CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will recommend vaccination against human papillomavirus according to current guidelines

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Human papillomavirus vaccine: Safe, effective, underused

ABSTRACT

Vaccination against human papillomavirus (HPV) is safe and effective. It is recommended for females age 9 to 26 and for males age 11 to 26, yet vaccination rates are low. We review the host immune response, the data behind the recommendations for HPV vaccination, and the challenges of implementing the vaccination program.

KEY POINTS

Two HPV vaccines are available: a quadrivalent vaccine against HVP types 6, 11, 16, and 18, and a bivalent vaccine against types 16 and 18.

HPV causes cervical cancer, genital warts, oropharyngeal cancer, anal cancer, and recurrent respiratory papillomatosis, creating a considerable economic and health burden.

The host immune response to natural HPV infection is slow and weak. In contrast, HPV vaccine induces a strong and long-lasting immune response.

The HPV vaccines have greater than 90% efficacy in preventing cervical dysplasia and genital warts that are caused by the HPV types the vaccine contains. They are as safe as other common prophylactic vaccines.

HPV vaccination has been challenged by public controversy over the vaccine's safety, teenage sexuality, mandatory legislation, and the cost of the vaccine.

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The vaccines against human papillomavirus (HPV) are the only ones designed to prevent cancer caused by a virus[1,2]—surely a good goal. But because HPV is sexually transmitted, HPV vaccination has met with public controversy.[3] To counter the objections and better protect their patients' health, primary care providers and other clinicians need a clear understanding of the benefits and the low risk of HPV vaccination—and the reasons so many people object to it.[3]

In this article, we will review:

- The impact of HPV-related diseases
- The basic biologic features of HPV vaccines
- The host immune response to natural HPV infection vs the response to HPV vaccines
- The clinical efficacy and safety of HPV vaccines
- The latest guidelines for HPV vaccination
- The challenges to vaccination implementation
- Frequently asked practical questions about HPV vaccination.

HPV-RELATED DISEASES: FROM BOTHERSOME TO DEADLY

Clinical sequelae of HPV infection include genital warts; cancers of the cervix, vulva, vagina, anus, penis, and oropharynx; and recurrent respiratory papillomatosis.[4–6]

Genital warts

HPV types 6 and 11 are responsible for more than 90% of the 1 million new cases of genital warts diagnosed annually in the United States.[7–10]

Bothersome and embarrassing, HPV-related genital warts can cause itching, burning,

erythema, and pain, as well as epithelial erosions, ulcerations, depigmentation, and urethral and vaginal bleeding and discharge.[11,12] Although they are benign in the oncologic sense, they can cause a good deal of emotional and financial stress. Patients may feel anxiety, embarrassment,[13] and vulnerability. Adolescents and adults who have or have had genital warts need to inform their current and future partners or else risk infecting them—and facing the consequences.

Direct health care costs of genital warts in the United States have been estimated to be at least $200 million per year.[14]

Cervical cancer

Cervical cancer cannot develop unless the cervical epithelium is infected with one of the oncogenic HPV types. Indeed, oncogenic HPV is present in as many as 99.8% of cervical cancer specimens.[15] HPV 16 and 18 are the most oncogenic HPV genotypes and account for 75% of all cases of cervical cancer. Ten other HPV genotypes account for the remaining 25%.[16]

In 2012, there were an estimated 12,170 new cases of invasive cervical cancer in the United States and 4,220 related deaths.[17] The cost associated with cervical cancer screening, managing abnormal findings, and treating invasive cervical cancer in the United States is estimated to be $3.3 billion per year.[18]

New cases of cervical cancer in the United States per year: > 12,000
Deaths from it: > 4,000

Although the incidence and the mortality rates of cervical cancer have decreased more than 50% in the United States over the past 3 decades thanks to screening,[19] cervical cancer remains the second leading cause of death from cancer in women worldwide. Each year, an estimated 500,000 women contract the disease and 240,000 die of it.[20]

Anal cancer

A recent study indicated that oncogenic HPV can also cause anal cancer, and the proportion of such cancers associated with HPV 16 or HPV 18 infection is as high as or higher than for cervical cancers, and estimated at 80%.[21]

The incidence of anal cancer is increasing by approximately 2% per year in both men and women in the general population,[22] and rates are even higher in men who have sex with men and people infected with the human immunodeficiency virus.[23]

Hu and Goldie[24] estimated that the lifetime costs of caring for all the people in the United States who in just 1 year (2003) acquired anal cancer attributable to HPV would total $92 million.

Oropharyngeal cancer

HPV types 16, 18, 31, 33, and 35 also cause oropharyngeal cancer. HPV 16 accounts for more than 90% of cases of HPV-related oropharyngeal cancer.[25]

Chaturvedi et al[6] tested tissue samples from three national cancer registries and found that the number of oropharyngeal cancers that were HPV-positive increased from 16.3% in 1984–1989 to 71.7% in 2000–2004, while the number of HPV-negative oropharyngeal cancers fell by 50%, paralleling the drop in cigarette smoking in the United States.

Hu and Goldie[24] estimated that the total lifetime cost for all new HPV-related oropharyngeal cancers that arose in 2003 would come to $38.1 million.[24]

Vulvar and vaginal cancers

HPV 16 and 18 are also responsible for approximately 50% of vulvar cancers and 50% to 75% of vaginal cancers.[4,5]

Recurrent respiratory papillomatosis

HPV 6 and 11 cause almost all cases of juvenile- and adult-onset recurrent respiratory papillomatosis.[26] The annual cost for surgical procedures for this condition in the United States has been estimated at $151 million.[27]

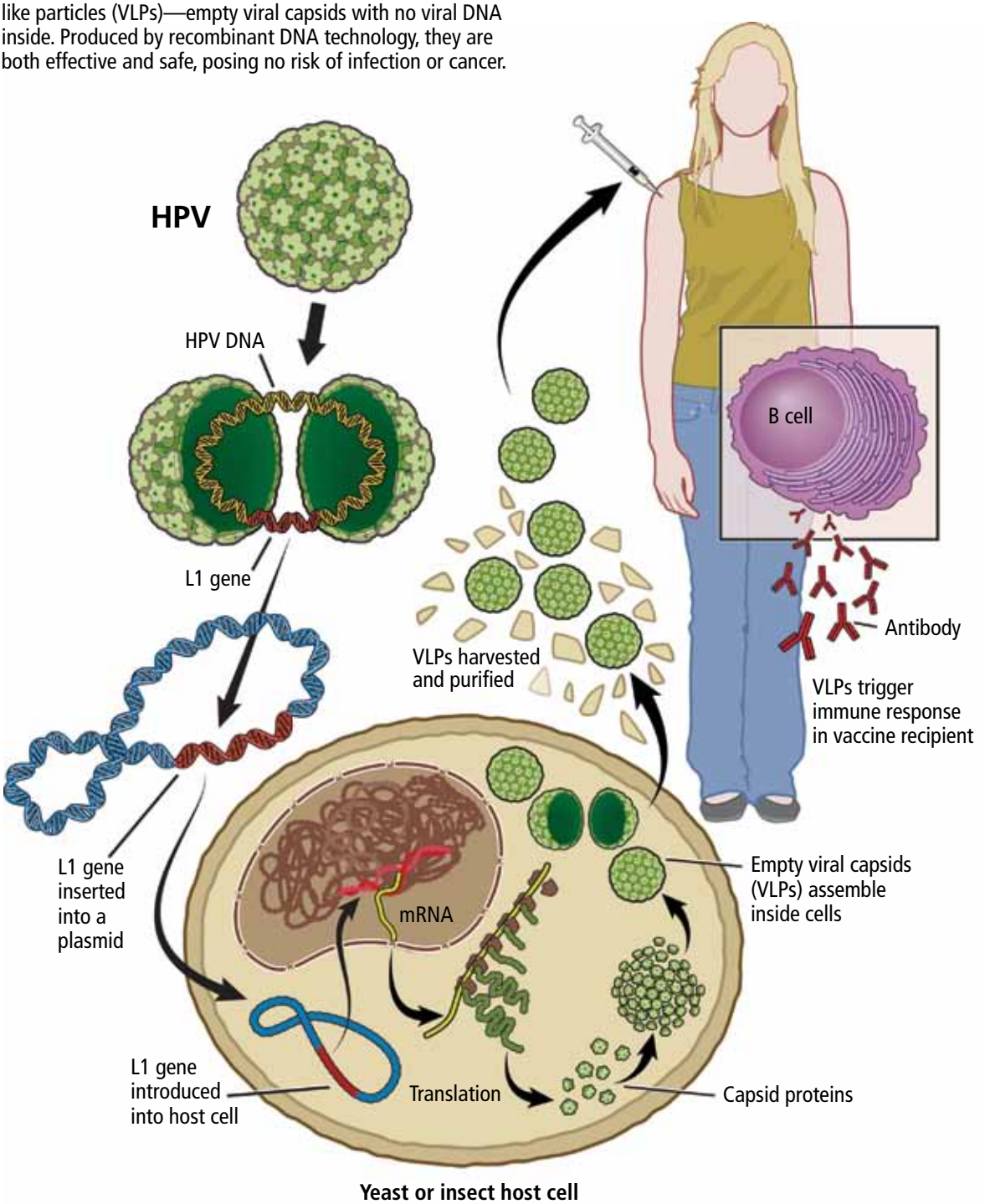
HPV VACCINES ARE NONINFECTIOUS AND NONCARCINOGENIC

Currently, two HPV vaccines are available: a quadrivalent vaccine against types 6, 11, 16, and 18 (Gardasil; Merck) and a bivalent vaccine against types 16 and 18 (Cervarix; GlaxoSmithKline). The quadrivalent vaccine was approved by the US Food and Drug Administration (FDA) in 2006, and the bivalent vaccine was approved in 2009.[28,29]

Both vaccines contain virus-like particles, ie, viral capsids that contain no DNA. HPV has a circular DNA genome of 8,000 nucleotides divided into two regions: the early region, for viral replication, and the late region,

How the HPV vaccines are produced

Vaccines against human papillomavirus (HPV) contain virus-like particles (VLPs)—empty viral capsids with no viral DNA inside. Produced by recombinant DNA technology, they are both effective and safe, posing no risk of infection or cancer.



Medical Illustrator: David Schumick

FIGURE 1

for viral capsid production. The host produces neutralizing antibodies in response to the L1 capsid protein, which is different in different HPV types.

In manufacturing the vaccines, the viral *L1* gene is incorporated into a yeast genome or an insect virus genome using recombinant DNA technology (**FIGURE 1**). Grown in culture, the yeast or the insect cells produce the HPV L1 major capsid protein, which has the intrinsic capacity to self-assemble into virus-like particles.[30–33] These particles are subsequently purified for use in the vaccines.[34]

Recombinant virus-like particles are morphologically indistinguishable from authentic HPV virions and contain the same type-specific antigens present in authentic virions. Therefore, they are highly effective in inducing a host humoral immune response. And because they do not contain HPV DNA, the recombinant HPV vaccines are noninfectious and noncarcinogenic.[35]

VACCINATION INDUCES A STRONGER IMMUNE RESPONSE THAN INFECTION

HPV infections trigger both a humoral and a cellular response in the host immune system.

HPV has several ways to evade the host immune system in natural infection

The humoral immune response to HPV infection involves producing neutralizing antibody against the specific HPV type, specifically the specific L1 major capsid protein. This process is typically somewhat slow and weak, and only about 60% of women with a new HPV infection develop antibodies to it.[36,37]

HPV has several ways to evade the host immune system. It does not infect or replicate within the antigen-presenting cells in the epithelium. In addition, HPV-infected keratinocytes are less susceptible to cytotoxic lymphocytic-mediated lysis. Moreover, HPV infection cause very little tissue destruction. And finally, natural cervical HPV infection does not result in viremia. As a result, antigen-presenting cells have no chance to engulf the virions and present virion-derived antigen to the host immune system. The immune system outside the epithelium has limited opportunity to detect the virus because HPV infection does not have a blood-borne phase.[38,39]

The cell-mediated immune response to early HPV oncoproteins may help eliminate established HPV infection.[40] In contrast to antibodies, the T-cell response to HPV has not been shown to be specific to HPV type.[41] Clinically, cervical HPV infection is common, but most lesions go into remission or resolve as a result of the cell-mediated immune response.[40,41]

In contrast to the weak, somewhat ineffective immune response to natural HPV infection, the antibody response to HPV vaccines is rather robust. In randomized controlled trials, almost all vaccinated people have seroconverted. The peak antibody concentrations are 50 to 10,000 times greater than in natural infection. Furthermore, the neutralizing antibodies induced by HPV vaccines persist for as long as 7 to 9 years after immunization.[42] However, the protection provided by HPV vaccines against HPV-related cervical intraepithelial neoplasia does not necessarily correlate with the antibody concentration.[43–47]

Why does the vaccine work so well?

Why are vaccine-induced antibody responses so much stronger than those induced by natural HPV infection?

The first reason is that the vaccine, delivered intramuscularly, rapidly enters into blood vessels and the lymphatic system. In contrast, in natural intraepithelial infection, the virus is shed from mucosal surfaces and does not result in viremia.[48]

In addition, the strong immunogenic nature of the virus-like particles induces a robust host antibody response even in the absence of adjuvant because of concentrated neutralizing epitopes and excellent induction of the T-helper cell response.[35,49,50]

The neutralizing antibody to L1 prevents HPV infection by blocking HPV from binding to the basement membrane as well as to the epithelial cell receptor during epithelial microabrasion and viral entry. The subsequent micro-wound healing leads to serous exudation and rapid access of serum immunoglobulin G (IgG) to HPV virus particles and encounters with circulatory B memory cells.

Furthermore, emerging evidence suggests that even very low antibody concentrations are sufficient to prevent viral entry into cervical epithelial cells.[46–48,51–53]

TABLE 1

Major trials of HPV vaccine

YEAR	CLINICAL TRIAL	STUDY POPULATION	HPV VACCINE	KEY CONCLUSIONS
2007	FUTURE I[54]	5,455 women from Latin America or North America, age 16–24	Quadrivalent	The vaccine was 100% effective in preventing HPV-related anogenital disease in women not previously infected with HPV The vaccine was also 100% effective in preventing cervical intraepithelial neoplasia (CIN) grades I, II, and III and carcinoma in situ
2007	FUTURE II[28]	12,000 women from Europe and Latin America, age 15–26	Quadrivalent	The vaccine was effective for the prevention of HPV 16- or 18-related CIN grades II and III and carcinoma in situ
2009	PATRICIA[29]	18,000 women from Europe or Asia Pacific, age 15–25	Bivalent	The vaccine was 92.9% effective for the prevention of CIN grades II and III, carcinoma in situ, or cancer
2011	Giuliano et al[55]	4,065 men, age 16–26	Quadrivalent	The vaccine was 90.4% effective in preventing external genital lesions associated with HPV types 6, 11, 16, and 18 in men not previously infected with HPV
2011	Palefsky et al[23]	598 men who have sex with men, age 16–26	Quadrivalent	The vaccine was 77.5% effective against anal intraepithelial neoplasia associated with HPV 6,11, 16, or 18 in men not previously infected with HPV

FUTURE = Females United to Unilaterally Reduce Endo/ectocervical Disease; PATRICIA = Papilloma Trial Against Cancer in Young Adults

THE HPV VACCINES ARE HIGHLY EFFECTIVE AND SAFE

The efficacy and safety of the quadrivalent and the bivalent HPV vaccines have been evaluated in large randomized clinical trials.[23,28,29,54,55] **TABLE 1** summarizes the key findings.

The Females United to Unilaterally Reduce Endo/ectocervical Disease (FUTURE I)[54] and FUTURE II[28] trials showed conclusively that the quadrivalent HPV vaccine is 98% to 100% efficacious in preventing HPV 16- and 18-related cervical intraepithelial neoplasia, carcinoma in situ, and invasive cervical cancer in women who had not been infected with HPV before. Similarly, the Papilloma Trial against Cancer in Young Adults (PATRICIA) concluded that the bivalent HPV vaccine is 93% efficacious.[29]

Giuliano et al[55] and Palefsky et al[23] conducted randomized clinical trials of the quadrivalent HPV vaccine for preventing genital disease and anal intraepithelial neoplasia in boys and men; the efficacy rates were 90.4%[55] and 77.5%.[23]

A recent Finnish trial in boys age 10 to 18 found 100% seroconversion rates for HPV 16 and HPV 18 antibodies after they received bivalent HPV vaccine.[56] Similar efficacy has been demonstrated for the quadrivalent HPV vaccine in boys.[57]

Adverse events after vaccination

After the FDA approved the quadrivalent HPV vaccine for girls in 2006, the US Centers for Disease Control and Prevention (CDC) conducted a thorough survey of adverse events after immunization from June 1, 2006 through December 31, 2008.[58] There were about 54 reports of adverse events per 100,000 distributed vaccine doses, similar to rates for other vaccines. However, the incidence rates of syncope and venous thrombosis were disproportionately higher, according to data from the US Vaccine Adverse Event Reporting System. The rate of syncope was 8.2 per 100,000 vac-

cine doses, and the rate of venous thrombotic events was 0.2 per 100,000 doses.[58]

There were 32 reports of deaths after HPV vaccination, but these were without clear causation. Hence, this information must be interpreted with caution and should not be used to infer causal associations between HPV vaccines and adverse outcomes. The causes of death included diabetic ketoacidosis, pulmonary embolism, prescription drug abuse, amyotrophic lateral sclerosis, meningoencephalitis, influenza B viral sepsis, arrhythmia, myocarditis, and idiopathic seizure disorder.[58]

Furthermore, it is important to note that vasovagal syncope and venous thromboembolic events are more common in young females in general.[59] For example, the background rates of venous thromboembolism in females age 14 to 29 using oral contraceptives is 21 to 31 per 100,000 woman-years.[60]

Overall, the quadrivalent HPV vaccine is well tolerated and clinically safe. Postlicensure evaluation found that the quadrivalent and bivalent HPV vaccines had similar safety profiles.[61]

Vaccination is contraindicated in people with known hypersensitivity or prior severe allergic reactions to vaccine or yeast or who have bleeding disorders.

Nearly all participants in trials of HPV vaccines have seroconverted

HPV VACCINATION DOES MORE THAN PREVENT CERVICAL CANCER IN FEMALES

The quadrivalent HPV vaccine was licensed by the FDA in 2006 for use in females age 9 to 26 to prevent cervical cancer, cervical cancer precursors, vaginal and vulval cancer precursors, and anogenital warts caused by HPV types 6, 11, 16, and 18. The CDC's Advisory Committee on Immunization Practices (ACIP) issued its recommendation for initiating HPV vaccination for females age 11 to 12 in March 2007. The ACIP stated that the vaccine could be given to girls as early as age 9 and recommended catch-up vaccinations for those age 13 to 26.[62,63]

The quadrivalent HPV vaccine was licensed by the FDA in 2009 for use in boys and men for the prevention of genital warts. In December 2010, the quadrivalent HPV vaccine received extended licensure from the FDA for use in males and females for the prevention of anal cancer. In October 2011, the ACIP voted to recommend routine use of the quadrivalent HPV vaccine for boys age 11 to 12; catch-up vaccination should occur for those age 13 to 22, with an option to vaccinate men age 23 to 26.

These recommendations replace the "permissive use" recommendations from the ACIP in October 2009 that said the quadrivalent HPV vaccine *may* be given to males age 9 to 26.[64] This shift from a permissive to an active recommendation connotes a positive change reflecting recognition of rising oropharyngeal cancer rates attributable to oncogenic, preventable HPV, rising HPV-related anal cancer incidence, and the burden of the disease in female partners of infected men, with associated rising health care costs.

The bivalent HPV vaccine received FDA licensure in October 2009 for use in females age 10 to 25 to prevent cervical cancer and precursor lesions. The ACIP included the bivalent HPV vaccine in its updated recommendations in May 2010 for use in girls age 11 to 12. Numerous national and international organizations have endorsed HPV vaccination.[65–71]

TABLE 2 outlines the recommendations from these organizations.

HPV VACCINATION RATES ARE STILL LOW

HPV vaccine offers us the hope of eventually eradicating cervical cancer. However, the immunization program still faces many challenges, since HPV vaccination touches on issues related to adolescent sexuality, parental autonomy, and cost. As a result, HPV immunization rates remain relatively low in the United States according to several national surveys. Only 40% to 49% of girls eligible for the vaccine received even one dose, and of those who received even one dose, only 32% to 53.3% came back for all three doses.[72–75] Furthermore, indigent and minority teens were less likely to finish the three-dose HPV vaccine series.

Why are the vaccination rates so low?

Parental barriers. In one survey,[73] reasons that parents gave for not having their daughters vaccinated included:

- Lack of knowledge of the vaccine (19.4%)

TABLE 2

Recommendations for human papillomavirus (HPV) vaccination

Advisory Committee on Immunization Practices (ACIP), 2007[62]
Routine vaccination of girls at age 11 or 12 with three doses of quadrivalent HPV vaccine
Vaccination can be initiated as early as age 9
Catch-up vaccination of females age 13–26
Vaccine should be given in a three-dose schedule intramuscularly; the second and third doses should be given 2 and 6 months after the first dose

ACIP, 2010[63]
Recommendation for bivalent HPV vaccine are the same as above

ACIP, 2010[64]
Quadrivalent HPV vaccine may be given to males age 9–26

World Health Organization Strategic Advisory Group of Experts on Immunization[65]
Vaccination of females not previously infected with vaccine-related HPV types at age 9–13

American Cancer Society, 2007[66]
Routine HPV vaccination for girls age 11 and 12; girls as young as 9 can get HPV vaccine
Vaccination for girls age 13–18 who have not yet received HPV vaccine or whose vaccination schedule was incomplete
Not enough evidence to recommend for or against catch-up vaccination of females age 19–26

American College of Obstetricians and Gynecologists, 2010[67]
Same as ACIP recommendations

American College of Physicians, 2011[68]
Same as ACIP recommendations

American Academy of Family Physicians, 2007[69]
Same as ACIP recommendations

American Academy of Pediatrics, 2007[70]
Same as ACIP recommendations

Society for Adolescent Health and Medicine, 2011[71]
Same as ACIP recommendations

- Lack of perceived need for the vaccine (18.8%)
- Belief that their daughter was not sexually active (18.3%)
- Clinician not recommending vaccination (13.1%).

In an effort to improve HPV vaccination rates,[41] several states proposed legislation for mandatory HPV vaccination of schoolgirls shortly after licensure of the quadrivalent HPV vaccine.[3] Since then, we have seen a wave of public opposition rooted in concerns and misinformation about safety, teenage sexuality, governmental coercion, and cost. Widespread media coverage has also highlighted unsubstantiated claims about side effects attributable to the vaccine that can raise parents' mistrust of vaccines.[76] Concerns have also been raised about a threat to parental autonomy in how and when to educate their children about sex.[77]

Moreover, the vaccine has raised ethical concerns in some parents and politicians that mandatory vaccination could undermine abstinence messages in sexual education and may alter sexual activity by condoning risky behavior.[78] However, a recent study indicated that there is no significant change in sexual behavior related to HPV vaccination in young girls.[79]

In 2012, Mullins et al[80] also found that an urban population of adolescent girls (76.4%

We have seen a wave of opposition to HPV vaccination rooted in concerns and misinformation about safety, teenage sexuality, government coercion, and cost

black, 57.5% sexually experienced) did not feel they could forgo safer sexual practices after first HPV vaccination, although the girls did perceive less risk from HPV than from other sexually transmitted infections after HPV vaccination ($P < .001$).[80] Inadequate knowledge about HPV-related disease and HPV vaccine correlated with less perceived risk from HPV after vaccination among the girls, and a lack of knowledge about HPV and less communication with their daughters about HPV correlated with less perceived risk from HPV in the mothers of the study population.[81]

Health-care-provider barriers. Physician endorsement of vaccines represents a key predictor of vaccine acceptance by patients, families, and other clinicians.[82–84] In 2008, a cross-sectional, Internet-based survey of 1,122 Texas pediatricians, family practice physicians, obstetricians, gynecologists, and internal medicine physicians providing direct patient care found that only 48.5% always recommended HPV vaccination to girls.[74] Of all respondents, 68.4% were likely to recommend the vaccine to boys, and 41.7% agreed with mandated vaccination. Thus, more than half of the physicians were not following the current recommendations for universal HPV vaccination for 11- to -12-year-olds.

In a survey of 1,013 physicians during the spring and summer of 2009, only 34.6% said they always recommend HPV vaccination to early adolescents, 52.7% to middle adolescents, and 50.2% to late adolescents and young adults.[85] Pediatricians were more likely than family physicians and obstetrician-gynecologists to always recommend HPV vaccine across all age groups ($P < .001$). Educational interventions targeting various specialties may help overcome physician-related barriers to immunization.[85]

Financial barriers. HPV vaccine, which must be given in three doses, is more expensive than other vaccines, and this expense is yet another barrier, especially for the uninsured.[86] Australia launched a government-funded program of HPV vaccination (with the quadrivalent vaccine) in schools in 2007, and it has been very successful. Garland et al[87] reported that new cases of genital warts have decreased by 73% since the program began, and the rate of high-grade abnormalities on Papanicolaou testing has declined by a small but significant amount.

For HPV vaccination to have an impact on public health, vaccination rates in the general population need to be high. In order to achieve these rates, we need to educate our patients on vaccine safety and efficacy and counsel vaccine recipients about the prevention of sexually transmitted infections and the importance of regular cervical cancer screening after age 21. Clinicians can actively "myth-bust" with patients, who may not realize that the vaccine should be given despite a history of HPV infection or abnormal Pap smear.

FREQUENTLY ASKED QUESTIONS

What if the patient is late for a shot?

The current recommended vaccination schedule for the bivalent and quadrivalent HPV vaccines is a three-dose series administered at 0, 2, and 6 months, given as an intramuscular injection, preferably in the deltoid muscle. The minimal dosing interval is 4 weeks between the first and second doses and 12 weeks between the second and third doses.

If circumstances preclude the completion of a series with the same vaccine, the other HPV vaccine can be used

The vaccines use different adjuncts with different specific mechanisms for immunogenicity; therefore, it is recommended that the same vaccine be used for the entire three-dose series. However, if circumstances preclude the completion of a series with the same vaccine, the other HPV vaccine may be used.[63] Starting the series over is not recommended.

Long-term studies demonstrated clinical efficacy 8.5 years after vaccination.[47] Amnestic response by virtue of activation of pools of memory B cells has been demonstrated, suggesting the vaccine may afford lifelong immunity.[88]

Is a pregnancy test needed before HPV vaccination?

The ACIP states that pregnancy testing is not required before receiving either of the available HPV vaccines.

A recent retrospective review of phase III efficacy trials and pregnancy registry surveillance data for both vaccines revealed no increase in spontaneous abortions, fetal malformations, or adverse pregnancy outcomes.[89] Data are limited on bivalent and quadrivalent

HPV vaccine given within 30 days of pregnancy and subsequent pregnancy and fetal outcomes. Both vaccines have been assigned a pregnancy rating of category B; however, the ACIP recommends that neither vaccine be given if the recipient is known to be pregnant. If pregnancy occurs, it is recommended that the remainder of the series be deferred until after delivery.[62]

It is not known whether the vaccine is excreted in breast milk. The manufacturers of both the bivalent and quadrivalent HPV vaccines recommend caution when vaccinating lactating women.[30,31]

Can HPV vaccine be given with other vaccines?

In randomized trials, giving the bivalent HPV vaccine with the combined hepatitis A, hepatitis B, meningococcal conjugate and the combined tetanus, diphtheria, and acellular pertussis vaccines did not interfere with the immunogenic response, was safe, and was well tolerated.[90,91] Coadministration of the quadrivalent HPV vaccine has been studied only with hepatitis B vaccine, with similar safety and efficacy noted.

The ACIP recommends giving HPV vaccine at the same visit with other age-appropriate immunizations to increase the likelihood of adherence to recommended vaccination schedules.[62]

Is HPV vaccination cost-effective?

Kim and Goldie[86] performed a cost-effectiveness analysis of HPV vaccination of girls at age 12 and catch-up vaccination up to the ages of 18, 21, and 26. For their analysis, they considered prevention of cancers associated with HPV types 16 and 18, of genital warts associated with types 6 and 11, and of recurrent respiratory papillomatosis. They also assumed that immunity would be lifelong, and current screening practices would continue.

They calculated that routine vaccination of 12-year-old girls resulted in an incremental cost-effective ratio of $34,900 per quality-adjusted life-year (QALY) gained. A threshold of less than $50,000 per QALY gained is considered reasonably cost-effective, with an upper limit of $100,000 considered acceptable.[92]

In the same analysis by Kim and Goldie,[86] catch-up vaccination of girls through age 18 resulted in a cost of $50,000 to $100,000 per QALY gained, and catch-up vaccination of females through age 26 was significantly less cost-effective at more then $130,000 per QALY gained. The vaccine was also significantly less cost-effective if 5% of the population was neither screened nor vaccinated, if a 10-year booster was required, and if frequent cervical cancer screening intervals were adopted.

This analysis did not include costs related to the evaluation and treatment of abnormal Pap smears and cross-protection against other HPV-related cancers.

The cost-effectiveness of HPV vaccination depends on reaching more girls at younger ages (ideally before sexual debut) and completing the three-dose schedule to optimize duration of immunity.[92] Appropriate modification of the current recommendations for the intervals of cervical cancer screening for vaccinated individuals will further improve the cost-effectiveness of vaccination. The inclusion of male vaccination generally has more favorable cost per QALY in scenarios in which female coverage rates are less than 50%[93] and among men who have sex with men.[94]

TO ERADICATE CERVICAL CANCER

Given the remarkable efficacy and expected long-term immunogenicity of HPV vaccines, we anticipate a decline in HPV-related cervical cancer and other related diseases in the years to come. However, modeling studies predicting the impact of HPV vaccination suggest that although substantial reductions in diseases can be expected, the benefit, assuming high vaccination rates, will not be apparent for at least another decade.[95] Furthermore, the current HPV vaccines contain only HPV 16 and 18 L1 protein for cancer protection and, therefore, do not provide optimal protection against all oncogenic HPV-related cancers.

The real hope of eradicating cervical cancer and all HPV-related disease relies on a successful global implementation of multivalent HPV vaccination, effective screening strategies, and successful treatment. ■

The ACIP recommends that neither vaccine be given if the recipient is known to be pregnant

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