

CASE STUDY

A 19-Year-Old, Sexually Active Woman



Presentation

Jane is a 19-year-old college student who arrives at your clinic for her annual Pap test, pelvic examination, and an oral contraceptive prescription. She is in excellent physical health and lives with 2 roommates near the local university that she attends. She has been sexually active for 3 years. Jane has expressed curiosity about human papillomavirus (HPV) vaccination; however, she has some reservations including whether the vaccine is safe and, more importantly, if it has been proven truly effective. Since Jane is within the age group recommended for “catch-up” vaccination and she has not yet received the quadrivalent HPV vaccine, you determine that this would be a great opportunity to discuss the vaccine with her.

What evidence should the clinician discuss with the patient to support the efficacy and safety of the quadrivalent HPV vaccine?

Comment

Two large-scale phase 3, randomized, double-blind, placebo-controlled trials examined the efficacy and safety of the quadrivalent HPV vaccine.^{1,2} The Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) trials examined the immune response produced by, as well as the clinical efficacy and safety of, the quadrivalent HPV vaccine. The FUTURE I study randomly assigned 5455 females between the ages of 15 and 26 years to receive either a 3-injection course of the quadrivalent HPV vaccine or placebo.¹ In the per-protocol analysis, for adolescent girls and women who had not previously been exposed to HPV 16 or 18, the efficacy of the vaccine was 100% compared with placebo (0 vs 65 cases, respectively) in preventing cervical intraepithelial neoplasia (CIN) 1 to 3 or adenocarcinoma in situ (AIS) associated with vaccine-related HPV types (Table 1).¹ The vaccine was also 100% effective compared with placebo (0 vs 60 cases, respectively) in preventing HPV vaccine-type-related genital warts, vulvar intraepithelial neoplasia (VIN)/vaginal intraepithelial neoplasia (VaIN), and perianal intraepithelial lesions. An analysis of the intention-to-treat population, which included females 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.¹

The FUTURE II study randomly assigned 12,167 adolescent girls and women between the ages of 15 and 26 to receive either a 3-injection course of the quadrivalent HPV vaccine or placebo, followed by periodic Pap and HPV tests during an average 3-year follow-up. For females who had not previously been exposed to HPV 16 or 18, the vaccine prevented 98% of CIN 2/3 and AIS in the per-protocol population (Figure 1, page 77).^{1,2}

An 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 evidence for the efficacy of the quadrivalent HPV vaccine. In the 17,129 females who were HPV 16/18

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negative at the start of the study, the vaccine was 99% effective against HPV 16/18-related CIN 2/3, AIS, and cervical cancer. In the intent-to-treat analysis of all randomized subjects (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.³

Table 1. Vaccine Efficacy Against External Anogenital, Vaginal, and Cervical Lesions Associated With HPV 6, 11, 16, or 18 or Regardless of HPV Type^a

End Point	Vaccine Group (N = 2723)			Placebo Group (N = 2723)			Efficacy
	No. of Subjects	No. of Cases	Rate per 100 Person-Years at Risk	No. of Subjects	No. of Cases	Rate per 100 Person-Years at Risk	Percent (95% CI)
Lesions associated with vaccine-type HPV							
<i>Per-protocol susceptible population^b</i>							
Condyloma	2261	0	0	2279	48	0.9	100 (92-100)
VIN grade 2 or grade 3 or ValN grade 2 or grade 3	2261	0	0	2279	9	0.2	100 (49-100)
CIN grade 2	2241	0	0	2258	21	0.4	100 (81-100)
CIN grade 3	2241	0	0	2258	17	0.3	100 (76-100)
<i>Unrestricted susceptible populations^c</i>							
Condyloma	2267	3	<0.1	2684	67	0.9	96 (86-99)
VIN grade 2 or grade 3 or ValN grade 2 or grade 3	2267	1	<0.1	2684	11	0.1	91 (37-100)
Cervical lesions ^d	2667	2 ^e	<0.1	2684	89 ^f	1.2	98 (92-100)

^aIn each category, a subject is counted only once, but some subjects are counted in more than 1 category;

^bThe per-protocol susceptible population was defined as subjects who were negative on PCR analysis and serologic testing for the relevant HPV type at enrollment, remained negative on PCR analysis for the same HPV type through 1 month after administration of the third dose of vaccine or placebo, received 3 doses of vaccine or placebo within 1 year, and did not have protocol violations; ^cThe unrestricted susceptible population included subjects who did not test positive for the relevant HPV type at enrollment; ^dOf subjects in the unrestricted susceptible population who received at least 1 dose of vaccine or placebo and had at least 1 follow-up visit after administration of the first dose, 2559 in the vaccine group and 2576 in the placebo group were included in the analysis for end points associated with vaccine-type HPV: 2282 and 2307, respectively, in the analysis for end points associated with HPV 6 and 11; 2159 and 2173, respectively, in the analysis for end points associated with HPV 16; and 2425 and 2452, respectively, in the analysis for end points associated with HPV 18; ^e1 subject in the vaccine group received 3 doses of placebo in error; ^fAmong the 89 subjects in the placebo group with end point events (cases, defined as consensus diagnosis) of cervical lesions associated with vaccine-type HPV presented according to the severity of the histologic findings, 46 subjects with CIN had grade 1 lesions, 17 had grade 2 lesions, 20 had grade 3 lesions, and 6 subjects had adenocarcinoma in situ.

Adapted from Garland SM et al.¹

The quadrivalent HPV vaccine was also found to be safe and well tolerated. 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 5 days postvaccination (Table 2).¹ Few subjects (0.1%) discontinued the study because of adverse events.^{1,2} Consistent with these findings, recent data presented at a meeting of the Advisory Committee on Immunization Practices (ACIP) found no major safety problems with the quadrivalent HPV vaccine at 2 years post-US Food and Drug Administration (FDA) approval.⁴⁻⁷

The patient asks for clarification on several points, including whether she is really a good candidate for vaccination. She is concerned that since she has been in a committed relationship for the last year, and has been sexually active for 3 years, that she may have “missed her opportunity” for protection.

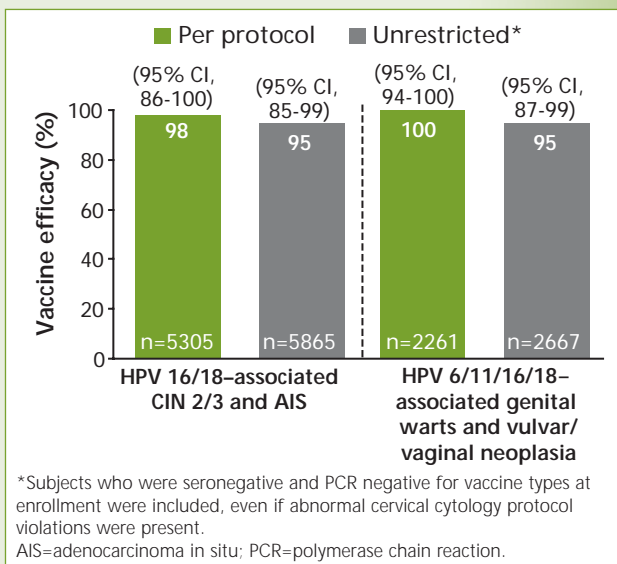


Figure 1. Quadrivalent HPV 6/11/16/18 vaccine: 3-year results. FUTURE II Study Group²; Garland SM et al.¹

Table 2. 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

The vaccine-related adverse experiences that were observed among recipients of quadrivalent HPV vaccine were at a frequency of at least 5.0% and also at a greater frequency than those observed among placebo recipients. Gardasil [package insert].⁸

Disease State Profile

Approximately 20 million Americans are currently infected with HPV, making it the most common sexually transmitted infection (STI). It has been estimated that 75% of all sexually active individuals will be exposed to HPV during their lifetimes,¹ with 6.2 million people becoming infected each year.² HPV infection is most commonly found among young, sexually active females aged 15 to 24 years. These individuals incur 74% of all new HPV infections.³ Moreover, 24.5% of adolescent females between the ages of 14 and 19 and 19.6% to 27.5% of adult women aged 25 to 59 years are also infected with HPV.^{4,5}

More than 100 different HPV strains have been identified, and they are classified as high and low risk based on oncogenic potential.⁶ High-risk HPV types, such as HPV 16 and 18, are associated with the development of high-grade cervical dysplasias and cervical cancer.⁷ HPV infection has been identified in >99% of all cervical cancers, with HPV types 16 and 18 responsible for approximately 70% of cases. Approximately 11,070 new cases of cervical cancer and 3870 related deaths are expected in the United States during 2008.⁸ 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.⁹ 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 45.¹⁰ Additionally, infection with high-risk HPV types can cause AIS, CIN grades 1 to 3, VIN, and ValN grades 2/3 (Table).¹⁰⁻¹⁴ High-risk HPV strains have also been implicated in vulvar, vaginal, anal, penile, and head and neck cancers.¹⁵

Infection with low-risk HPV types, such as HPV 6 and 11, can lead to low-grade cervical dysplasias, condyloma acuminata (genital warts), and recurrent respiratory papillomatosis, a rare but potentially fatal disease (Table). HPV types 6 and 11 are responsible for approximately 90% of cases of genital warts, which affect about 1 million sexually active Americans per year.¹⁶ About two thirds of women exposed to HPV types 6 or 11 develop genital warts within 3 years,¹⁷ with the risk of infection rising as the number of sexual partners increases.^{18,19}

Prevention of HPV Infection

Currently available treatment options for genital warts and cervical, vaginal, and vulvar cancer precursors include local approaches that remove the lesion such as cryotherapy, electrosurgery, laser therapy, and surgical excision.²⁰ Genital warts also may be treated with topical pharmacologic agents. However, none of these therapies are curative.

Recognition that HPV is the main etiologic agent in cervical cancer suggests that a prophylactic vaccine could reduce the incidence of HPV infection and, therefore, achieve disease control. Recently, 2 prophylactic HPV vaccines have been developed that stimulate the production of neutralizing antibodies to protect against HPV infection. The quadrivalent vaccine consists of recombinant capsid protein L1 virus-like particles derived from the 4 different

Table. Common HPV Types Associated With Benign and Malignant Disease

HPV Types	Manifestations	
High risk	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82	Low-grade cervical changes ¹² High-grade cervical changes ¹² Cervical cancer ^{7,12} Other anogenital cancers ¹² Head and neck cancer ¹³
Low risk	6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81	Benign low-grade cervical changes ¹² Condylomata acuminata ¹² (genital warts) Recurrent respiratory papillomatosis ¹⁴

Muñoz N et al⁷; Koutsky LA et al¹²; Hansson BG et al¹³; Wiatrak BJ.¹⁴

types of HPV (6, 11, 16, and 18) which, combined, account for approximately 70% of all invasive cervical cancers, 60% of high-grade CIN lesions, and >90% of genital warts, both in the United States and globally.⁶ Approved by the FDA in 2006, the availability of the quadrivalent HPV vaccine offers an opportunity to decrease the burden of HPV infection and its sequelae. An investigational bivalent HPV vaccine, which protects against types 16 and 18, is currently under FDA review.

References

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CASE STUDY**A 19-Year-Old, Sexually Active Woman****What information can the clinician provide to reassure the patient that she is still a good candidate for the quadrivalent HPV vaccine?****Comment**

The quadrivalent HPV vaccine is approved by the FDA for the prevention of HPV 6/11/16/18–associated cervical cancer, vaginal cancer, vulvar 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.^{8,9} In addition, the Centers for Disease Control and Prevention (CDC) recommends catch-up vaccination for females aged 13 to 26 years who have not been previously vaccinated or who have not completed the full series.¹⁰

Although Jane has been sexually active for 3 years and maximum benefit is achieved by vaccinating before the onset of sexual activity, there are still advantages to administering HPV vaccination to sexually active women. A number of studies have shown that the prevalence of HPV infection is high after sexual debut; however, infection with all 4 vaccine types is rare. Therefore, most women will still benefit from vaccination even if they are already sexually active.¹¹

After this discussion, the patient still seems hesitant and then admits that her greatest concern comes from the stories she has read on the Internet about people contracting HPV from the vaccine. She knows that not everything on the Web is credible or accurate, but still, the idea frightens her.

What is the best information the clinician can provide to address Jane's concern about contracting HPV from the vaccine?**Comment**

The quadrivalent HPV vaccine is not a live virus vaccine; it is prepared from highly purified virus-like particles of the major capsid L1 protein of HPV types 6, 11, 16, and 18. 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. Therefore, this patient should not be concerned about contracting HPV from the quadrivalent HPV vaccine.⁸

Jane is reassured but asks if she will still need to be screened for cervical cancer after she receives the vaccination series.

What should the clinician stress about preventive screening for cervical cancer after HPV vaccination?**Comment**

The availability of the quadrivalent HPV vaccine has not changed recommendations for cervical cancer screening.¹⁰ This is due to the fact that the vaccine will not provide protection against all types of HPV that cause cervical cancer. In addition, women may not obtain the vaccine's full benefits if they have already acquired a vaccine HPV type prior to vaccination.

Pap testing and screening for HPV DNA or HPV antibodies are not needed before vaccination at any age.¹⁰

After more thought and additional questions, Jane thinks receiving the vaccine is the right decision for her, but is concerned when the clinician reminds her that there is a 3-dose requirement for completing the vaccination series. If she receives the first dose today, she will be on Spring break when the second dose is scheduled in 1 month.

Should the clinician administer the first dose at this appointment, or wait until Jane returns from her vacation?

Comment

Jane's anticipation that she will not be able to receive the 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 administered no sooner than 12 weeks after the second dose, and 24 weeks after the first dose.¹²

CASE STUDY

A 12-Year-Old Girl With a Resistant Parent



Presentation

Jenny is a 12-year-old girl who comes to your office for a routine check-up with her mother.

She is healthy and lives with both of her parents and 2 siblings.

You review Jenny's records and determine that this would be an ideal time to discuss HPV vaccination with both the patient and her mother. Jenny has not likely been exposed to HPV at this age and, thus, could receive the maximum benefit from vaccination. However, her mother protests that she is too young for HPV vaccination.

What evidence can the clinician offer to address this common parental concern?

Comment

HPV transmission can occur with any kind of sexual or genital contact with an infected individual.¹³ HPV infection is often acquired soon after the onset of sexual activity. Indeed, approximately one third of females become infected with HPV within 24 months of their first sexual encounter.¹¹ Condoms offer only partial protection against HPV transmission.¹⁴

Due to the sexually transmitted nature of HPV, parental resistance can be a major barrier to vaccination.¹⁵ 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.¹⁵ In a large national opinion poll, only 49% of American mothers would permit HPV vaccination of their 9- to 12-year-old daughters, 68% would allow vaccination of their 13- to 15-year-old daughters, and 86% would permit the vaccination of their 16- to 18-year-old daughters.¹⁶

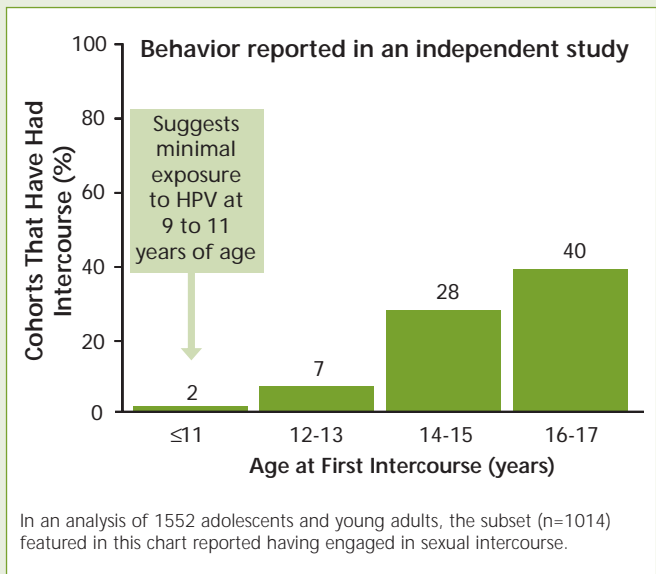


Figure 2. The most effective time to vaccinate is before exposure. Centers for Disease Control and Prevention¹⁷; Kaiser Family Foundation.¹⁸

Although research has shown that the most effective age for girls to be vaccinated is between 9 and 11 years of age, when exposure to HPV is at its lowest (Figure 2),^{17,18} 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 thus do not need to be vaccinated.¹⁹ These beliefs contradict evidence that risk-based vaccination of girls is less effective than universal vaccination based on age.

Family Education

Patient education is likely to increase vaccine acceptance. Indeed, a brief educational intervention about HPV and HPV vaccination has demonstrated success in increasing parental acceptance of the vaccine. When parents of children and adolescents aged 10 to 15 years were surveyed before and after HPV vaccine education, results indicated that the number of subjects who wanted HPV vaccination for their children increased by 20%.²⁰ Parental belief that HPV vaccination would benefit their children's health is a strong predictor of vaccine acceptability.²¹ Therefore, parent-patient-clinician discussions regarding benefits and safety should lead to greater acceptance of HPV vaccination.

Additionally, the ACIP recommends routine vaccination of females aged 11 to 12 years with 3 doses of quadrivalent HPV vaccine.¹⁰ The vaccination series can be started as young as 9 years of age. These recommendations are based on several considerations, including studies that show the quadrivalent HPV vaccine is safe and effective; achievement of high antibody titers when vaccinated at age 11 to 12 years; onset of sexual activity in the United States at a young age; and the high prevalence of HPV acquisition among young sexually active individuals.¹⁰ Ideally, HPV vaccination should be administered before initiation of sexual activity, and duration of protection should extend for many years, providing protection when exposure through sexual activity might occur.¹⁰ The patient's mother is still concerned and is particularly worried that her daughter may not be fully protected from HPV infection.

What information can the clinician provide regarding the duration of HPV protection with the quadrivalent HPV vaccine?

Comment

A subset of participants (n = 241) in the phase 2 quadrivalent HPV vaccine study is being followed for 5 years to assess the duration of protection with the vaccine. In a combined analysis of all participants through year 3 and a subset through year 5, the efficacy against vaccine-type persistent infection or disease was 96% and efficacy against vaccine-type-related CIN or genital warts was 100%. These data provide encouraging information regarding long-term vaccine efficacy as protection against clinically relevant disease.²² Follow-up studies are planned to determine the duration of protection among women enrolled in the phase 3 studies through year 3.

Jenny's mother says she would like to discuss the matter with her husband and asks, if they decide they would like to follow this course of action, whether Jenny could receive the HPV vaccine at a visit in the future, when she is scheduled to receive other vaccinations.

CASE STUDY

A 12-Year-Old Girl With a Resistant Parent

What information can the clinician provide regarding coadministration of the quadrivalent HPV vaccine with other vaccines?

Comment

Patients and their parents may be counseled that HPV vaccination may be administered during the same visit as the hepatitis B vaccine, as the immunogenicity of either vaccine is not compromised.¹⁰ 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 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.

CASE STUDY**A 42-Year-Old Woman
With Rheumatoid Arthritis****Presentation**

Marie is a 42-year-old woman who arrives at your clinic for a check-up. She was divorced 2 years ago and lives alone. Her only active medical condition is rheumatoid arthritis, which is controlled with immunosuppressive medication. Since Marie has recently begun dating again, she expresses concerns about STIs, and inquires about HPV vaccination. This is a great opportunity for the clinician to discuss HPV vaccine efficacy in adult women and the potential risks and benefits of vaccination within this age group.

What counseling points should the clinician provide to this patient regarding HPV vaccination?**Comment**

Although HPV vaccination is currently approved by the FDA 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 3).²³ Additionally, data collected by the National Cancer Institute have shown that cervical cancer incidence and mortality are greatest in women ≥ 50 years of age.²⁴

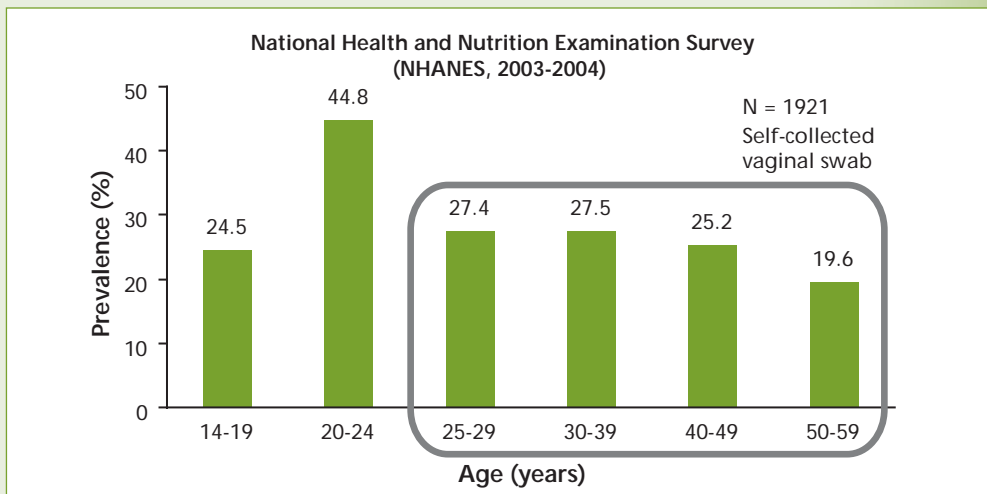


Figure 3. HPV infection remains prevalent among women 25 to 59 years of age. Adapted from Dunne EF et al.²³

CASE STUDY

A 42-Year-Old Woman With Rheumatoid Arthritis

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.²⁵ 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-, 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 4).²⁶

Marie has read about the FDA-approved quadrivalent HPV vaccine, but inquires about other available HPV vaccines.

What is the most current data available to share with the patient regarding other HPV vaccines in development?

Comment

A bivalent HPV vaccine, which protects against HPV types 16 and 18, is currently under review by the FDA. According to interim results from a large phase 3 trial called the Papilloma Trial Against Cancer in Young Adults (PATRICIA), the bivalent HPV vaccine has shown >90% efficacy against high-grade CIN 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.²⁷ The bivalent HPV vaccine also demonstrated 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 5).²⁸

Additional support for the bivalent HPV vaccine was noted in a phase 2 study extension in which 776 women who received all 3 doses of the bivalent HPV vaccine or placebo and were

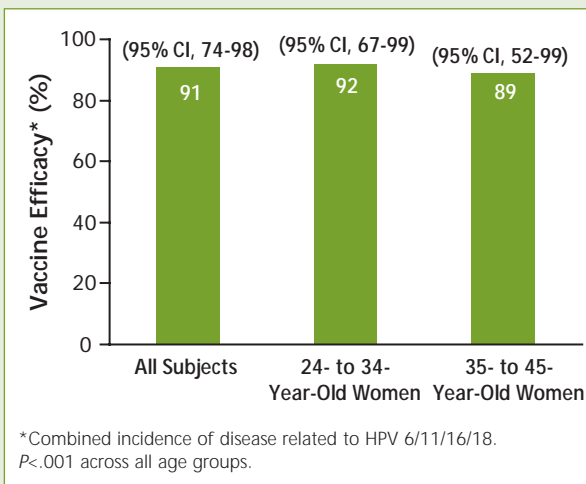


Figure 4. Quadrivalent HPV 6/11/16/18 vaccine efficacy in adult women. Luna J et al.²⁶

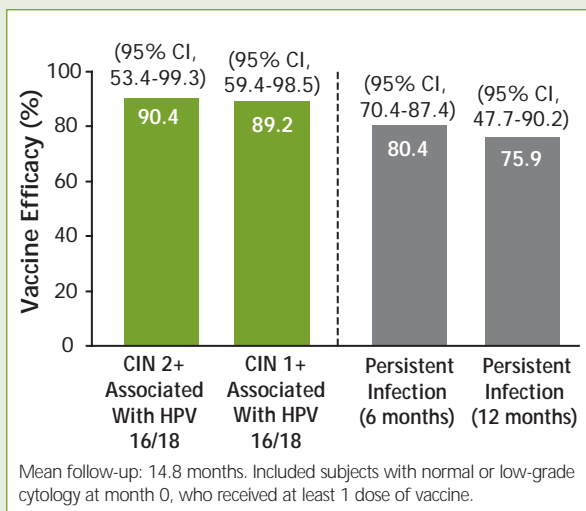


Figure 5. Phase 3 bivalent HPV 16/18 vaccine interim analysis: efficacy. Paavonen J et al.²⁸

followed up for ≤ 4.5 years. In this analysis, the bivalent HPV vaccine was 97% and 100% effective in preventing HPV 16/18-related incidents and persistent infection, respectively, during the combined initial and follow-up phases. More than 98% of vaccine 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.²⁷ 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. Taken together, these data suggest that the bivalent vaccine remains efficacious for a significant period of time postvaccination.²⁹

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.³⁰

Vaccine-related adverse events that occurred in $\geq 5\%$ 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 postvaccination (Table 3).²⁸

Based on the little research she has done on her own, Marie is aware that HPV vaccination has the potential to offer additional protection but admits she has not come across any detailed data.

What information can the clinician provide regarding other potential benefits of HPV vaccination?

Comment

Besides protecting females against the 2 most common oncogenic forms of HPV, the quadrivalent vaccine may also provide cross-protection against other common oncogenic strains. In a combined analysis of 10 HPV strains (31, 33, 35, 39, 45, 51, 52, 56, 58, and 59), which

Table 3. Phase 3 HPV 16/18 Interim Analysis: Adverse Events

Injection site symptoms*	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*		
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†	381 (12.4)	337 (10.9)
Rash	312 (10.1)	258 (8.4)
Urticaria	298 (9.7)	244 (7.9)

*Participants who reported a specified symptom within 7 days of vaccine injection.

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

Paavonen J et al.²⁸

CASE STUDY**A 42-Year-Old Woman With Rheumatoid Arthritis**

account for approximately an additional 20% of cervical cancers worldwide, the quadrivalent vaccine showed cross-protection that reduced incidence of precursor lesions by about 38%.³¹ The effect was most dramatic with strains 31 and 45, where protection reached about 45%.

The bivalent vaccine was also found to be significantly efficacious against 6-month persistent infection in HPV strains 31 (36%), 45 (60%), and 52 (32%), and 12-month persistent infection across all nonvaccine oncogenic HPV types (27%).²⁸ Together, these data suggest that the HPV types 16 and 18 antigens in both the quadrivalent and bivalent vaccines induce modest cross-protection against several high-risk nonvaccine HPV types that cause 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. Additionally, HPV vaccination is associated with a reduced incidence of abnormal Pap test results and the need for cervical procedures and surgery.³²

The patient should also be informed that HPV is implicated in a substantial portion of penile cancers in men, as well as anal and oropharyngeal cancers in both men and women.³³ The quadrivalent HPV vaccine is being evaluated in a randomized, double-blind, placebo-controlled study involving 4065 men aged 16 to 26 years. Preliminary data show the quadrivalent HPV vaccine was 90% effective in preventing external genital lesions (genital warts or penile/perineal/perianal intraepithelial neoplasia) associated with any vaccine-related HPV type in the per-protocol population at 7 months.^{34,35} Results should help determine whether adding men to vaccination programs will decrease the morbidity and mortality associated with HPV-related diseases in men.

Finally, Marie asks if her immunosuppressive medication will interfere with the efficacy of HPV vaccination.

What can the clinician tell the patient about current knowledge regarding vaccine efficacy in the immunocompromised?

Patients with an impaired immune response, due to underlying illness or the use of immunosuppressive medications, may have reduced antibody response to the vaccine.³

Conclusion

The clinical burden of disease that results from HPV infection is substantial and extends from genital warts and cytologic abnormalities to cervical, vaginal, and vulvar cancers and their associated precursor lesions. In addition, HPV is implicated in anal, penile, and head and neck cancers. Thus, HPV-related disease constitutes a significant health burden and remains a public health problem worldwide. The approval of the first HPV vaccine has been heralded as a major breakthrough. In clinical trials, the quadrivalent HPV vaccine was highly effective in preventing persistent HPV infection, cervical cancer and its precursor lesions, vaginal and vulvar cancers, and genital warts caused by HPV types 6, 11, 16, or 18 among girls and women who had not already been infected with the respective HPV type. The ACIP has recommended the quadrivalent HPV vaccine for girls 11 to 12 years of age, catch-up vaccination for girls and women 13 to 26 years of age, and permissive use in girls as early as age 9. A bivalent HPV 16/18 vaccine has also shown promise in clinical studies and is currently under FDA review.

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