommon, or even unproven, as in the case of MMR.<sup>20</sup> Consequently, it is extremely important that physicians and other health care providers have the appropriate factual information when discussing vaccines and immunizations with their patients and/or their patients' parents. It is also important that physicians understand the concerns of parents and not casually dismiss them. Physicians may need to explain the difference between causal and coincidental association, ie, just because an event occurred after immunization does not mean that it was directly caused by it.<sup>20</sup> Physicians should also be aware that parents are interested in the risks of a vaccine to their particular child rather than to children in general.<sup>19</sup> In the cases of diseases that have long been preventable because of vaccination, such as measles, accounts of children who have suffered from the disease may help to personalize the disease for those who have no memory or experience of it. In the case of HPV vaccines, it may be helpful to ask whether the parents have ever known someone who had cervical cancer and then explain the link to HPV and the role of the preventive vaccine.

Such education about a disease state may improve vaccine acceptance. In a study from Augusta, Georgia, parents of 10- to 15-year-old adolescent boys and girls were surveyed about their knowledge and acceptance of the HPV vaccine.<sup>21</sup> They were then read an HPV educational fact sheet and resurveyed. After the intervention, approximately 75% of the parents wanted their children vaccinated; 37% of parents initially opposed to and 65% of parents undecided about the HPV vaccine subsequently supported HPV vaccination. Parents opposed to vaccination believed that, if vaccinated, their children were more likely to become sexually active at a younger age and also that vaccines in general were not helpful.<sup>21</sup>

### Discussing HPV Vaccines With Patients and Parents

Physicians and other health care providers may use discussion of the recommendations for HPV immuniza-

tion of adolescents as an opportunity to educate patients and parents; they may also use this as an opportunity to engage patients and their parents in a discussion about sexual activity, sexually transmitted diseases, and the risks of HPV. Some individuals may confuse HPV with other STIs, especially genital herpes.<sup>22</sup> If this is the case, it is important to distinguish the diseases and point out that HPV is responsible for almost 100% of cases of cervical cancer as well as genital warts. Health care providers may wish to incorporate the Centers for Disease Control's fact sheet on genital HPV infection (available at [www.cdc.gov/std/HPV/STDFact-HPV.htm](http://www.cdc.gov/std/HPV/STDFact-HPV.htm))<sup>1</sup> as part of their educational efforts.

Education about the HPV vaccine should include a discussion of vaccine effectiveness and common adverse effects of the vaccine. For example, the quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine was 100% effective in preventing cervical intraepithelial neoplasia (CIN) grade 2/3 and adenocarcinoma *in situ* of the cervix and 98% effective in preventing genital warts due to these HPV strains in persons who were previously HPV-negative and who received all 3 vaccine doses.<sup>23</sup> Parents and patients should be reminded that HPV types 16 and 18 cause the majority of, but not all, cases of cervical cancer or CIN 2/3, whereas HPV types 6 and 11 cause more than 90% of genital warts and the majority of cases of CIN 1.<sup>24,25</sup>

### An Office-Based Approach to Implementing HPV Vaccination Recommendations

The ACIP now recommends that the 3 doses of the quadrivalent HPV vaccine be given to girls when they are 11 to 12 years of age. However, the vaccination series can be started as early as 9 years of age at the discretion of the health care provider. Girls and women 13 to 26 years of age should also receive the vaccine, preferably before the onset of sexual activity.<sup>4,5</sup>

A number of barriers to implementing these recommendations exist. Adolescents may not come in for regular "well-teen" visits. However, the visit for a sports or camp physical can be used as a "well-teen" visit and an opportunity to administer the increasing numbers of immunizations that are now being recommended for adolescents. Family physicians' concerns about administering HPV vaccines include availability of the vaccine at a reasonable cost and affordability for those without insurance or whose health insurance plan will not cover the vaccine. In a study conducted

prior to the release of the ACIP recommendations, most family physicians agreed that 9 to 13 years of age is the ideal age range for girls to receive HPV vaccination; however, they report a higher intention to recommend HPV vaccination to older versus younger adolescents.<sup>26</sup> Another barrier to physicians vaccinating 10- to 15-year-old patients is parental refusal or reluctance because of their concerns about vaccine safety or beliefs that their child already receives too many immunizations.

Female family physicians experienced with adolescents were more likely to recommend a vaccine against cervical cancer. Physician belief that HPV vaccination leads to long-lasting immunity and does not cause adverse side effects also promotes favorable attitudes among physicians toward HPV immunization. However, endorsements by organizations such as the American Academy of Family Physicians are the strongest and most consistent predictors of physician recommendations for HPV vaccination.<sup>26</sup>

### Conclusion

Immunization against HPV promises to significantly decrease the development of cervical cancer and genital warts. Family physicians and other health care providers should educate parents and patients about the role of HPV in causing these conditions and the effectiveness of the vaccine, while they also engage families in discussions about STIs. They should emphasize that HPV is often carried without symptoms and that immunization is most effective if the series is completed prior to the onset of sexual activity. Coverage of the cost of the vaccine by the Vaccines for Children Program and third-party payers will be essential if HPV immunization is to become widespread. ■

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## ► New Options in HPV Prevention

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**POSTTEST**

- How many individuals in the United States are estimated to be infected with human papillomavirus (HPV)?
  - 500,000
  - 1 million
  - 5 million
  - 20 million
- High-risk HPV types are associated with which of the following diseases?
  - Cervical cancer
  - Other anogenital cancers (ie, anal, penile, vaginal, and vulvar cancers)
  - Head and neck cancer
  - All of the above
- According to the 5-year follow-up efficacy data with the quadrivalent HPV vaccine, the vaccine was found to be \_\_\_ effective at preventing HPV 16- and 18-related cervical intraepithelial neoplasia and HPV 6- and 11-related genital warts.
  - 15%
  - 55%
  - 75%
  - 100%
- Immunogenicity-bridging studies with the quadrivalent HPV vaccine demonstrated higher levels of geometric mean titers in boys and girls compared with adults.
  - True
  - False
- The Advisory Committee on Immunization Practices (ACIP) voted in June 2006 to recommend the quadrivalent HPV vaccine for
  - Routine vaccination of girls 11 to 12 years of age
  - Vaccination in girls as young as 9 years of age (per discretion of clinician)
  - Catch-up vaccination for adolescent girls and women 13 to 26 years of age who have not been previously vaccinated
  - All of the above

**REQUEST FOR CREDIT**

If you wish to receive acknowledgement for participating in this activity, please complete the posttest (select the best answer to each question), along with this evaluation form verifying your participation. The posttest and evaluation form can be faxed to (212) 661-8338, ATTN: CME Department.

**POSTTEST ANSWER KEY**

1 \_\_\_\_\_ 2 \_\_\_\_\_ 3 \_\_\_\_\_ 4 \_\_\_\_\_ 5 \_\_\_\_\_

**EVALUATION FORM [HPV-0251]** (Please print clearly)

NAME (LAST, FIRST, M.I.) \_\_\_\_\_ DEGREE \_\_\_\_\_

ACADEMIC TITLE \_\_\_\_\_ SPECIALTY \_\_\_\_\_

AFFILIATION \_\_\_\_\_

ADDRESS (NO P.O. BOXES, PLEASE) \_\_\_\_\_

CITY, STATE, ZIP \_\_\_\_\_

TELEPHONE \_\_\_\_\_ FAX \_\_\_\_\_

E-MAIL \_\_\_\_\_

LICENSED IN \_\_\_\_\_

LAST FOUR DIGITS OF YOUR SOCIAL SECURITY NUMBER OR AMA ME NUMBER \_\_\_\_\_

SciMed is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

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I certify that I have participated in the CME activity entitled *New Options in HPV Prevention* for a total of \_\_\_\_\_ hours.

SIGNATURE \_\_\_\_\_ DATE \_\_\_\_\_

SciMed respects and appreciates your opinion. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form and fax it to (212) 661-8338, ATTN: CME Department.

Circle the appropriate response (1 = poor/not at all; 2 = fair/not very; 3 = satisfactory; 4 = good/very; 5 = outstanding/extremely)

**Extent to which activity met the identified objectives**

How much did participating in this activity enhance your ability to:

Describe the relationship between HPV types 16 and 18 and cervical cancer 1 2 3 4 5

Discuss the relationship between HPV types 6 and 11 and genital warts, recurrent respiratory papillomatosis, and abnormal cervical cytology 1 2 3 4 5

Summarize the safety, efficacy, and immunogenicity of HPV vaccines in large clinical trials 1 2 3 4 5

Identify practical strategies for implementing successful HPV vaccination programs in clinical practice 1 2 3 4 5

**Overall effectiveness of the activity**

The content presented:

Was timely and will influence how I practice 1 2 3 4 5

Will assist me in improving patient care 1 2 3 4 5

Fulfilled my educational needs 1 2 3 4 5

Avoided commercial bias or influence 1 2 3 4 5

If you rated "1" or "2" regarding commercial bias, please provide comments.

**Logistically:**

The format and materials were useful 1 2 3 4 5

What was the most positive part of this activity?

**Impact of the activity**

Will your practice change as a result of participating in this activity? Yes No

Please describe any change(s) you plan to make in your practice as a result of this supplement.

How committed are you to making these changes? 1 2 3 4 5

**Future activities**

Do you feel future activities on this subject matter are necessary and/or important to your practice? 1 2 3 4 5

Please suggest educational needs or practice-related problems in which you have interest for future activities.

**What method of learning do you most prefer?**

- Live meeting (eg, symposium)
- Enduring materials (eg, monograph, journal supplement)
- Multimedia (eg, CD-ROM, Web-based activities)

**Follow-up**

As part of our continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

- YES, I would be interested in participating in a follow-up survey.
- NO, I would not be interested in participating in a follow-up survey.

Additional comments about this activity:

- YES, I am interested in receiving future educational materials.

A SUPPLEMENT TO

**THE JOURNAL OF**  
**FAMILY**  
**PRACTICE**

NOVEMBER 2006

New options in

# HPV

Prevention

