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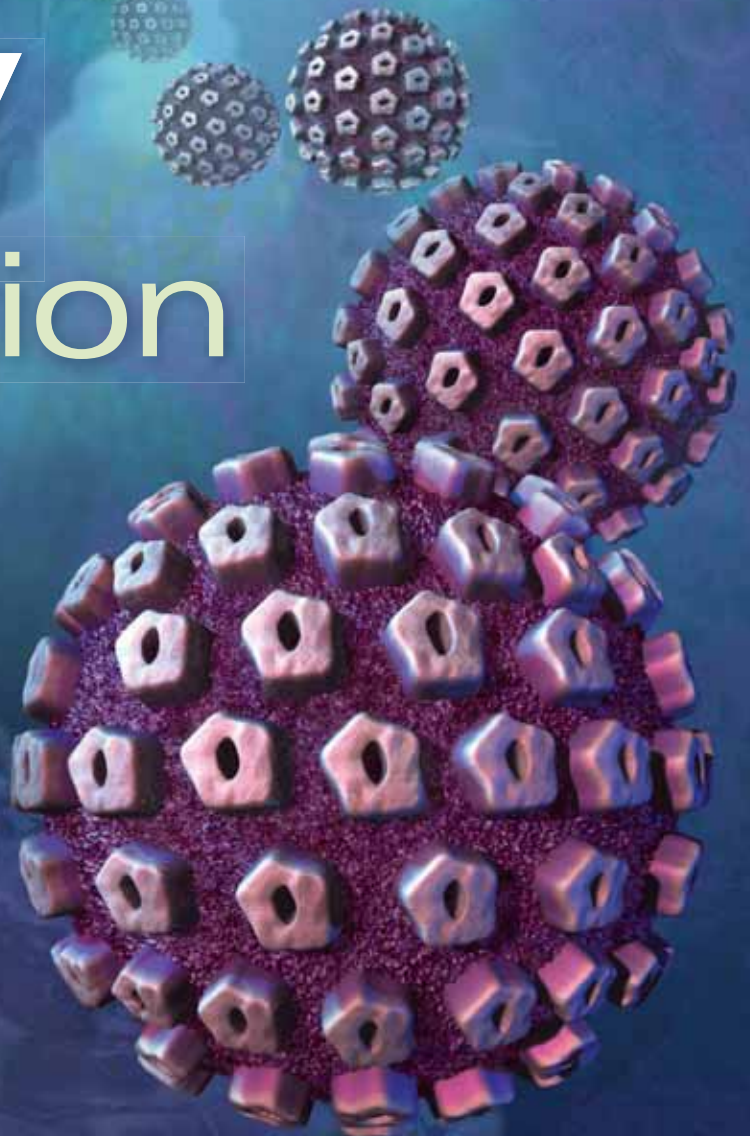
## MANAGEMENT

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July 2006

# New options in HPV Prevention



**Human Papillomavirus:  
Epidemiology, Natural History,  
and Clinical Sequelae**

▶ Mark Spitzer, MD

**Current Cervical Cancer  
Screening Guidelines and Impact  
of Prophylactic HPV Vaccines**

▶ Michael A. Gold, MD, FACOG, FACS

**Reducing HPV-related Clinical  
Disease Through Vaccination**

▶ J. Thomas Cox, MD

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# New options in HPV Prevention

## Mark Spitzer, MD

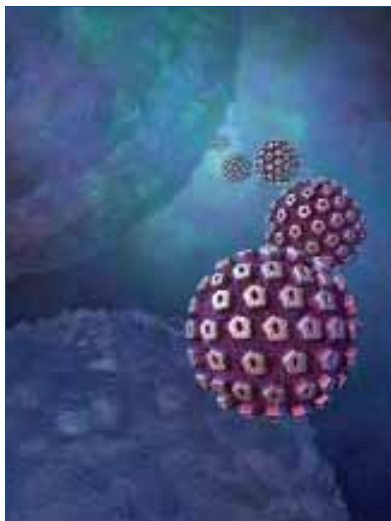
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## Introduction ..... S3

## Human Papillomavirus: Epidemiology, Natural History, and Clinical Sequelae

Mark Spitzer, MD ..... S5

## Current Cervical Cancer Screening Guidelines and Impact of Prophylactic HPV Vaccines

Michael A. Gold, MD, FACOG, FACS ..... S11

## Reducing HPV-related Clinical Disease Through Vaccination

J. Thomas Cox, MD ..... S18

## Posttest and Evaluation Form ..... S23

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### Target Audience

This activity has been designed to meet the educational needs of gynecologists 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 natural history of HPV infection and the health burden of cervical cancer and genital warts
- Discuss recent safety and efficacy clinical findings with prophylactic HPV vaccines
- Review current guidelines for assessing and managing cervical cytological abnormalities

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# Introduction

**H**uman papillomavirus (HPV) is a highly prevalent sexually transmitted infection that affects three quarters of sexually active adults at some point in their lifetime. High-risk HPV types are responsible for virtually all cases of cervical cancer and most cases of other anogenital cancers (eg, anal, vaginal, vulvar, and penile). Low-risk HPV types are associated with the majority of cases of low-grade cervical lesions, genital warts, and recurrent respiratory papillomatosis (RRP). A quadrivalent HPV vaccine has recently been approved by the US Food and Drug Administration (FDA) for the prevention of HPV 6/11/16/18-related cervical cancer, cervical/vaginal/vulvar precancer, cervical intraepithelial neoplasia (CIN), and genital warts in young women (ages 9-26). A bivalent vaccine is also currently in late stages of development. The HPV vaccines are expected to deliver the promise of reducing the burden of HPV-related disease and complement routine cervical cytologic screening. This supplement will review the epidemiology and natural history of HPV infection, HPV vaccine safety and efficacy data, and recent updates to cervical cytologic screening and abnormal cervical cytology management guidelines.

HPV currently affects 20 million adults in the United States, and an estimated 6.2 million sexually active adults will acquire the infection each year.<sup>1</sup> Sexually active young women have the highest HPV infection rates,<sup>2</sup> and approximately 75% of sexually active men and women will acquire an HPV infection during their lifetimes.<sup>3</sup> More than 40% of young women will become infected with HPV in the 3 years following the onset of sexual activity,<sup>4</sup> underscoring the need for patients, parents, and health care providers to understand the risks, HPV-related sequelae, prevention options, and appropriate screening recommendations.

HPV is present in most anogenital cancers, namely cervical, anal, penile, vaginal, and vulvar cancer.<sup>5,6</sup> Infection with high-risk, oncogenic HPV types is the known cause of cervical cancer, with more than 70% of cervical cancer cases associated with HPV types 16 and 18.<sup>5,7</sup> Genital warts, abnormal cervical cytology, and RRP are strongly linked to low-risk HPV infection, with HPV

types 6 and 11 associated with more than 90% of all genital warts cases and most cases of RRP.<sup>8-10</sup>

Although cervical cytologic screening efforts have dramatically decreased the incidence of cervical cancer, the American Cancer Society estimated approximately 9700 new cases and 3700 deaths due to cervical cancer will occur in 2006.<sup>11</sup> Because HPV is the primary etiologic agent of cervical cancer, the most recent updates to cervical screening guidelines now include the use of HPV DNA testing.<sup>12,13</sup> This cost-effective technique has demonstrated high sensitivity in identifying women at risk for high-grade cervical lesions and carcinoma.<sup>14</sup> Up until recently, the prevention of HPV-related disease was limited to screening programs; however, the approval of a quadrivalent HPV vaccine has provided a new strategy for reducing the burden of HPV-related disease.

In June 2006, a quadrivalent HPV vaccine was approved by the FDA for the prevention of cervical cancer; cervical precancers [CIN 2/3 and adenocarcinoma *in situ* (AIS)]; vulvar precancers [vulvar intraepithelial neoplasia (VIN) 2/3]; and vaginal precancers [vaginal intraepithelial neoplasia (VaIN) 2/3] caused by HPV types 16 and 18, as well as genital warts and CIN 1 caused by HPV types 6/11/16/18 in girls and women (ages 9-26). Approval of the quadrivalent vaccine was based predominantly on data from phase 2 and 3 trials in young women (ages 16-26).<sup>15-17</sup> Two additional studies demonstrated an even more robust anti-HPV immune response in boys and girls (ages 9-15),<sup>18,19</sup> supporting the efficacy of administering the vaccine to children and adolescents prior to onset of sexual activity to maximize the prophylactic effect. A bivalent HPV vaccine protecting against HPV types 16 and 18 is currently in late stages of development and has demonstrated 100% efficacy in preventing persistent HPV 16/18 infection and CIN in phase 2 trials. Phase 3 trials of the bivalent vaccine are underway.

The approval of a vaccine protecting against HPV 6/11/16/18-related cervical cancer, vaginal/vulvar precancers, AIS, CIN, and genital warts marks an important milestone for the practice of obstetrics and gynecology. Although the implementation of vaccination against HPV is expected to substantially reduce the incidence of HPV-

related disease, this approach will need to be considered a complementary strategy with routine cervical cytologic screening. Clinicians who routinely administer vaccines will need to provide parents and patients with important information on the long-term benefits of HPV vaccination to help foster acceptance.

This supplement will review the epidemiology and natural history of HPV infection, the most recent safety and efficacy data for HPV vaccines approved and in clinical development, and recent updates to routine cervical cytologic screening guidelines.

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# Human Papillomavirus: Epidemiology, Natural History, and Clinical Sequelae

Mark Spitzer, MD

**H**uman papillomavirus (HPV) infection constitutes a major public health concern, in part because it represents the highest incidence of newly acquired sexually transmitted infections (STIs) in the United States.<sup>1</sup> More significantly, specific types of HPV (referred to as high-risk HPV types) are implicated in the etiology of cervical cancer and other genital cancers, while other types of HPV (low-risk HPV types) cause genital warts, abnormal cervical cells, and recurrent respiratory papillomatosis (RRP). Although cervical cytologic screening programs have achieved enormous success at reducing cervical cancer morbidity, the addition of a prophylactic HPV vaccination is expected to further reduce HPV-related morbidity and mortality.

## KEY POINTS

- High-risk, oncogenic HPV types 16 and 18 are responsible for approximately 70% of cervical cancer cases, whereas low-risk types 6 and 11 cause approximately 90% of genital warts cases.
- The highest rates of HPV infection have consistently been found in sexually active women younger than 25 years of age, and more than three quarters of sexually active adults will be infected with at least 1 HPV type during their lifetime.
- In 2 large prospective trials, 5% to 27% of women who tested positive for HPV 16 or 18 developed CIN 3 or cervical cancer within a 3-year period.
- A successful HPV-vaccination program for high- and low-risk HPV types, in conjunction with regular screening, is expected to substantially reduce the morbidity associated with HSIL, cervical cancer, and genital warts.

## Incidence and Prevalence of HPV

Approximately 20 million Americans and 630 million persons worldwide are infected with HPV. In the United States, approximately 6.2 million individuals will acquire a new infection each year.<sup>2,3</sup> HPV infection rates are highest in sexually active women younger than 25 years of age.<sup>4</sup> In young HPV-negative women, the cumulative incidence for a first HPV infection has been estimated at 32% at 24 months and 43% at 36 months.<sup>5,6</sup> Still, physicians should note that more than three quarters of sexually active men and women are infected with at least 1 HPV type during their life spans.<sup>7</sup> Although much less studied, the prevalence of HPV infection in men is estimated to be similar to that of women.<sup>8</sup>

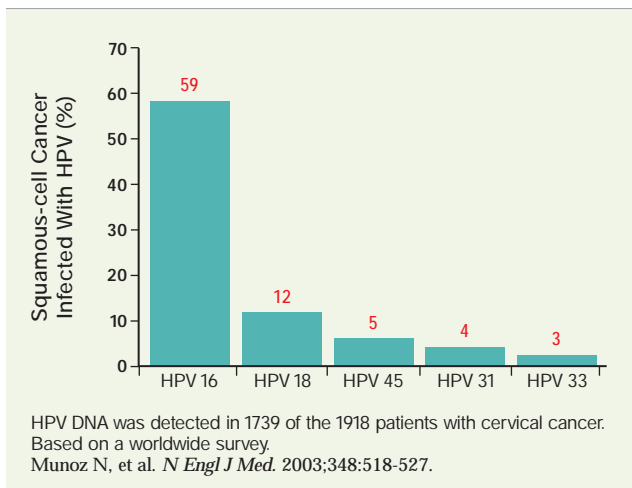
## HPV Types and Oncogenic Risk in Women: A Review of the Literature

More than 100 types of HPV have been discovered, of which approximately 35 infect the genital tract<sup>9-11</sup> and are also classified by their oncogenic risk. High-risk types are found in the vast majority of cervical and anogenital cancers, including vaginal, vulvar, penile, and anal cancers.<sup>12,13</sup> Most importantly, HPV types 16 and 18 are implicated in approximately 70% and 80% of all cases of cervical cancer and cervical adenocarcinoma, respectively (FIGURE 1).<sup>12,14</sup>

These 2 types are strongly implicated in the development of high-grade cervical lesions. In a large, prospective trial of more than 20,000 women, HPV status was evaluated at enrollment. Almost 10% of women with HPV 16 infection and 5% of women with HPV 18 infection developed cervical intraepithelial neoplasia (CIN) 3 within 36 months. At 3 years of follow-up, women who were HPV DNA negative at enrollment developed a 1% cumulative

**FIGURE 1**

**Prevalence of HPV types that cause cervical cancer**



incidence of incident CIN 3 or cervical cancer.<sup>15</sup> At 10 years follow-up, 17% of the women who were infected with HPV 16 at enrollment had developed CIN 3 or higher, as had 14% of those infected with HPV 18 at enrollment.<sup>15</sup>

Similar findings were reported in a study of Seattle college students who were closely monitored at 4-month intervals. Among women with any HPV infection at study initiation, the risk of developing CIN 2 or 3 was 11%. The risk in women infected with HPV 16 or 18 at study onset totalled 27% over the 36-month study duration. The median time to detection of CIN 2 or 3 after discovery of HPV infection was only 14 months.<sup>16</sup> These results suggest that even in the absence of abnormal cytology, women who are positive for HPV types 16 or 18 should be followed more closely than is customary following abnormal cytologic results.<sup>17</sup>

Among 331 HPV-negative, sexually active young women, the risk of acquiring a high-risk infection has been shown to be almost twice that of acquiring a low-risk type of infection. During more than 12 months of follow-up, the estimated cumulative probabilities of acquiring a high-risk, oncogenic HPV type was 32%, while the risk of acquiring a low-risk type was 18%.<sup>18</sup> Clinicians should note that, although low-risk HPV types are much less likely to be associated with cancer development, their effects are of concern. Low-risk HPV infection has been related to the development of genital warts, abnormal cervical cytologic study results, and RRP; specifically, HPV types 6 and 11 have been linked to more than 90% of all genital warts cases and the vast majority of cases of RRP.<sup>19-21</sup>

**HPV Infection in Men**

HPV infection in men has not been well studied, possibly because HPV-associated diseases are more common in women and HPV DNA is more difficult to detect in men.<sup>8,21</sup> However, the estimated prevalence of any type of HPV infections in men is 45%; the estimated prevalence for HPV 16 is 15%.<sup>21</sup> More research in this area is needed: Men are clearly implicated in the transmission of HPV and are susceptible to HPV-related diseases, such as genital warts, as well as anal and penile cancers.<sup>22</sup>

**Cervical Cancer Screening and HPV-Related Disease**

Organized cervical cancer screening with the Pap test began about 40 years ago; since then, the incidence of cervical cancer in the United States has decreased by 75%.<sup>23</sup> Cervical cancer remains a major public health concern. The American Cancer Society estimates that approximately 3700 women will die as a result of cervical cancer in 2006.<sup>24</sup> No treatment for HPV infection currently exists, so prevention and regular cervical cancer screening provide the best mechanisms to address HPV-related disease. While an estimated 93% of all women 18 years or older have had a Pap test, 60% of women diagnosed with cervical cancer have not been screened in 5 years or more.<sup>25,26</sup> Women who have not been screened within the past 3 years share the following characteristics: low family income, high school graduate or lower educational level, unmarried status, and no health insurance (<65 years of age only).<sup>27</sup>

A study of 833 women who had cervical cancer and who were long-term members of a prepaid comprehensive health plan revealed similar characteristics: older age, residence in an area of high poverty, and low education level.<sup>28</sup> In this investigation, 56% of women with cervical cancer had not had a Pap test in the past 3 years despite the fact that 81% had seen a doctor during that interval and 63% had had 3 or more visits.<sup>28</sup>

**Other Consequences of HPV: Genital Warts and RRP**

Genital warts (ie, condyloma acuminata) are a common consequence of HPV infection, most often with HPV types 6 and 11.<sup>13,20</sup> Approximately 1% of sexually active American adults aged 15 to 49 years have visible genital warts, which account for more than 300,000 initial visits to physician's offices each year.<sup>13,29</sup> Although almost always benign in nature, genital warts can be socially stig-

matizing, and current treatments do not reliably prevent recurrence or decrease infectivity because the underlying HPV infection often persists.<sup>30</sup>

RRP is a rare, yet potentially fatal consequence of HPV infection that is most commonly associated with infection with HPV 6 and/or 11.<sup>31</sup> This infection is characterized by laryngeal papillomas, which are manifested within the first 5 years of life and typically are difficult to treat. RRP is also known to occur in adults.<sup>32</sup> Medical and surgical treatments for RRP are often palliative, leaving the patient with significant physical and psychological distress.<sup>33</sup>

### Factors in Transmission of HPV

In most instances, anogenital HPV is acquired through sexual contact.<sup>13,34</sup> Although rare, HPV infections have been documented in virgins. Initial HPV infection occurs when HPV virions penetrate the epithelial layers of the external genitalia or cervix through microabrasions to reach the basal stem cells. There, HPV DNA replicates as the basal cells differentiate and progress to the surface of the epithelium.<sup>35</sup> The majority of HPV infections clear spontaneously; however, abnormal cervical cytology and cancer can occur following persistent infection of the host cells, possible integration of HPV DNA into the host genome, and the accumulation of additional mutations in the infected host cells.<sup>36,37</sup> In rare cases, HPV can be transmitted vertically from mother to baby during delivery, which may result in RRP or genital warts.<sup>2</sup>

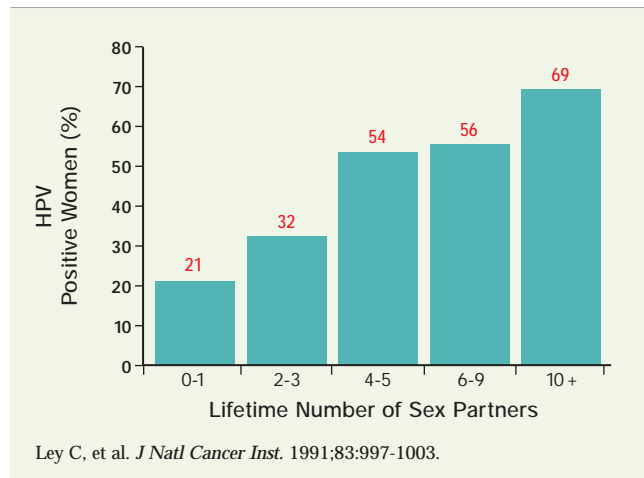
The high incidence of HPV infection in young women is due not only to the onset of sexual activity, heightened levels of sexual activity, and having multiple partners but also to the stage of development of the cervix.<sup>4,38</sup> The transformation zone on the cervix is the site most often associated with cervical cancers. At puberty, this region contains immature epithelium and is therefore more easily penetrated by viral infections. At menopause, the transformation zone disappears, thus contributing to the lower rate of new HPV infections in older women.<sup>38</sup>

### Risk Factors for HPV Infection

Risk factors for acquiring HPV infection follow a pattern similar to other STIs, which is not surprising because of the necessity of skin-to-skin sexual contact for transmission. The total number of sexual partners is

**FIGURE 2**

**Risk of HPV infection in young women and number of sexual partners**

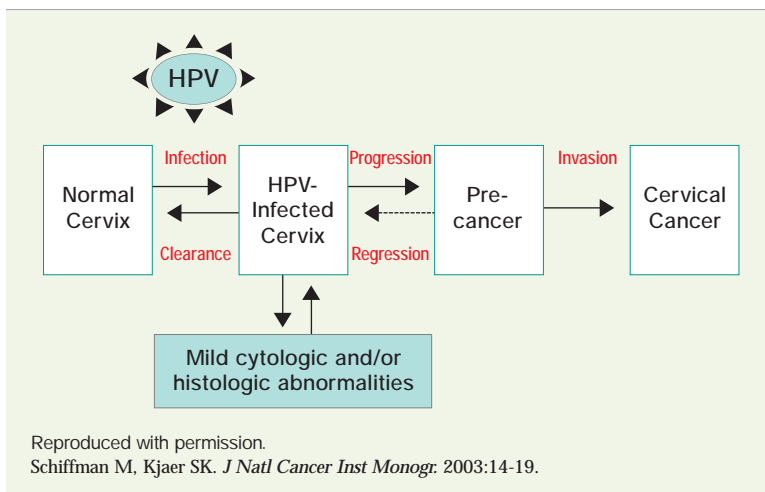


a significant predictor of HPV-infection prevalence in women (FIGURE 2).<sup>4</sup> Additional sexual behavior-related risks for women include the number of recent partners and history of other STIs.<sup>39</sup> Risk factors for HPV infection in men are similar to those in women; however, the data supporting these risk factors are less consistent. The strongest predictors for men include number of lifetime and recent sexual partners, lack of circumcision, same-sex sexual intercourse, and age.<sup>8,40</sup> The Centers for Disease Control and Prevention have determined that condoms do not prevent HPV infection; however, meta-analyses suggest that their use may be associated with a lower risk of HPV-related disease, including genital warts and cervical neoplasias/cancer.<sup>23,41</sup>

Immunosuppression and environmental factors may also play a role in the acquisition of HPV infection. Renal transplant patients receiving immunosuppressive therapies and women with human immunodeficiency virus (HIV) infection are at elevated risk for HPV infection, which may be due to a reduced ability to repress a latent infection.<sup>42,43</sup> Adolescent women who are HIV positive are 5 times more likely to develop high-grade squamous intraepithelial lesion (HSIL) compared with their HIV-negative counterparts, placing them at substantially greater risk for the development of cervical cancer.<sup>44</sup> Other possible risk factors for HPV infection include smoking history, parity, and use of oral contraception; however, these risk factors have been hypothesized to be confounded with risks associated with sexual behavior.<sup>23</sup>

**FIGURE 3**

**The natural history of HPV infection and cervical cancer**



among women who test positive at least 3 times for high-risk HPV types compared with HPV-negative women.<sup>36,48</sup> Prospective studies estimate 15% to 30% of women who test positive for high-risk HPV types will develop HSILs within a 4-year period.<sup>10</sup>

HSILs eventually may lead to cervical cancer.<sup>38</sup> The rate of progression from HSIL to invasive cervical cancer is estimated at 1.44% during a 2-year period.<sup>49</sup> This rate is based on population-based screening data and may be influenced by the patient's age, as younger women would be expected to have lower incidence rates. Infection with HPV 16 has a high risk for persistence and development of cervical cancer; the progression rate from HPV 16 infection to cervical carcinoma *in situ* has been estimated at 7 to 12 years, underscoring the importance of routine cervical cytologic screening.<sup>12,50</sup>

**Treatment Costs of HPV Infection**

The treatment of HPV-related disease is associated with a financial burden estimated at \$5 billion annually (in 2004 US dollars).<sup>45</sup> An estimated 1.4 million men and women in the United States have genital warts, which are associated with treatment costs per case ranging from \$285 to \$6700.<sup>46</sup> Cases of CIN are associated with an average cost of \$1709 and 7.2 follow-up visits.<sup>47</sup> Among all cervical HPV-related diseases, treatment is estimated at \$26,415 per 1000 women (based on 1998 US female population and in 2002 US dollars) with the greatest costs incurred by women aged 20 to 29 years (\$51,863 per 1000 women).<sup>46</sup> Cervical cytologic screening accounts for 90% of spending of funds for HPV-related diseases; however, the benefits are clearly seen by the substantial decline in the incidence of cervical cancer cases in the United States over the past 4 decades.<sup>23,47</sup>

**Natural History of HPV Infection**

Although the majority of HPV infections regress following initial infection, persistent HPV infection remains a serious concern because it may lead to cervical cancer (FIGURE 3).<sup>29</sup> Among young women with a prevalent HPV infection, 60% to 75% become HPV negative after 30 months, and the median duration of HPV infection is estimated at 8 months.<sup>5,36</sup> Both high-risk and low-risk HPV types have the potential to cause low-grade squamous intraepithelial lesions of the cervix. The risk of HSIL development is estimated to be 14 times higher

**Preventing HPV Infection**

Cervical cytologic screening programs have made remarkable achievements in detecting HPV-related disease, giving clinicians an opportunity to prevent the most severe consequences (cancer); however, this strategy can only detect—not prevent—precancerous cervical lesions. Prophylactic HPV vaccines are expected to dramatically reduce HPV-related morbidity and mortality, as well as the economic and emotional impact associated with HPV infection and related diseases.

A prophylactic quadrivalent vaccine that protects against high-risk HPV 16 and 18 and also offers protection against the 2 most common genital wart-causing HPV types (6 and 11) has recently become commercially available. Two phase 3 trials of the quadrivalent vaccine demonstrated 100% efficacy in preventing HPV 6/11/16/18-related CIN 1-3, genital warts, and vulvar/vaginal neoplasia for up to 2 years.<sup>51,52</sup> The quadrivalent HPV vaccine is indicated for the prevention of HPV 6/11/16/18-related cervical cancer, genital warts, cervical adenocarcinoma *in situ*, as well as cervical (CIN 1-3), vaginal, and vulvar intraepithelial neoplasias in girls and women 9 to 26 years of age.

Phase 2 clinical trials of a bivalent vaccine directed against HPV 16 and 18 have demonstrated that it is highly efficacious at protecting against incident and persistent cervical infections with those high-risk HPV types.<sup>53,54</sup> Phase 3 trials are ongoing.

## Conclusion

HPV is the most prevalent STI in the United States, and young women are at the highest risk for newly acquired infection. Persistent infection with high-risk HPV types (16 and 18) is strongly predictive of cervical neoplasias and cancer. Infection with low-risk HPV types (6 and 11) is associated with an overwhelming majority of cases of genital warts and RRP. The reduction in cervical cancer mortality achieved with cervical cytology screening programs has been dramatic, but the incidence of cervical neoplasias and cancer remains a public health burden. In conjunction with routine screening, prophylactic HPV vaccines that protect against the most common HPV types should further decrease the incidence in HPV-related disease morbidity and mortality.

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# Current Cervical Cancer Screening Guidelines and Impact of Prophylactic HPV Vaccines

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The implementation of widespread cervical cytologic screening programs has dramatically reduced cervical cancer morbidity and mortality. As understanding of the biology of cervical cell abnormalities has improved, screening and cytologic classification guidelines have been updated to improve surveillance. Prevention and early detection screening efforts, such as the Pap test, have led to a reduction in the incidence of cervical cancer which substantially declined in the United States during the past 40 years.<sup>1</sup> Still, cervical cancer remains the second most prevalent cancer in women

worldwide with approximately 500,000 new cases diagnosed each year.<sup>2</sup> In 2006, an estimated 9700 cases of cervical cancer are expected to be diagnosed in the United States (and 3700 deaths will be attributed to cervical cancer).<sup>3</sup> Half of the cases of cervical cancer will occur in women never screened and an additional 10% will occur in women not screened within the past 5 years, underscoring the importance of regular cervical cytologic screening for prevention.<sup>4</sup>

Although screening has led to dramatic improvements in diagnosis and treatment, the sensitivity and specificity of Pap tests range, respectively, from 47% to 58% and 69% to 95%.<sup>5,6</sup> Because of the strong association of high-risk human papillomavirus (HPV) infection and cervical cell abnormalities, the latest cytologic classification system and screening guidelines have incorporated evidence-based recommendations, including HPV DNA testing to improve the sensitivity and reduce the burden of cervical cancer screening.

## KEY POINTS

- HPV DNA testing with cervical cytology increases the sensitivity of detecting high-risk lesions.
- Reflex HPV DNA testing is cost-effective and eliminates a return to the clinician's office following an ASC-US result.
- A quadrivalent vaccine protecting against both high-risk (16/18) and low-risk (6/11) HPV types was recently approved by the US Food and Drug Administration for girls and women from 9 to 26 years of age for the prevention of cervical cancer, cervical precancers, vulvar/vaginal precancers, low-grade cervical lesions, and genital warts. A bivalent vaccine to protect against HPV 16/18 is currently being tested in phase 3 trials and is expected to reduce the incidence of type-specific cases of cervical cancer and abnormal cervical cells.
- HPV vaccination in conjunction with cervical cytologic screening programs is expected to further reduce the risk of cervical cancer.

## Classification of Cervical Cytology: The Bethesda System

The Bethesda System for reporting the results of cervical cytologic testing was initially developed in 1988 to provide a uniform system of terminology. It was updated in 1991 to incorporate laboratory and clinical experience, classifying cervical abnormalities into squamous intraepithelial lesions (SILs) of high (HSIL) or low (LSIL) grade in place of the cervical intraepithelial neoplasia (CIN) categories. The division of SIL was based on evidence that LSILs often regress, whereas HSILs are more commonly associated with persistence of HPV infection and a higher risk of the development of cervical cancer.<sup>7</sup>

**TABLE 1**

**Bethesda System 2001 (abridged)**

<b>SPECIMEN ADEQUACY</b>
<ul style="list-style-type: none"> <li>• Satisfactory for evaluation (describe presence or absence of endocervical/transformation zone component and any other quality indicators, eg, partially obscuring blood, inflammation, etc)</li> <li>• Unsatisfactory for evaluation ... (specify reason)             <ul style="list-style-type: none"> <li>- Specimen rejected/not processed (specify reason)</li> <li>- Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (specify reason)</li> </ul> </li> </ul>
<b>GENERAL CATEGORIZATION</b>
<ul style="list-style-type: none"> <li>• Negative for intraepithelial lesion or malignancy</li> <li>• Epithelial cell abnormality</li> <li>• Other</li> </ul>
<b>INTERPRETATION/RESULT</b>
<b>NEGATIVE FOR INTRAEPITHELIAL LESION OR MALIGNANCY</b>
<b>Organisms</b>
<ul style="list-style-type: none"> <li>• Trichomonas vaginalis</li> <li>• Fungal organisms morphologically consistent with Candida species</li> <li>• Shift in flora suggestive of bacterial vaginosis</li> <li>• Bacteria morphologically consistent with Actinomyces species</li> <li>• Cellular changes consistent with herpes simplex virus</li> </ul>
<b>Other nonneoplastic findings (Optional to report: list not inclusive)</b>
<ul style="list-style-type: none"> <li>• Reactive cellular changes associated with             <ul style="list-style-type: none"> <li>- Inflammation (includes typical repair)</li> <li>- Radiation</li> <li>- Contraceptive intrauterine device (IUD)</li> </ul> </li> <li>• Glandular cells, status posthysterectomy</li> <li>• Atrophy</li> </ul>
<b>EPITHELIAL CELL ABNORMALITIES</b>
<b>Squamous Cell:</b>
<ul style="list-style-type: none"> <li>• Atypical squamous cells             <ul style="list-style-type: none"> <li>- Of undetermined significance (ASC-US)</li> <li>- Cannot exclude HSIL (ASC-H)</li> </ul> </li> <li>• Low-grade squamous intraepithelial lesion (LSIL) encompassing: HPV/mild dysplasia/CIN 1</li> <li>• High-grade squamous intraepithelial lesion (HSIL) encompassing: moderate and severe dysplasia, carcinoma <i>in situ</i> (CIS)/CIN 2 and CIN 3</li> <li>• Squamous cell carcinoma</li> </ul>
<b>Glandular Cell</b>
<ul style="list-style-type: none"> <li>• Atypical (AGC)             <ul style="list-style-type: none"> <li>- Endocervical cells</li> <li>- Endometrial cells</li> <li>- Not otherwise specified (NOS)</li> </ul> </li> <li>• Atypical (AGC), favor neoplastic             <ul style="list-style-type: none"> <li>- Endocervical cells</li> <li>- Not otherwise specified (NOS)</li> </ul> </li> <li>• Endocervical adenocarcinoma <i>in situ</i> (AIS)</li> <li>• Adenocarcinoma</li> </ul>
<b>OTHER</b>
<ul style="list-style-type: none"> <li>• Endometrial cells (in a woman 40 or more years of age) (Specify if "negative for squamous intraepithelial lesion")</li> </ul>
<b>EDUCATIONAL NOTES AND SUGGESTIONS (optional)</b>
Adapted with permission. Solomon D, et al. <i>JAMA</i> . 2002;287:2114-2119.

The Bethesda Workshop reconvened in 2001 to incorporate the most up-to-date research and expert opinions regarding cervical neoplasias and screening techniques (TABLE 1). A major change replaced the term “diagnosis” with “interpretation” or “result” to clarify the fact that cervical cytologic screening is a test and not a diagnosis. In addition, specimen adequacy was updated to 2 categories: “satisfactory for evaluation” or “unsatisfactory for evaluation.”<sup>6</sup>

In terms of epithelial cell abnormalities, atypical squamous cells (ASCs) were qualified as either “of undetermined significance” (ASC-US) or “cannot exclude HSIL” (ASC-H).<sup>7</sup> The differentiation was intended to alert clinicians to a greater likelihood of the presence of CIN 2 and 3 in ASC-H samples.<sup>7,8</sup> This goal appears to have been achieved; in 1 report, the use of the 2001 Bethesda System and an ASC-H classification was associated with a 10-fold risk of having a high-grade cervical lesion.<sup>9</sup>

The classification of glandular abnormalities was also significantly revised by eliminating the term “atypical glandular cells of undetermined significance” to prevent confusion with ASC-US. Glandular cell abnormalities are now classified as “atypical glandular cells” (AGCs), either endocervical, endometrial, or not otherwise specified (NOS). Atypical glandular cells favor neoplasia, either endocervical or NOS; endocervical adenocarcinoma *in situ* (AIS); or adenocarcinoma. In addition, an “other” category was added to identify endometrial cells in women 40 years or older. Such cells may indicate a risk for an endometrial abnormality.<sup>7</sup>

■ **Current Guidelines to Assess Cervical Cytologic Abnormalities**

If detected early, invasive cervical cancer is one of the most successfully treated cancers with a 5-year survival rate of 92%. Survival for women with preinvasive lesions is nearly 100%.<sup>3</sup> Substantial reductions in cervical cancer morbidity and mortality have been attributed to cervical cytologic screening, considered one of the greatest successes in medicine and public health.<sup>10</sup> A number of organizations have made recommendations regarding the optimal timing of routine cervical cancer screening, including the American Cancer Society (ACS), American College of Obstetricians and Gynecologists (ACOG), and the US Preventive Services Task Force (USPSTF).<sup>11-13</sup>

**Guidelines for initiating screening**

The guidelines of ACS, ACOG, and USPSTF recommend that initial screening should occur approximately 3 years

**TABLE 2**
**Cervical cytology screening guideline recommendations**

Timing	ACS <sup>11</sup>	ACOG <sup>12</sup>	USPSTF <sup>13</sup>
Initiate screening	3 years after initiating sexual intercourse and before age 21	3 years after initiating sexual intercourse and before age 21	3 years after initiating sexual intercourse and before age 21
Up to age 30	Annual screening with conventional Pap or every 2 years with liquid Pap	Annually	Every 3 years following 2-3 consecutive normal results
Older than age 30	Every 2-3 years* <sup>†</sup> or screening every 3 years when adding HPV DNA testing to conventional or liquid Pap	Every 3 years following 3 consecutive normal results <sup>†</sup>	Every 3 years following 2-3 consecutive normal results
Cease screening	Age 70 following 3 consecutive, adequate negative Pap tests within the past 10 years <sup>†</sup>	No upper age limit recommended	Age 65 following recent adequate normal Pap results
Total hysterectomy	Screening not indicated. <sup>†</sup> Women with a history of CIN 2 or 3 should continue screening until 3 consecutive negative Pap test results within the past 10 years	Screening not indicated. <sup>†</sup> Women with a history of CIN 2 or 3 should continue screening until 3 consecutive negative Pap test results within the past 10 years	Screening not indicated

\*Assuming women have had 3 consecutive satisfactory/normal results

<sup>†</sup>Assuming no additional high-risk factors (eg, history of in utero diethylstilbestrol exposure, are HIV+, or are immunocompromised)

after the initiation of sexual intercourse and no later than 21 years of age.<sup>11-13</sup> The rationale for this timing is based on evidence that screening prior to the 3-year period will identify and lead to overtreatment of cervical lesions that frequently regress spontaneously.<sup>11</sup> Among adolescent and young women, more than 70% of HPV infections regress within 24 months of initial infection.<sup>14</sup> In young women, LSIL is typically transient with only a 3% risk of progressing to HSIL in a 36-month period.<sup>15</sup> Adolescents who may not need a cervical cytologic screening should still obtain appropriate health care, including the assessment of health risks and contraception, as well as screening for sexually transmitted diseases.<sup>11</sup>

### Recommendations differ for screening after age 21

The guidelines cited above vary slightly in their recommendations for screening after the age of 21. For women up to age 30, the ACS recommends annual screening with a conventional Pap test or every 2 years with a liquid-based Pap test, whereas ACOG recommends annual screening with a Pap test of either type.<sup>11,12</sup> The USPSTF recommends screening every 3 years following 3 consecutive normal Pap results.<sup>13</sup> Until recently, it was widely believed that liquid-based Pap tests are more sensitive than conventional Pap tests; however, a recent comprehensive review of studies assessed cervical cytologic test sensitivity and specificity. The authors reported that con-

ventional and liquid-based Pap tests provide equal efficacy.<sup>16</sup> For women older than 30 years of age, the frequency of screening can be lengthened to every 2 to 3 years provided 2 to 3 consecutive negative cytology results previously have been obtained.<sup>11-13</sup>

### Cessation of screening: current guidelines

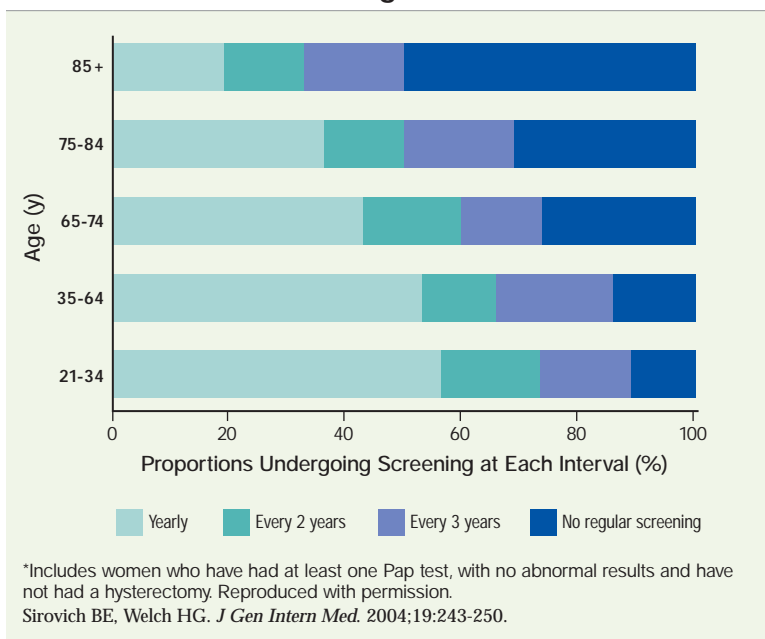
The USPSTF guidelines recommend cessation of screening at age 65 following consistent, negative Pap test results.<sup>13</sup> The ACS recommends that screening cease at age 70, following 3 consecutive, negative Pap test results and no positive cervical cytologic test results within the past 10 years. Even after age 70, cervical cytologic screening may be required in women who have human immunodeficiency virus (HIV) infection, are immunosuppressed, have a history of cervical cancer, or have been exposed to diethylstilbestrol in utero. Cytologic screening is unnecessary in women who have undergone a total hysterectomy unless CIN 2 or 3 has been documented. For these patients, 3 consecutive negative cytologic screening results are sufficient for discontinuation of screening.<sup>11,12</sup> A full comparison of cervical cancer screening recommendations is found in TABLE 2.

### Current guidelines for HPV DNA testing

Both ACS and ACOG have endorsed the use of the Pap test combined with HPV DNA screening in women 30 years and older. Those women who have negative results

**FIGURE 1**

**Screening frequency among US women\* exceeds guidelines**



**Management of Abnormal Cervical Cytologic Results**

Cervical cytologic screening yields an estimated 4% rate of ASC-US or ASC-H results, requiring further management or intervention.<sup>9</sup> In an effort to provide evidence-based recommendations for the management of women with cervical cytologic abnormalities, the American Society for Colposcopy and Cervical Pathology (ASCCP) published consensus guidelines in 2002 based on the 2001 Bethesda System.<sup>21</sup> These incorporated comprehensive literature reviews and data from ALTS, which were designed to evaluate various triage and management plans for low-grade cervical cytologic abnormalities.<sup>19,21</sup>

Initial management recommendations of the ASCCP vary depending on cytologic screening results. Repeat cytologic screening, colposcopy, or reflex HPV DNA testing for high-risk types is recommended for women with ASC-US. The HPV DNA testing is preferred because of its superior sensitivity to

for both cervical cytologic screening and high-risk type HPV DNA tests should be screened no more frequently than every 3 years.<sup>11,12</sup> The use of “reflex” HPV testing following an ASC-US Pap test is a cost-effective and more sensitive technique for identifying CIN 2 or higher when compared with cervical cytologic screening alone. In reflex testing, a sample for a high-risk HPV DNA test is obtained at the same time that cervical cytologic testing is performed. When liquid-based cytologic testing is used, the residual fluid from the cytologic specimen is suitable for HPV DNA testing.<sup>12,17,18</sup> Reflex HPV DNA testing does not appear to be particularly useful or cost-effective for managing women with LSIL cytologic results. Data from Atypical Squamous Cells of Undetermined Significance (ASCUS)/LSIL Triage Study (ALTS) revealed that approximately 83% of women with LSIL test positive for HPV DNA. This suggests that HPV DNA testing would not be cost-effective in women with low-grade cervical lesions.<sup>19</sup> Despite low specificity for low-grade cervical lesions, HPV DNA testing significantly increases the sensitivity of predicting HSIL and carcinoma; a prospective study demonstrated that women with negative cervical cytologic screens and positive HPV DNA test results were at much higher risk compared with women who were HPV DNA negative (assessed at 1 to 2 year intervals during a 5-year period).<sup>20</sup>

repeat cytology, as well as the convenience of eliminating a return to the clinician’s office. For women with ASC-H, LSIL, AGC, or AIS, an immediate colposcopy is preferred as the initial management option. Cytologic findings of HSIL indicate a significant risk of CIN 2 or 3 or cervical cancer, so immediate colposcopy with endocervical assessment is recommended. Further follow-up measures depend on the outcome of the assessment and are outlined in detail by the ASCCP.<sup>21</sup>

**Strategies to Reduce the Burden of Cervical Cancer Screening**

Approximately 11% of women receive no regular cervical cytologic screening.<sup>22</sup> However, many women receive cervical cytologic screening more frequently than required by current guidelines. More than half of all women without a history of abnormal smears receive Pap tests annually, although guidelines recommend biennial or triennial screening (FIGURE 1).<sup>11,12,22</sup> Investigations have suggested that excessive screening may lead to increased detection of abnormal results that likely would resolve spontaneously. Thus, unnecessary referrals for colposcopy and follow-up screening may occur.<sup>22,23</sup> In a cost-effectiveness modeling study, biannual Pap tests screening with HPV DNA testing represents a more cost-effective screening

strategy compared with cytologic testing alone at 2-year intervals.<sup>24</sup>

Patients for whom repeat screening is indicated often experience high levels of anxiety and psychological distress, perhaps because they have difficulty understanding that an abnormal Pap test result is not synonymous with a diagnosis of cancer. Studies have shown that women who need rescreening because of inadequate samples perceive themselves to be at higher risk for cervical cancer than do women with normal results. Anxiety about inadequate results may lead to lower rates of adherence for follow-up screening; an estimated 10% to 61% of women are noncompliant with recommendations for repeat screening or colposcopy.<sup>25,26</sup> False-positive results also cause anxiety and possible reluctance to participate in future screening.<sup>27</sup> The associations between suspected abnormal cytologic results, emotional burden, and future screening attendance highlight the importance of communication between the clinician and patient regarding the realistic risks of cervical cancer.<sup>28</sup>

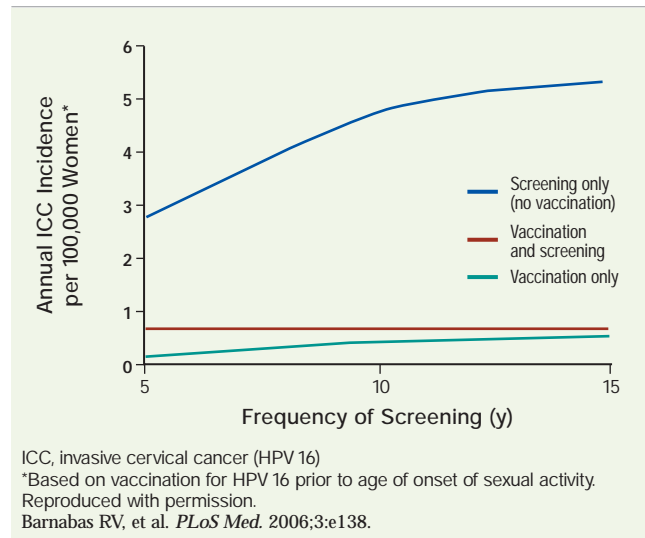
### Role of HPV Vaccine in Cervical Cancer Prevention

Vaccines that protect against the most common HPV types are expected to dramatically reduce the incidence of cervical cancer and other HPV-related diseases. HPV types 16 and 18 are prevalent in 70% to 80% of cases of cervical cancer.<sup>29,30</sup> Vaccination-modeling studies in women predict that vaccination against HPV 16/18 prior to the onset of sexual activity could potentially reduce overall rates of cervical cancer by 60% and would be expected to reduce the risk of cervical cancer associated with HPV 16 or 18 by 91% to 95%.<sup>31,32</sup> Furthermore, vaccination is anticipated to complement cervical cytologic screening and further reduce the risk of cervical cancer (FIGURE 2).<sup>32</sup>

A quadrivalent HPV vaccine has recently been approved by the US Food and Drug Administration (FDA) and is indicated for the prevention of HPV 6/11/16/18-related cervical cancer, genital warts, CIN, AIS, and vaginal/vulvar neoplasia in girls and young women (ages 9-26). The quadrivalent vaccine protects against HPV types 16/18, as well as the 2 most common low-risk HPV types 6/11. Although HPV 6 and 11 carry a low risk for causing cervical cancer, these 2 HPV types are associated with more than 97% of cases of genital warts, a condition that occurs in approximately 1% of the sexually active population.<sup>33,34</sup> Furthermore, HPV types 6 and 11 have been correlat-

**FIGURE 2**

**Effect of adding HPV vaccination to cervical cytologic screening programs on preventing invasive cervical cancer at different screening intervals**



ed with the development of CIN and recurrent respiratory papillomatosis (RRP), a rare, yet potentially fatal disease that can be transmitted from mother to child.<sup>35,36</sup> Two large phase 3 studies, Females United to Universally Reduce Endo-ectocervical (FUTURE I and II) disease, evaluating this vaccine have recently been completed and demonstrated 100% efficacy in protecting women against HPV 16/18-related CIN 1-3, AIS, cervical cancer, vulvar/vaginal neoplasia or cancer, and genital warts for up to 2 years.<sup>37,38</sup> Among women who were partially adherent to the vaccine protocol (ie, did not receive all 3 vaccinations), the quadrivalent vaccine demonstrated 97% efficacy in preventing HPV 6/11/16/18-related CIN 1-3, AIS, and cervical cancer and 95% efficacy in preventing genital warts and vulvar/vaginal neoplasias, suggesting that the quadrivalent vaccine is highly effective even in “real world” practice.<sup>37,38</sup>

A bivalent vaccine protecting against high-risk HPV types 16/18 is in clinical trials and has demonstrated 92% and 100% efficacy in preventing incident and persistent infection, respectively, in young women (15-25 years old) during an 18-month period.<sup>39</sup> A follow-up study demonstrated significant vaccine efficacy in preventing HPV 16/18 infection and 100% efficacy in preventing HPV 16/18-related CIN for up to 4.5 years.<sup>40</sup> Phase 3 trials of this vaccine are currently underway.

To maximize the public health benefit, prophylactic vaccines for HPV ideally should be administered to children and adolescents prior to the onset of sexual activity. An estimated 7.4% of children younger than 13 are sexually active and up to two thirds of 12th graders have had sexual intercourse.<sup>40</sup> Both high- and low-risk types of HPV infection also occur in men, suggesting that vaccination strategies should include boys and young men to further reduce the risk of HPV infection and transmission.<sup>41</sup> Vaccination-bridging studies support earlier vaccination in both genders, as boys and girls 10 to 15 years of age demonstrate significantly higher HPV titer levels following vaccination for HPV types 6/11/16/18 compared with 16- to 23-year-old women.<sup>42</sup>

HPV vaccination against high-risk types 16 and 18 is expected to dramatically reduce the incidence of abnormal cervical cells and cervical cancer, thus resulting in fewer follow-up screening procedures and treatments. Furthermore, HPV vaccines that also protect against low-risk types 6 and 11 are expected to prevent most cases of genital warts, RRP, and other cervical cytologic abnormalities caused by these HPV types. Assuming successful HPV vaccination programs, screening programs for cervical cancer will still be needed because candidate HPV vaccines are type specific and are not expected to protect against other genital HPV types.<sup>43</sup> The progression of cervical lesions to invasive cancer takes many years; therefore, the full impact of HPV vaccination programs in preventing cervical cancer would not be expected to be realized for a number of years.<sup>44</sup> Furthermore, routine cervical cytologic screening will remain necessary because some women will already be infected with HPV or will be outside of the HPV vaccination guidelines. Vaccination against HPV should be considered as a complementary strategy to further prevent cervical cancer and other HPV-related disease in addition to routine screening programs per guidelines. Furthermore, preventive vaccines that reduce HPV-related morbidity and mortality may also reduce the psychological distress associated with diagnosis and management.

## Conclusion

Infection with high-risk HPV types 16 and 18 is highly prevalent and is the primary etiologic agent for cervical cancer. These high-risk HPV types have also been implicated as the cause of the majority of cases of vaginal, vulvar, anal, and penile cancers. Low-risk HPV types 6 and

11 have been associated with the majority of cases of genital warts and RRP. Until recently, efforts to prevent HPV-related disease have been limited to screening programs. Recent revisions to clinical screening guidelines for cervical cytology have included HPV DNA testing as a cost-effective strategy that increases the predictive power to detect high-risk cervical lesions.

A quadrivalent HPV vaccine, formulated to protect against both high (16/18)-risk and low (6/11)-risk HPV types, was recently approved by the FDA for girls and women 9 to 26 years of age for the prevention of cervical cancer, cervical precancers, vulvar/vaginal precancers, low-grade cervical lesions, and genital warts. A bivalent HPV vaccine is currently being evaluated in phase 3 trials. When used in conjunction with cervical cytology screening, HPV vaccination is expected to substantially reduce the lifetime risk of cervical cancer, as well as health care costs and psychological distress associated with abnormal cytology.

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# Reducing HPV-related Clinical Disease Through Vaccination

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The morbidity and mortality related to human papillomavirus (HPV) infection constitute a major public health concern with many implications. HPV is a small DNA virus enclosed in an icosahedral protein capsid. Significantly, HPV infects only epithelial tissue, producing lesions that range from genital warts to cervical and other anogenital cancers.<sup>1</sup> In humans, more than 100 types of HPV have been identified with an estimated 40 types that infect the genital tract.<sup>2,3</sup>

## KEY POINTS

- The quadrivalent HPV vaccine was recently approved by the US Food and Drug Administration and is indicated for the prevention of HPV 6/11/16/18-related cervical cancer, genital warts, cervical adenocarcinoma *in situ*, as well as cervical, vaginal, and vulvar intraepithelial neoplasias in girls and women (ages 9-26).
- Phase 2 trials of a bivalent HPV vaccine that provides protection against the 2 most common cervical cancer-causing types, HPV 16 and 18, demonstrated that the vaccine is >90% and 100% effective at preventing incident and persistent HPV 16/18-associated infections for the first 4.5 years of follow-up.
- Immune responses to the quadrivalent HPV vaccine are approximately 2-fold higher in boys and girls compared with adolescent and young adult women, suggesting that vaccine efficacy may be maximized if administered to boys and girls before they become sexually active.
- If 70% of 12-year-old girls currently living in the United States were vaccinated against multiple high-risk HPV types, that would prevent an estimated 224,255 cases of HPV, 3316 cases of cervical cancer, and 1340 deaths from cervical cancer during their lifetimes.

The HPV types are generally classified based on whether they are associated with the development of cervical, vulvar, vaginal, penile, anal, and certain oropharyngeal cancers.<sup>1</sup> High-risk types have the capability to cause these cancers, whereas low-risk types do not. Cervical cancer is one of the prevailing causes of cancer death in women worldwide and is the most serious potential consequence of high-risk HPV infection.<sup>4</sup> Infection with HPV is necessary for the development of cervical cancer and is detected in more than 99% of all cases.<sup>5</sup> The 2 most important high-risk types are HPV 16 and 18. These 2 types are responsible for approximately 70% of cases of cervical cancer, with persistent HPV 16 infection alone responsible for more than half the cases.<sup>6</sup> They are also the most common genital HPV types found in routine population screening of normal women.<sup>6,7</sup>

The low-risk HPV types are associated with the development of cervical intraepithelial neoplasia (CIN 1 and some CIN 2), genital warts, and recurrent respiratory papillomatosis (RRP).<sup>8-10</sup> Infection of low-risk HPV 6 or 11 is the most common cause of genital warts; it is detected in approximately 97% of cases of condyloma acuminata.<sup>9</sup> Types 6 and 11 are also responsible for an estimated 80% of cases of RRP, a relatively rare but serious condition in children and adults that typically results from HPV transmission from mother to child during delivery. RRP commonly requires multiple surgical interventions to remove the obstructions from the larynx.<sup>10-12</sup>

## ■ HPV Virus-like Particle Vaccines Are not Infectious or Oncogenic

Historically, a number of vaccines have been developed using attenuated viruses, including smallpox, measles, and polio.<sup>13,14</sup> Developing a potential HPV vaccine with a live, attenuated virus has proved problematic because HPV is difficult to cultivate *in vitro*. Additionally, many had concerns regarding the administration of even an

attenuated vaccine containing DNA known to be potentially oncogenic. Therefore, noninfectious HPV vaccines have been developed using recombinant L1 capsid proteins synthesized in yeast, which organize into empty virus-like particles (VLPs) identical to the capsid surrounding the naturally occurring viral DNA, yet containing no genetic material.<sup>15,16</sup> The lack of genetic material in HPV VLPs removes any possibility that the vaccine could induce HPV manifestations, including cancer, and the inclusion of the protein capsid makes it an ideal candidate for use as a prophylactic HPV vaccine targeting rejection of the capsid when it first comes into contact with the epithelium.

### ■ HPV Vaccines Elicit a Strong Immune Response to HPV Infection: A Review of the Literature

Proof of principal studies of candidate monovalent HPV vaccines for types 11, 16, and 18 have been conducted to evaluate their immunogenicity and safety. Young women were predominantly studied (one trial included men); those who completed the protocol received 3 inoculations, typically at 0, 2, and 6 months.<sup>15-18</sup> Vaccines protecting against these 3 HPV types demonstrated that HPV VLPs induce type-specific antibody titers that are significantly higher than those produced by natural infection.<sup>15-18</sup> Among women receiving an HPV 18 vaccine, 86% had serologically converted at 3 months and 100% at 7 months postvaccination.<sup>15</sup> Immune responses to HPV are type-specific; therefore, vaccines combining HPV VLPs for multiple, common HPV types would be expected to increase their efficacy in preventing HPV-related disease.

### ■ Bivalent HPV Vaccine Protects Against High-risk HPV Types 16/18

A bivalent HPV vaccine is currently under development that protects against the 2 most common oncogenic, high-risk HPV types: 16 and 18. A phase 2 placebo-controlled, randomized clinical trial involving more than 1000 young women (ages 15-25) vaccinated with an HPV 16/18 bivalent vaccine on Day 1, Month 1, and Month 6 demonstrated 92% efficacy against incident HPV 16 and 18 infections and 100% efficacy against persistence of either of these 2 types.<sup>19</sup> Women receiving all 3 HPV 16/18 vaccinations were included in a follow-up study of up to 4.5 years, which demonstrated continued efficacy against infection by these 2 types, as well as no cases of type-specific CIN.<sup>20</sup> Furthermore, the vaccine was

well tolerated and not associated with any serious adverse effects related to the vaccination.<sup>19</sup> Phase 3 trials of the bivalent vaccine are currently underway.

### ■ Quadrivalent HPV Vaccine Protects Against High- (16/18) and Low- (6/11) risk HPV Types

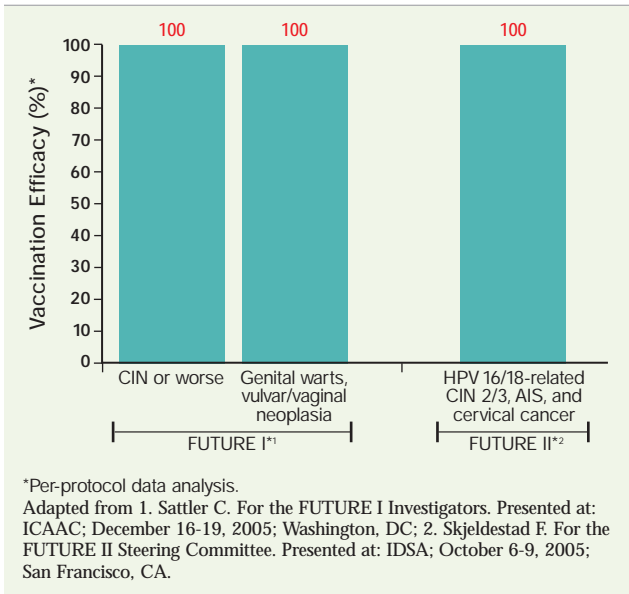
Recently, a quadrivalent HPV vaccine has become commercially available; it offers protection against HPV types 16 and 18, as well as the 2 most common HPV types (6 and 11) associated with genital warts and RRP. The quadrivalent vaccine is indicated for the prevention of HPV 6/11/16/18-related cervical cancer, genital warts, cervical adenocarcinoma *in situ* (AIS), as well as cervical, vaginal, and vulvar intraepithelial neoplasias in girls and women (ages 9-26).

A phase 2 study involving more than 1000 women (ages 16-23) randomly assigned to receive the quadrivalent 6/11/16/18 vaccine or placebo on Day 1, Month 2, and Month 6 demonstrated 89% and 100% efficacy in the prevention of HPV 6/11/16/18-related persistent infection and disease, respectively.<sup>21</sup> The quadrivalent vaccine was also 100% effective at preventing genital warts.<sup>21</sup> The vaccine was well tolerated with no vaccine-related serious adverse events reported.<sup>21</sup>

The HPV vaccines are prophylactic and designed to be administered, ideally, prior to the onset of sexual activity. Although the preponderance of HPV studies have included young women, men are at similar risk for HPV infection and implicated in the transmission of HPV.<sup>22</sup> The majority of adolescents become sexually active prior to completing high school; therefore, a study with the quadrivalent HPV 6/11/16/18 vaccine was developed to assess immunogenicity and safety in a younger sample of sexually naïve girls and boys (ages 10-15).<sup>23,24</sup> Girls and boys receiving the quadrivalent vaccine demonstrated geometric mean titers (GMTs) of type-specific antibodies at Month 7 (1 month following the third and final vaccine injection) that were 1.67 to 2.7 times higher than those observed when the vaccine was administered to adolescents and young women (ages 16-23).<sup>24</sup> Side effects were similar and minor in both the placebo and vaccine groups.<sup>24</sup> An additional 1-year study in children and adolescents (ages 9-15) receiving the quadrivalent vaccine further supports the previous findings of a robust anti-HPV immune response, as this trial also showed that GMTs were substantially higher in boys and girls when compared with adults receiving the quadrivalent vaccine.<sup>25</sup> Taken

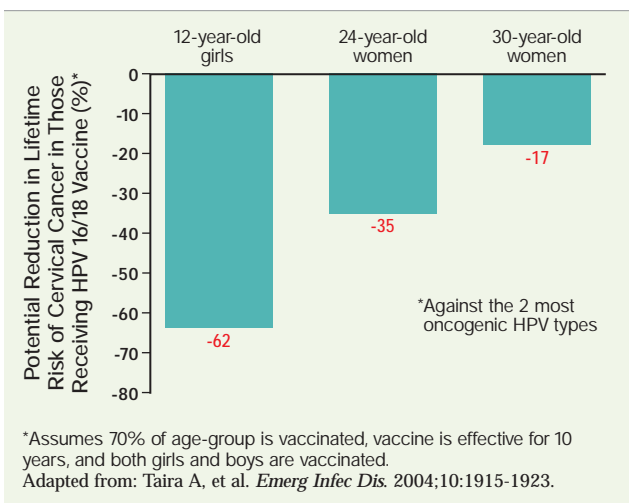
**FIGURE 1**

**HPV vaccine reduces incidence of HPV 6/11/16/18-related CIN, AIS, cancer, and genital warts**



**FIGURE 2**

**Lifetime risk reduction for cervical cancer after vaccination**



together, the results of these 2 trials support the high immunogenicity and safety of the quadrivalent HPV vaccine in boys and girls (ages 9-15), and the potential for a stronger immune response following vaccine administration.

**Clinical Impact of Quadrivalent HPV Vaccine on Preventing HPV-related Disease: Phase 3 Trial Results**

Two large phase 3 trials of the quadrivalent HPV 6/11/16/18 vaccine, referred to as Females United To Unilaterally Reduce Endo-ectocervical (FUTURE) disease, have demonstrated promising results. In FUTURE I, 5455 women (ages 16-23) were randomly assigned to receive the quadrivalent HPV vaccine or placebo on Day 1, Month 2, and Month 6 with Pap tests performed at regular intervals.<sup>26</sup> Following a 2-year follow-up, the vaccine demonstrated 100% efficacy in preventing HPV 6/11/16/18-related CIN, genital warts, and vulvar/vaginal neoplasia in women receiving all 3 vaccinations who were naïve to these 4 types at Day 1 and through the period of vaccination [the per-protocol (PP) population]. Vaccine efficacy was 97% in the modified intention to treat (MITT) population. This population included women who were naïve to all 4 types at Day 1 but who did not complete all 3 injections or had 1 more of these HPV types detected prior to receiving all 3 doses.<sup>26</sup> FUTURE II, a similarly designed trial involving 12,167 women (ages 16-23), reported 100% efficacy in the prevention of HPV 16/18-related CIN 2/3, AIS, and cancer through 2 years of follow-up in the PP population (FIGURE 1).<sup>27</sup> In contrast, 21 cases of CIN 2/3 or AIS related to these 2 types developed in the group receiving the placebo. Efficacy remained high at 97% in the MITT population.<sup>27</sup> The results of FUTURE I and II demonstrate that the quadrivalent HPV 6/11/16/18 vaccine has the potential to substantially reduce the risk of HPV infection and related diseases, even among women representing a “real world” population that may not be completely adherent to the vaccination schedule or who have already become sexually active.

**Projected Long-term Health Benefits of HPV Vaccination**

Vaccination against the most common pathologic HPV types has the potential to alleviate many of the burdens associated with HPV infection. Cost-effectiveness modeling studies have concluded that if 70% of 12-year-old girls currently living in the United States were vaccinated against high-risk HPVs, an estimated 224,255 cases of HPV infection, 3316 cases of cervical cancer, and 1340 deaths from cervical cancer would be prevented during the lifetime of this cohort.<sup>28</sup> Furthermore, the estimated lifetime risk of developing cervical cancer would be reduced by approximately 62% for 12-year-

old girls who receive an HPV 16/18 vaccine prior to exposure to either of these 2 types. For the population as a whole, the model assumes that 70% of all 12-year-old girls are vaccinated and that the vaccine efficacy lasts 10 years (FIGURE 2).<sup>29</sup> The model also shows lifetime cervical cancer risk reductions for 24- and 30-year-old women who opt for catch-up vaccination the first year of availability.<sup>29</sup> The emotional distress and concerns about developing cervical cancer that often accompanies an abnormal cervical cytologic result should also be reduced coincident with the reduction in the number of abnormal Pap test reports following widespread HPV vaccination.<sup>30</sup>

Prevention programs that include HPV vaccination must continue to provide cervical cytologic screening, as not all HPV types responsible for cervical cancer are in the vaccine, and women already exposed to 1 or more of these types, or not receiving the vaccine, will continue to be at risk. Combining HPV vaccination prior to the age of onset of sexual intercourse with routine cervical screening beginning later than presently recommended would be most cost-effective and have the greatest impact on cervical cancer incidence and mortality. However, recommendations for the age of onset of screening will likely remain age 21 or 3 years from first intercourse until duration of vaccine efficacy and other unknown parameters become clear.<sup>31</sup>

## Fostering Acceptance of an HPV Vaccine

To maximize the prophylactic protection of an HPV vaccine, the ideal population for HPV immunization includes children and adolescents before they become sexually active. Some parents have been concerned that vaccination of their children against a sexually transmitted infection (STI) may be construed as permission to engage in early and promiscuous sexual activity.<sup>32</sup> Consent for immunization against HPV may also become a barrier for adolescents who are unable to discuss sexual issues with their parents.<sup>33</sup>

Clinicians who administer vaccines will be the primary source of information for patients and adolescents about the benefits of HPV vaccination.<sup>34</sup> One study reported that, among parents and guardians initially opposed to or undecided regarding HPV vaccination for their children, the rate of acceptance of vaccination increased from 23% to 37% and 22% to 65%, respectively, following participation in an educational program.<sup>35</sup> These results highlight the importance of educational initiatives designed to promote vaccine acceptance

by effectively communicating the risks and consequences associated with HPV infection.

## Conclusion

Vaccines have historically provided a cost-effective means of reducing the burden associated with potentially fatal diseases such as polio and smallpox. A vaccine directed against the most common high-risk HPV types (16 and 18) is expected to reduce the incidence of CIN 2/3, cervical cancer, and abnormal cervical cells. In addition, vaccinating against common low-risk HPV types (6 and 11) should provide protection against the majority of genital warts and cases of RRP. A bivalent HPV vaccine that protects against HPV types 16 and 18 has demonstrated promising results in phase 2 studies. A quadrivalent vaccine that protects against HPV types 6, 11, 16, and 18 is now available and indicated for the prevention of HPV-related disease, including cervical cancer, AIS, CIN 1-3, vaginal/vulvar neoplasia, and genital warts in girls and young women (ages 9-26). For an HPV vaccine to be most effective, it should be administered to adolescents and children before they become sexually active; immunogenicity-bridging data support this concept as girls and boys demonstrate greater immune responses to HPV vaccination than do young adults. Providing patients and their families with information about HPV vaccination will allow them to make informed and educated decisions regarding HPV vaccination, thereby yielding the greatest public health benefits.

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## ► New Options in HPV Prevention

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