

Prevention Is Now a Reality: Reducing the Burden of Cervical Cancer and Other HPV-Related Diseases

What We Know About HPV

- ➔ Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States
- ➔ Infection with high-risk (ie, oncogenic) HPV types (16, 18) is associated with the development of cervical, anogenital, and oropharyngeal cancers as well as high-grade cervical change, whereas infection with low-risk types (6, 11) is associated with the development of genital warts, low-grade cervical change, and recurrent respiratory papillomatosis
- ➔ Two vaccines have been developed that protect against infection caused by the most common high-risk HPV types and thus prevent HPV-related disease. The currently available quadrivalent vaccine also protects against the 2 most common low-risk HPV types

Learning Objectives

After completing this activity, participants should be better able to:

- ➔ Describe the epidemiology and health consequences of HPV infection
- ➔ Review the latest clinical data on HPV vaccines
- ➔ Summarize the benefits of HPV vaccination for discussion with patients and their parents
- ➔ Implement practical strategies to overcome barriers to HPV vaccination

Prevalence of HPV

More than 20 million Americans are infected with human papillomavirus (HPV), currently the most common sexually transmitted infection (STI) in the United States. It is

HPV vaccination offers an opportunity to prevent HPV infection and the health consequences of HPV-associated diseases

Should risk-based strategies be used to identify candidates for HPV immunization? See page 73

estimated that 75% of all sexually active individuals will be exposed to HPV at some point in their lives,¹ with about 6.2 million people becoming infected each year.² HPV places a large economic burden on the healthcare system—at \$1.6 billion annually, HPV ranks second only to HIV in direct medical costs incurred from STIs.³

Human papillomavirus infection is most commonly found among young, sexually active females. Persons between the ages of 15 and 24 years constitute 74% of all new HPV infections.⁴ Although prevalence peaks between the ages of 20 and 24 years, the Centers for Disease Control and Prevention (CDC) reported that 24.5% of adolescent females between 14 and 19 years of age are infected with HPV. However, HPV infection is also prevalent among adult 25- to 59-year-old women, at a rate of 20% to 28%.^{5,6} Furthermore, recent studies have demonstrated that up to 73% (depending on the anatomic site tested) of the male population is also infected with HPV.⁷ Clearly, HPV infection is a problem not only for sexually active young women, but also for all sexually active adults.

HPV Types and Associated Risks

There are more than 100 different types of HPV, which are classified into 2 broad groups based on oncogenic potential: high-risk and low-risk types.⁸ High-risk HPV types can lead to high-grade cervical dysplasias and cancer. The high-risk types are also implicated in many anal, penile, and head and neck cancers, whereas infection with low-risk HPV types can lead to low-grade cervical dysplasias, genital warts, and recurrent respiratory papillomatosis (RRP), a rare but potentially fatal disease. In women, HPV infection has been identified in >99% of all cervical cancers, with HPV types 16 and 18 being responsible for about 70% of cases (Figure 1). HPV infection can also cause adenocarcinoma in situ (AIS), cervical intraepithelial neoplasia (CIN) grades 1 to 3, vulvar intraepithelial neoplasia (VIN), and vaginal intraepithelial neoplasia (VaIN) grades 2 and 3.⁹ HPV types 6 and 11 are responsible for >90% of genital warts and the majority of cases of RRP.^{10,11}

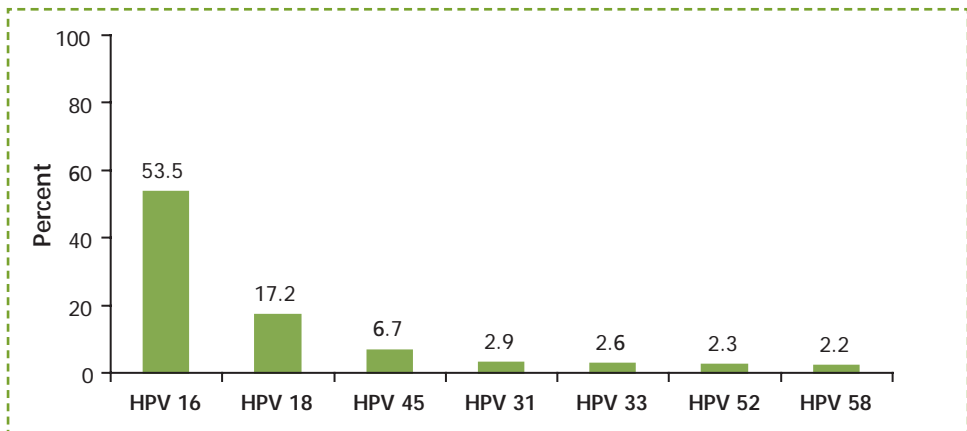


Figure 1. Relative contribution of HPV types to cervical cancer: all world regions combined. Muñoz N et al.¹⁶

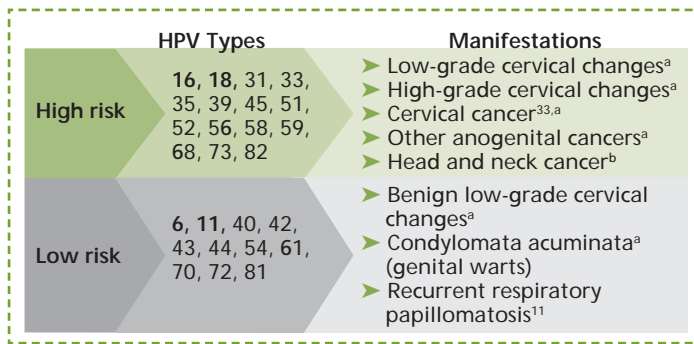


Figure 2. Common HPV types associated with benign and malignant disease. Wiatrak BJ¹¹; Muñoz N et al³³; Koutsky LA et al. *Epidemiol Rev*. 1988; 10:122-163^a; Hansson BG et al. *Acta Otolaryngol*. 2005;125: 1337-1344.^b

Clinical Manifestations of HPV Infection

High-Risk HPV Infection in Women

In women, infection with high-risk HPV types can have many adverse outcomes, including abnormal cytology or cancer of the cervix, as well as head and oropharyngeal, vulvar/vaginal, and anal cancers (Figure 2). Cervical cancer, the most common HPV-related cancer, is the second most common cancer in women worldwide—an estimated 400,000 to 500,000 cases are diagnosed annually.^{9,12} In the United States, the estimated incidence of cervical cancer is 8.4 cases per 100,000 women.¹³ While Pap screening has reduced the incidence and morbidity, approximately 11,070 new cases of cervical cancer and 3870 related deaths are still expected in the United States during 2008.¹⁴ In addition, an estimated 2 million cases of abnormal cervical cytology occur each year due to infection with low- and high-risk HPV types, including 1.25 million low-grade and 330,000 high-grade cases of squamous intraepithelial lesions.¹⁵ Although cervical cytologic change and cancer can be caused by many of the high-risk HPV types, >80% of cases can be attributed to only 4 types: 16, 18, 31, and 45.¹⁶ It is also thought that HPV will be responsible for 60% to 90% of the 5670 cases of vulvar/vaginal cancers expected to occur in 2008.^{14,17} Furthermore, HPV is implicated in approximately 90% of anal cancers and 12% to 76% of oropharyngeal cancers, which affect both men and women.^{9,18}

High-Risk HPV Infection in Men

Recent studies have demonstrated that up to 73% of the male population is infected with HPV DNA at many different anatomic sites, including the glans, urethra, corona, shaft, scrotum, foreskin, anus, rectum, and perianal areas, and in semen and urine specimens.⁷ In men, debilitating conditions associated with infection by high-risk HPV types include penile, anal, and oropharyngeal cancers. Approximately 1250 cases of penile cancer are expected in 2008, 40% of which will be attributed to HPV.^{9,14}

Infection With Low-Risk HPV Types in Men and Women

The many strains of low-risk HPV can cause genital warts, low-grade cervical dysplasia, and RRP. HPV types 6 or 11 are responsible for approximately 90% of cases of genital warts, which affect about 1 million sexually active Americans (1% of the population) per year, causing emotional distress and significant treatment burden.¹⁹ About two-thirds of

women exposed to HPV type 6 or 11 develop genital warts within 3 years,²⁰ with the risk of infection rising as the number of sexual partners increases (Figure 3).^{10,21} The majority of genital warts cases are asymptomatic, although many patients report painless bumps, pruritus, and discharge. The presentation of genital warts is frequently associated with cauliflower-like lesions and single or multiple pearly, filiform, or plaque-like papules.²²

Recurrent respiratory papillomatosis is also caused by HPV infection in about 80% of all

cases, usually by HPV types 6 and 11.²³ The condition is characterized by recurring papillomas in the respiratory tract that require multiple surgical interventions. Although RRP is rare (incidence of 3.96 per 100,000 children), fatalities can result from severe airway obstruction, pulmonary failure, or malignant transformation. RRP is thought to occur as a result of vertical transmission of HPV infection from a mother to her infant, although infection via sexual contact is also possible.¹¹ RRP can also manifest several years after infection as juvenile- or adult-onset cases.²⁴ All types of RRP are associated with high treatment costs and significant morbidity.²⁵

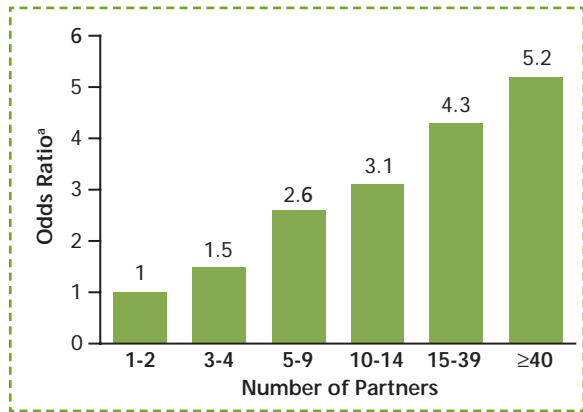


Figure 3. Number of sexual partners and risk of genital warts. ^aAdjusted for years since first sexual intercourse, lifetime number of regular partners, smoking, chlamydia, and even Pap smear. Munk C et al.²¹

Transmission and Natural History of HPV Infection

HPV can be transmitted by almost any type of sexual activity, and having a large number of lifetime sexual partners is the leading risk factor.²⁶ HPV infection is often acquired soon after the onset of sexual activity—within 24 months in approximately one-third of women.²⁷ Additional risk factors for HPV infection in women are sexual behavior (eg, earlier age at first intercourse), the presence of vulvar warts, infection with herpes simplex virus, having an older sex partner, having a new sex partner, and using illegal drugs within the last year.^{28,29}

Risk factors for HPV infection for men include having a high number of sexual partners and having sex with men.^{30,31} Condoms offer partial protection against HPV transmission.³²

In women, most HPV infections are transient and become undetectable 1 to 2 years after infection, even with highly sensitive diagnostic tests. Persistent infection, however, is a serious health concern, since it is more likely to lead to cervical cancer (Figure 4).¹⁵ Persistence of HPV infection and the development of cervical cancer are especially common with infections caused by HPV type 16.³³ The median duration of HPV infection is approximately 8 months; approximately 70% of infected young women become HPV seronegative after 24 months.^{34,35} However, even with only transient HPV infection, HPV-related disease is still a significant cause of morbidity in the majority of these women.

Primary Prevention of HPV Infection

Two vaccines have been developed to protect against the most common strains of HPV. A US Food and Drug Administration (FDA)-approved quadrivalent HPV vaccine is available that protects against the 2 most common high-risk HPV types (16 and 18) and the 2 most common low-risk HPV types (6 and 11); and an investigational bivalent HPV vaccine, which protects against types 16 and 18, is currently under FDA review.

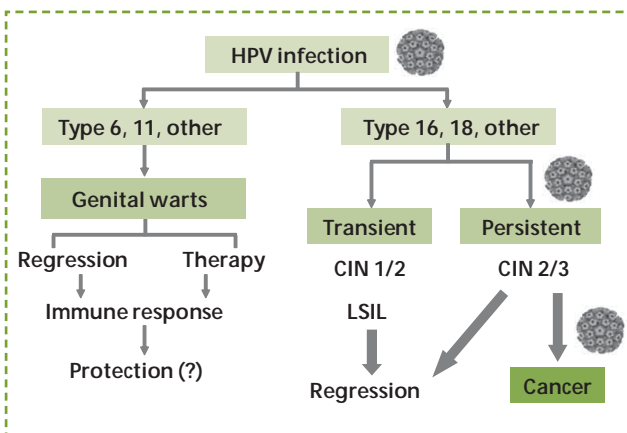


Figure 4. The natural history of HPV and cervical cancer. LSIL = low-grade squamous intraepithelial lesion. Adapted from Schiffman M, Kjaer SK. *J Natl Cancer Inst Monogr.* 2003;31:14-19.

Quadrivalent HPV Vaccine

Clinical Results

The Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) trials were large-scale, phase 3, randomized, double-blind, placebo-controlled studies that examined the immune response produced by, as well as the clinical efficacy and safety of, the quadrivalent HPV vaccine in females 15 to 26 years of age. The average duration of follow-up was 3 years.

FUTURE I enrolled 5455 females aged 16 to 23 years who were followed up for an average of 3 years after receipt of 3 doses of either vaccine or placebo. Pap tests were performed regularly. In the per-protocol analysis, the quadrivalent HPV vaccine was 100% effective compared with placebo (0 vs 65 cases, respectively) in preventing CIN 1 to 3 or AIS associated with vaccine-related HPV types. The vaccine was also 100% effective compared with placebo (0 vs 60 cases, respectively) in preventing HPV vaccine-type-related genital warts, VIN/VaIN, and perianal intraepithelial lesions. An analysis of the intention-to-treat population, which included women with prevalent infection or disease caused by vaccine- and nonvaccine-type HPVs, showed a reduction in the incidence of cervical and vulvar/vaginal lesions, regardless of the causative HPV type, by 20% and 34%, respectively.³⁶

FUTURE II enrolled 12,167 females aged 15 to 26 years who received 3 doses of either vaccine or placebo, followed by periodic Pap and HPV tests during an average 3-year follow-up. In this study, quadrivalent HPV vaccine efficacy was 98% against CIN 2/3 and AIS in the per-protocol population (Figure 5). In the placebo group, 42 females were diagnosed with CIN 2/3, cervical cancer, or AIS associated with HPV type 16, 18, or both, compared with only 1 female in the vaccine group. In this single case, the subject tested positive for HPV 52 at baseline and in 5 histology specimens collected thereafter.³⁷

Further analysis of data from a combined enrollment of 20,583 females aged 16 to 26 years from FUTURE I, FUTURE II, and 2 earlier-phase trials provided additional

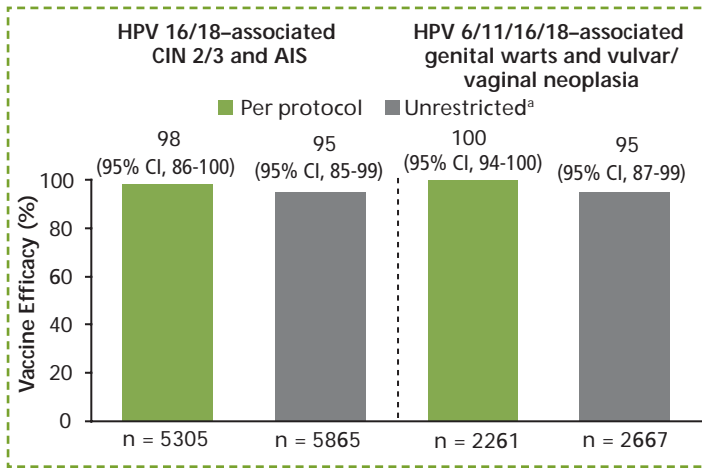


Figure 5. Quadrivalent HPV 6/11/16/18 vaccine: 3-year results.

^aSubjects who were seronegative and PCR negative for vaccine types at enrollment were included, even if abnormal cervical cytology protocol violations were present. AIS = adenocarcinoma in situ; PCR = polymerase chain reaction. Garland SM et al³⁶; FUTURE II Study Group.³⁷

evidence for the efficacy of the quadrivalent HPV vaccine. The primary end point in this analysis at the mean 3-year follow-up was HPV 16/18-related CIN 2/3, AIS, or cervical cancer. In the 17,129 women who were HPV 16/18 negative at the start of the study, vaccine efficacy was a statistically significant 99% for the primary end point. In the intent-to-treat analysis of all randomized women (including those who were positive for HPV type 16 or 18 at the start of the study), vaccine efficacy was 44%, with all but 1 case occurring in vaccine recipients who were previously HPV type 16 or 18 positive.³⁸

In the FUTURE studies, adverse events among recipients of the quadrivalent HPV vaccine included pain, swelling, erythema, and fever. With the exception of fever, all were injection-site reactions that occurred within 1 to 5 days postvaccination (Table 1). Few subjects (0.1%) discontinued due to adverse events.^{36,37}

Although the quadrivalent HPV vaccine has demonstrated consistent efficacy in large clinical trials, duration of protection is equally important toward reducing the burden of HPV-related disease. In a study in which 241 females aged 16 to 23 years were followed up for ≤5 years with regularly scheduled gynecological screening and Pap testing, the quadrivalent HPV vaccine was associated with 96% reduction

TABLE 1

Adverse Events Postvaccination With Quadrivalent HPV Vaccine

Injection Site (1 to 5 days postvaccination)			
	Quadrivalent HPV Vaccine (%) (n = 5088)	Placebo (aluminum) (%) (n = 3470)	Placebo (saline) (%) (n = 320)
Pain	83.9	75.4	48.6
Swelling	25.4	15.8	7.3
Erythema	24.6	18.4	12.1
Systemic Adverse Events (1 to 15 days postvaccination)			
	Quadrivalent HPV Vaccine (%) (n = 5088)	Placebo (%) (n = 3790)	
Fever	10.3	8.6	

Few subjects (0.1%) discontinued due to adverse experiences. Gardasil [package insert].⁴¹

in the combined incidence of HPV type 6/11/16/18–related persistent infection or disease. At 5 years postenrollment, the vaccine also reduced HPV type 6/11/16/18–related CIN and genital warts by 100%, providing encouraging information regarding long-term vaccine efficacy in protection against clinically relevant disease.³⁹ In addition, a challenge dose of quadrivalent HPV vaccine administered at month 61 induced immune memory, further confirming the long-lasting immunogenicity of the vaccine.⁴⁰

Based on results from the FUTURE I and II studies, in June 2006 the quadrivalent HPV vaccine was approved by the FDA for the prevention of HPV 6/11/16/18–associated cervical cancer, AIS, CIN grades 1 to 3, VIN and VaIN grades 2 and 3, and genital warts in girls and women aged 9 to 26 years.⁴¹ Subsequently, the CDC added the quadrivalent HPV vaccine to its list of recommended vaccines for administration to all 11- to 12-year-old girls, girls and women aged 13 to 26 years who have not yet been vaccinated or completed the vaccination series, as well as girls as young as 9 years of age at the clinician’s discretion. The availability of the quadrivalent HPV vaccine has not changed recommendations for cervical cancer screening.⁴²

Bivalent HPV Vaccine

Clinical Results

The Papilloma Trial Against Cancer in Young Adults (PATRICIA) was a large, phase 3, randomized, placebo-controlled trial designed to assess the efficacy of the bivalent HPV 16/18 vaccine in preventing CIN 2/3 lesions associated with HPV type 16 or 18 in 18,644 females aged 15 to 25 years who were sero- and DNA-negative for the vaccine HPV types at baseline. Median follow-up was 14.8 months. In an interim analysis of the trial data, the bivalent HPV vaccine demonstrated 90% efficacy in preventing CIN 2/3 lesions and 89% efficacy against CIN 1-3 lesions in women uninfected with HPV type 16 or 18 but possibly infected with other oncogenic HPV types (Figure 6).⁴³

Further support for bivalent HPV vaccine efficacy comes from a phase 2 study extension in which 776 women who received all 3 doses of the bivalent HPV vaccine or placebo were followed up for ≤4.5 years. In this analysis, the bivalent HPV vaccine was 97% and 100% effective at preventing HPV 16/18–related incidents and persistent infection, respectively, during the combined initial and follow-up phases. More than 98% of vaccine

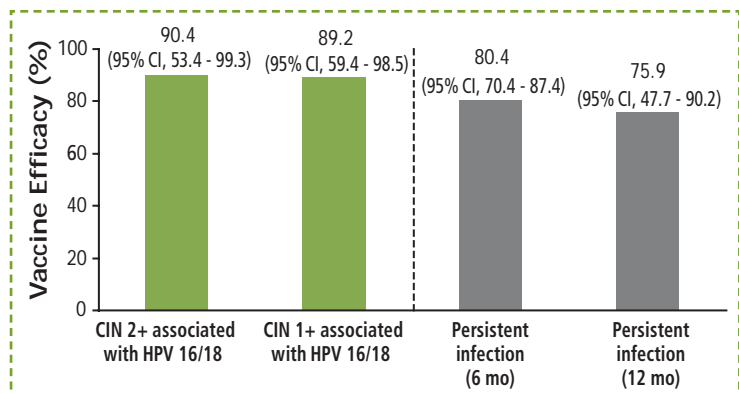


Figure 6. Phase 3 bivalent HPV 16/18 vaccine interim analysis: efficacy. Mean follow-up: 14.8 months. Included subjects with normal or low-grade cytology at month 0, who received at least 1 dose of vaccine. Paavonen J et al.⁴³

recipients remained seropositive for HPV 16 and 18 at all time points, with an immune response that was significantly higher than that seen in natural infection.⁴⁴ When these 776 women were re-analyzed 6.4 years after vaccination, 98% had remained HPV 16 and 18 seropositive, with 100% vaccine efficacy against CIN 2/3. This further demonstrates that the vaccine remains efficacious for a significant period of time postvaccination.⁴⁵

Vaccine-related adverse events that occurred in $\geq 5.0\%$ of bivalent HPV vaccine recipients, and more frequently than those observed with placebo, included pain, swelling, redness, fatigue, headache, myalgia, gastrointestinal upset, arthralgia, elevated body temperature, urticaria, and rash. All adverse events occurred within 1 to 7 days post-vaccination (Table 2).⁴³

The bivalent HPV vaccine is currently under review by the FDA.

Expanding Benefits of HPV Prevention

Cross-Protection With High-Risk Nonvaccine HPV Types

Although most occurrences of high-risk HPV-related disease are a result of type 16 or 18 infections, many other high-risk HPV types contribute to the overall disease burden. HPV types are organized into genera and species based on their L1 (major capsid protein) gene. HPV type 16 is part of the A9 family, which also includes HPV types 31, 33, 35, 52, and 58; whereas type 18 is part of the A7 family that includes HPV types 39, 45, 59, and 66. Since these other nonvaccine HPV types contain capsid protein genes similar to those found in strains 16 and 18, it is possible that HPV vaccines may confer some cross-protection against these nonvaccine types.^{43,46} When

TABLE 2

Phase 3 HPV 16/18 Interim Analysis: Adverse Events

Injection site symptoms ^a	Vaccine Group (%) (n = 3077)	Control Group (%) (n = 3080)
Pain	2786 (90.5)	2402 (78.0)
Redness	1348 (43.8)	841 (27.6)
Swelling	1292 (42.0)	609 (19.8)
General symptoms ^a		
Fatigue	1771 (57.6)	1652 (53.6)
Headache	1665 (54.1)	1579 (51.3)
Myalgia	1606 (52.2)	1382 (44.9)
Gastrointestinal	850 (27.6)	841 (27.3)
Arthralgia	633 (20.6)	551 (17.9)
Raised temperature ^b	381 (12.4)	337 (10.9)
Rash	312 (10.1)	258 (8.4)
Urticaria	298 (9.7)	244 (7.9)

^aParticipants who reported a specified symptom within 7 days of vaccine injection.

^bDefined as axillary or oral temperature $\geq 37.5^\circ\text{C}$.

Paavonen J et al.⁴³

data from the FUTURE studies were analyzed, the quadrivalent HPV vaccine demonstrated a combined 45% efficacy against persistent infection with HPV types 31 or 45, and an overall efficacy of 28% against HPV types 31, 33, 45, 52, or 58. The study also showed the quadrivalent HPV vaccine to be 62% effective in preventing HPV 31- or 45-related CIN 2/3 or AIS. An overall 38% efficacy was demonstrated in preventing CIN 2/3 or AIS caused by any of the 10 evaluated high-risk HPV types.⁴⁶ The bivalent vaccine was significantly efficacious against 6-month persistent infection with HPV types 31 (36%), 45 (60%), and 52 (32%), and 12-month persistent infection across all nonvaccine oncogenic HPV types (27%).⁴³ Together, these data indicate that the HPV type 16 and 18 antigens in both the quadrivalent and bivalent vaccines induce modest cross-protection against several high-risk nonvaccine HPV types that underlie 20% of all cervical cancers. Although findings of cross-protection are not completely consistent for both vaccines, modest degrees of cross-protection against nonvaccine oncogenic HPV types may translate to a substantial reduction in disease incidence.

Reduction in Cervical Procedures and Abnormal Pap Test Results

Organized screening has reduced cervical cancer rates, but it can be a very costly process. Although screening for cervical cancer has reduced its incidence, in the United States the costs of testing for and treating cervical abnormalities are higher than \$2 billion per year. An analysis of combined data from 3 randomized, placebo-controlled studies of 18,150 females aged 16 to 26 years, who were followed up for an average of 4 years, demonstrated a reduction in the number of abnormal Pap test results, colposcopies, cervical biopsies, and definitive therapies among recipients of the quadrivalent HPV vaccine. In addition, administration of the quadrivalent HPV vaccine to this group of women reduced the incidence of cervical procedures and abnormal Pap test results regardless of the causative HPV strain.⁴⁷

Preventing HPV-Related Disease in Adult Women

Although HPV vaccination is currently approved by the FDA only for 9- to 26-year-old females, women >26 years of age remain at risk for HPV infection and its related diseases. Data from the National Health and Nutrition Examination Survey (NHANES) showed that although HPV infection is most prevalent in women between 20 and 24 years of age (45%), infection also remains prevalent in women 25 to 59 years of age (20% to 28%) (Figure 7).⁵ Additionally, data collected by the National Cancer Institute have shown that cervical cancer incidence and mortality are greatest in women ≥ 50 years of age.⁴⁸

Recent data have demonstrated that the quadrivalent HPV vaccine is highly efficacious in adult women, as very few have been exposed to all vaccine HPV types. The placebo-controlled FUTURE III study included 3817 women aged 24 to 45 years to assess the efficacy of the quadrivalent HPV vaccine in an older population. The vaccine was 91% effective in reducing the combined incidence of HPV 6-, 11-, 16-, and 18-associated persistent infection (as defined by the detection of the same HPV type ≥ 2 times over the approximate median follow-up period of 6 to 12 months), CIN, or external genital lesions (Figure 8).⁴⁹ Although no published efficacy data currently exist for the bivalent HPV vaccine in adult women, it has demonstrated immunogenicity in females between 15 and 55 years of age.⁵⁰

Prevention Is Now a Reality: Reducing the Burden of Cervical Cancer and Other HPV-Related Diseases

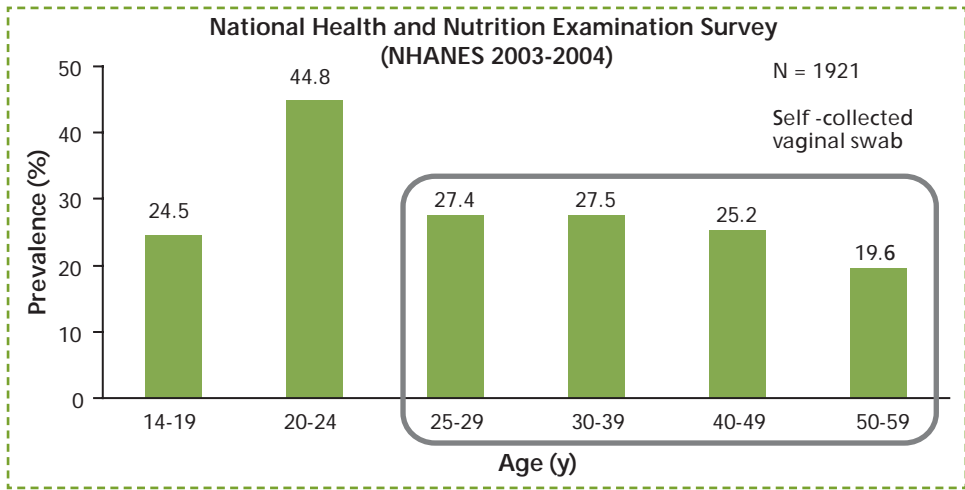


Figure 7. HPV infection remains prevalent among women 25 to 59 years of age. Adapted from Dunne EF et al.⁵

Preventing HPV-Related Diseases in Men

Human papillomavirus is implicated in a substantial portion of penile cancers in men, as well as anal and oropharyngeal cancers in both men and women.⁹ The quadrivalent HPV vaccine is currently being evaluated in a randomized, placebo-controlled study involving 3400 heterosexual men aged 16 to 23 years, and 600 men aged 16 to 26 years who have sex with men. Results should help determine whether adding males to vaccination programs will decrease the morbidity and mortality associated with HPV-related diseases in men.

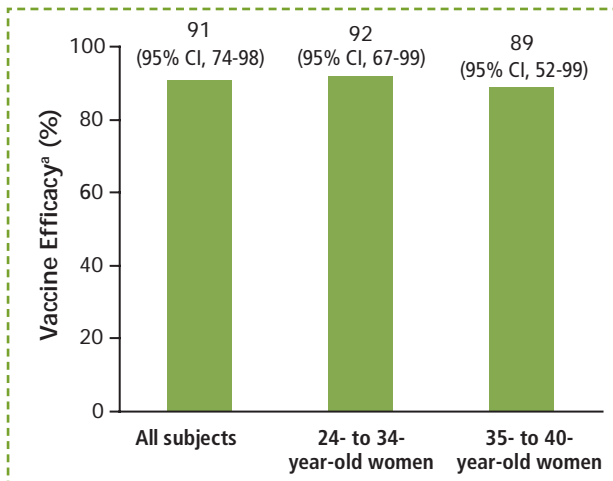


Figure 8. Quadrivalent HPV 6/11/16/18 vaccine efficacy in adult women. ^aCombined incidence of disease related to HPV 6/11/16/18. *P* < .001 across all age groups. Luna J et al, for the FUTURE III Investigators.⁴⁹

Fostering HPV Vaccination Acceptance

Acceptability of HPV vaccines is occasionally met with some resistance from parents and patients because of the sexually transmitted nature of HPV. Parental perceptions that their children are at low risk for HPV infection or do not need vaccination until after the onset of sexual activity are major barriers to the acceptance of HPV vaccination of children.⁵¹ In a large national opinion poll, only 49% of American mothers would permit HPV vaccination

HPV

of their 9- to 12-year-old daughters, 68% would allow vaccination of their 13- to 15-year-old daughters, and 86% would permit vaccination of their 16- to 18-year-old daughters (Figure 9).⁵² Although research has shown that the most effective age for girls to be vaccinated is between 9 and 11 years old, when exposure to HPV is at its lowest,⁵³ some parents express concern that vaccination against HPV infection would promote earlier onset of sexual activity in their children, or believe that their children are at low risk for acquiring HPV infection and do not need to be vaccinated.⁵⁴ This belief contradicts the evidence that risk-based vaccination is less effective than vaccination (universal) based on age; when vaccination is based upon predetermined risk factors, many women who are HPV negative would theoretically not be vaccinated, and many of those who are already HPV infected would receive the vaccination. Therefore, every effort should be made to vaccinate all indicated women as early as possible.²⁹

Endorsement of the HPV vaccine by healthcare professionals is also likely to increase vaccine acceptance. A recent survey of parents found that healthcare providers rank among the most trusted sources of information and guidance regarding vaccination.⁵⁵ Also, a survey of members of a large, professional medical society found that this group believes their recommendation would be the most important variable in vaccine distribution by other healthcare professionals in their society. When nurse practitioners were surveyed, the most important factor influencing their willingness to recommend sexually transmitted disease vaccination was a recommendation from the American Academy of Pediatrics. Taken together, these results indicate that professional healthcare organization recommendations are important for the acceptability and uptake of the HPV vaccine.⁵⁶

A brief educational intervention about HPV and HPV vaccination has also demonstrated success in increasing parental acceptance of the vaccine (Figure 10). When parents of children aged 10 to 15 years were surveyed before and after HPV vaccine education, it was found that the number of subjects who wanted HPV vaccination for their children increased by 20% after reading the educational material.⁵⁷ Parental belief that the HPV

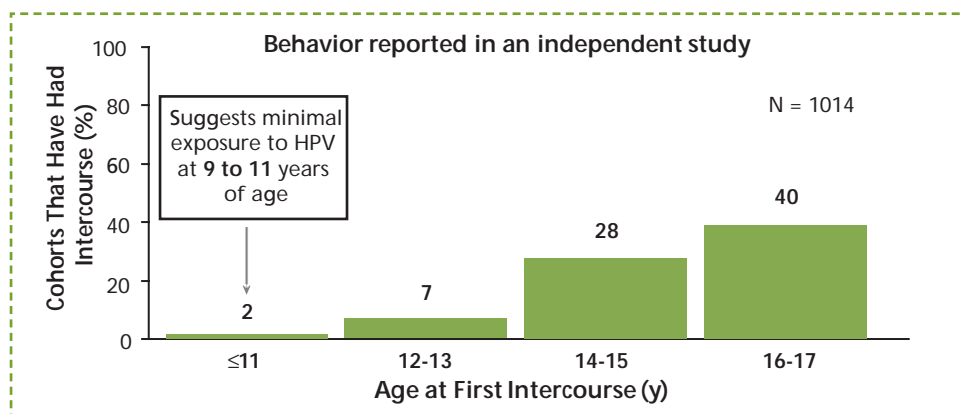


Figure 9. The most effective time to vaccinate is before exposure. Centers for Disease Control and Prevention⁵³; Kaiser Family Foundation. *National Survey of Adolescents and Young Adults: Sexual Health Knowledge, Attitudes and Experiences*. Henry J. Kaiser Family Foundation; 2003.

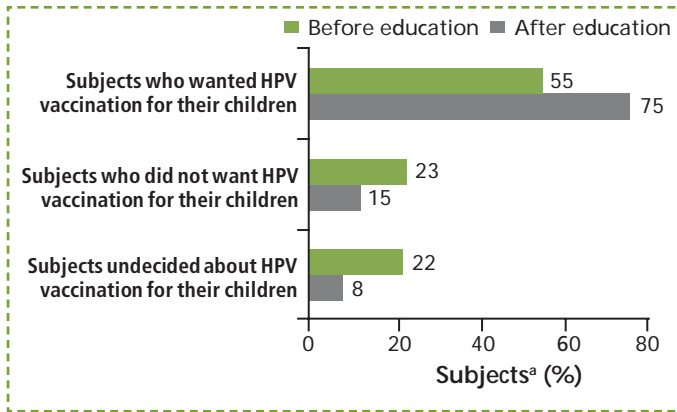


Figure 10. Educational intervention improves parental acceptance of HPV vaccination. ^aSubjects were parents or guardians of 10- to 15-year-old boys and girls. Davis K et al.⁵⁷

vaccine would be beneficial to improving their children's health is a strong predictor of vaccine acceptability.⁵⁸ Therefore, parent-patient-clinician discussions regarding benefits and safety should lead to greater acceptance of HPV vaccination.

PCE Takeaways

- HPV infection occurs in sexually active women and men of all ages
- More than three-quarters of sexually active adults are exposed to HPV at some point
- Young, sexually active women are at highest risk for HPV infection
- The 2 most common high-risk HPV types (16, 18) are associated with most cases of high-grade cervical dysplasia as well as cervical, penile, anal, and oropharyngeal cancers
- The 2 most common low-risk HPV types (6, 11) are associated with low-grade cervical dysplasia, genital warts, and RRP
- The burden of HPV-related diseases remains a public health concern despite screening programs that have helped reduce cervical cancer mortality rates
- HPV vaccination that protects against the most common high- and low-risk HPV types, together with routine cervical screening, is expected to make a substantial impact on HPV-related morbidity and mortality
- A quadrivalent HPV vaccine is approved for use in females aged 9 to 26 years for the prevention of HPV 6-, 11-, 16-, and 18-associated conditions including cervical cancer, CIN, VIN, VaIN, AIS, and genital warts; a bivalent HPV 16/18 vaccine is under review by the FDA
- The CDC recommends routine quadrivalent HPV vaccination for girls aged 11 to 12 years (with availability for girls ≥ 9 years) and catch-up vaccination for adolescent girls ≥ 13 years and women ≤ 26 years
- Implementation of universal, age-based HPV vaccination strategies based on CDC recommendations ensures that all eligible girls and women have access to and potential benefit from HPV vaccination
- Education of parents, patients, and clinicians about HPV infection and related diseases, together with recommendations from professional societies, will be important to the success of HPV vaccination initiatives

CASE STUDY

18-Year-Old Female Student Who Has Not Received HPV Vaccination

Presentation

The patient is an 18-year-old woman with an unremarkable medical history. She has come to the college health clinic for her annual Pap test, pelvic examination, and an oral contraceptive prescription.

Physical Examination

- ➔ Blood pressure: 119/76 mm Hg
- ➔ Height: 64 in
- ➔ Weight: 120 lb

Medications

- ➔ Diphenhydramine 25 mg, as needed for sleep
- ➔ Ibuprofen 200 mg as needed for headache

Because this sexually active patient has not yet received HPV vaccination and is within the indicated age group, the patient's healthcare provider suggests that the patient receive HPV vaccination.

Clinical Decision Point

This patient has been sexually active for approximately 3 years. Should she receive the quadrivalent HPV vaccine?

- ➔ Yes
- ➔ No

Comment

Although maximum benefit is achieved by vaccinating before the onset of sexual activity, there are still advantages to administering HPV vaccination to sexually active women. Even though prevalence of HPV infection is high after sexual debut, infection with all 4 vaccine types is rare; therefore, most women will still benefit from vaccination even if they are already sexually active.²⁷ Also, the CDC recommends that all females aged 13 to 26 years receive catch-up vaccination, regardless of sexual history. Pap or HPV testing is not needed prior to vaccination.⁴² Based on these factors, this patient should be offered HPV vaccination.

Clinical Decision Point

After the clinician explains that the completion of the vaccination series with the quadrivalent HPV vaccine requires a 3-dose regimen, the patient states she will be on spring break when the second dose is scheduled in 1 month. Should she still receive the vaccine at this visit or wait until she returns from break?

- ➔ Receive the vaccine
- ➔ Wait until after vacation

Comment

The patient's anticipation that she will not be able to receive her second dose of the quadrivalent HPV vaccine on time should not prevent her from receiving the first dose of vaccine during this visit. According to vaccination "catch-up" guidelines published by the CDC, a vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. In fact, the only restriction regarding when she can receive the second and third doses of the vaccine is the minimum recommended interval between doses: the second dose should be given no sooner than 4 weeks after the first; and the third dose should be given no sooner than 12 weeks after the second dose, and 24 weeks after the first dose.⁵⁹

The patient also expresses concerns about adverse events associated with the HPV vaccine. Although fear of adverse events is one of the main reasons patients avoid vaccination, the quadrivalent HPV vaccine is generally safe and well tolerated. The vaccine-related adverse events that occurred at a frequency $\geq 5.0\%$ (and more frequently than those observed among placebo recipients) included pain, swelling, erythema, and

fever. With the exception of fever, these were all injection-site reactions that occurred within 1 to 5 days postvaccination. In clinical trials, few subjects (0.1%) discontinued the vaccination regimen due to adverse events.⁴¹ Therefore, the patient should be informed that other than some short-term injection-site reactions, similar to those seen in many other widely used vaccines, she most likely will not experience any adverse events as a result of vaccination with the quadrivalent HPV vaccine.

Clinical Decision Point

The patient also expresses concerns about contracting HPV from the vaccine. Are these concerns warranted?

- Yes
- No

Comment

Since the quadrivalent HPV vaccine uses components of the viral protein shell rather than HPV DNA to elicit an immunogenic response, the vaccine cannot cause HPV infection. Furthermore, the vaccine does not contain an attenuated form of the live virus; it is prepared from highly purified virus-like particles of the major capsid L1 protein of HPV types 6, 11, 16, and 18. Therefore, this patient should not be concerned about contracting HPV from the quadrivalent HPV vaccine.⁴¹

Clinical Decision Point

The patient wants to know if she can discontinue periodic Pap tests if she receives the HPV vaccine. Should patients discontinue their Pap tests after receiving the vaccine?

- Yes
- No

Comment

Although the quadrivalent HPV vaccine is very effective against HPV types 6, 11, 16, and 18 and is modestly effective against several of the oncogenic nonvaccine HPV types, patients should still follow routine cervical screening procedures. Cervical screening is an invaluable tool for detection of abnormal cervical cytological changes and cervical cancer and should not be discontinued because of the availability of HPV vaccination.⁴²

On September 12, 2008, the FDA approved expanded indications for the quadrivalent HPV vaccine for the prevention of vaginal and vulvar cancers caused by HPV types 16 and 18 in girls and women aged 9 to 26 years.⁶⁰

Questions From Symposium Participants



➔ **Q:** Can the quadrivalent HPV vaccine be administered during the same visit as other vaccines?

A: Studies have shown that immunogenicity is not compromised when the quadrivalent HPV vaccine is administered during the same visit as the hepatitis B vaccine. Although concomitant administration has not been studied with any other vaccines, the quadrivalent HPV vaccine is not a live vaccine and it has no components that can adversely impact the efficacy of other vaccines. Therefore, the quadrivalent HPV vaccine can be administered in the same visit as other appropriate vaccines, such as the tetanus, diphtheria, and pertussis (Tdap) and quadrivalent meningococcal conjugate (MCV4) vaccines. Administering all vaccines during the same visit increases the likelihood that children, adolescents, and adults will receive each of the recommended vaccines on schedule.

➔ **Q:** How should the quadrivalent HPV vaccine be stored?

A: The quadrivalent HPV vaccine should be refrigerated (not frozen) in an environment between 36° and 46° F to ensure maximum efficacy and safety. The vaccine should also be protected from light.

➔ **Q:** In the event of a power/refrigeration failure, what should be done with the quadrivalent HPV vaccine?

A: If there is a power/refrigeration failure, the affected quadrivalent HPV vaccines should be marked and transferred to a working refrigerator. The vaccine handler should record the temperature inside the malfunctioning refrigerator and the length of time the vaccines remained outside the appropriate temperature range. The manufacturer should then be contacted for further instruction.

➔ **Q:** What are the minimum dosing intervals for the quadrivalent HPV vaccine?

A: The minimum dosing interval between doses 1 and 2 of the HPV vaccine is 4 weeks, and the minimum dosing interval between doses 2 and 3 is 12 weeks. Inadequate doses of the vaccine or doses received before the end of the minimum dosing interval should be readministered.

➔ **Q:** If the quadrivalent HPV vaccine schedule is interrupted, should the previous dose be readministered?

A: If the quadrivalent HPV vaccine schedule is interrupted, the vaccine series does not need to be restarted. The next dose should be given as soon as possible, and the following dose (if applicable) should not be administered before the minimum dosing interval.

➔ **Q:** Is there any benefit to offering HPV vaccination to patients who are already sexually active?

A: Although the maximum benefit from HPV vaccination is achieved when it is administered before the onset of sexual activity, there are still advantages to vaccinating women who are sexually active. Even though prevalence of HPV infection is high after initiation of sexual activity, infection with all 4 vaccine types is rare; therefore, most women will still benefit from vaccination even if they are already sexually active. In addition, the CDC has recommended that all females aged 13 to 26 years receive catch-up vaccination, regardless of their sexual history. Furthermore, Pap or HPV testing is not necessary prior to vaccination of sexually active individuals.

➔ **Q:** Because HPV is sexually transmitted, is there a benefit in vaccinating males?

A: The greatest disease burden from HPV infection is borne by women; therefore, the pivotal FUTURE I and FUTURE II trials, which led to FDA approval of the quadrivalent HPV vaccine, were focused on women for the prevention of cervical cancer, abnormal cervical cytology, and genital warts. However, as in women, HPV infection in men is associated with lesions, ranging from genital warts to invasive cancers, and remains an important public health concern. Men infected with HPV play a role as carriers or vectors of the virus and may spread disease to their partners during sexual activity, potentially leading to cervical cancer in women and other HPV-related anogenital diseases in both men and women. A randomized, placebo-controlled trial evaluating the efficacy of the quadrivalent HPV vaccine in the prevention of HPV-related disease in heterosexual men and men who have sex with men is underway.

➔ **Q:** What is the prevalence of anogenital HPV among men, and at which male body sites are infections found?

A: Recent studies have demonstrated that up to 73% of the male population carry HPV DNA at numerous anatomic sites. Anogenital HPV infection in men can lead to penile cancer, anal cancer, and genital warts. HPV infection in men is also associated with oropharyngeal cancer and RRP. A recent study found that 25% of the heterosexual men studied were infected with anal HPV and that 33% of those infections were with an oncogenic type.

➔ **Q:** Can the quadrivalent HPV vaccine be administered to immunosuppressed (eg, HIV-positive) females?

A: Studies have shown HPV infection to be almost twice as common in HIV-positive females as in HIV-negative females. However, even though HIV-positive females are much more likely to be infected with HPV types 6, 11, 16, and 18, they are still very unlikely to be infected with all 4 types at the same time and could potentially benefit from being vaccinated with the quadrivalent HPV vaccine. Because the quadrivalent HPV vaccine is a noninfectious vaccine, it can be administered to females who are immunosuppressed as a result of disease or medication. However, patients

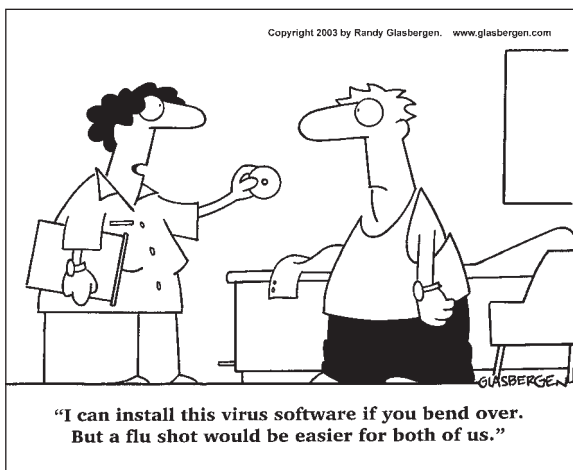
should be counseled that the immune response and vaccine efficacy in these females may be lower than in immunocompetent females. Studies are ongoing to assess the efficacy and safety of the quadrivalent and bivalent HPV vaccines in immunosuppressed females.

➔ **Q:** Should the quadrivalent HPV vaccine be given to pregnant women?

A: The quadrivalent HPV vaccine is not recommended for administration during pregnancy. Although the vaccine has not been associated causally with any maternal adverse events during pregnancy or in the developing fetus, limited data regarding vaccination during pregnancy are available. In addition, if a woman should become pregnant between HPV vaccine doses, the remaining doses should be held until after pregnancy.

➔ **Q:** How effective are risk-based strategies in selecting females to receive the quadrivalent HPV vaccine?

A: Recent studies have shown that a risk factor-based approach to selecting which females should receive the quadrivalent HPV vaccine is inadequate. Using a risk-factor-based approach leaves many eligible women who are at-risk without vaccination, because all females are inevitably at risk for HPV infection once they become sexually active. Therefore, it is important that every effort be made to vaccinate all females prior to the onset of sexual activity.



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