

Deep dive into HPV vaccines

A safety and efficacy refresher

by SANGINI S. SHETH, MD, MPH, FACOG; AND YIFAN EMILY CHANG, MD

Human papillomavirus (HPV) infection is associated with genital warts, precancerous lesions, and cancers in both men and women. Many cervical, vaginal, vulvar, anal, and oropharyngeal cancers are attributable to HPV, with cervical cancer constituting 84% of all HPV-associated tumors.¹ Although most HPV infections clear naturally or become dormant thanks to the immune system, a significant number of women will develop cervical dysplasia after HPV exposure, and a subset of these women will eventually progress to cervical cancer. It is estimated that by age 50, approximately 80% of all women will have had exposure to or been infected with 1 type of HPV; approximately

10% of these women will proceed to develop persistent HPV infection, which increases their risk of cervical cancer.¹ Studies have shown a causal relationship between HPV and cervical cancer, and high-risk HPV serotypes such as HPV-16 and HPV-18 are connected to 70% of cervical cancer cases.^{2,3} HPV vaccines were developed to prevent HPV-related diseases by stimulating the production of neutralizing antibodies that protect against type-specific HPV infection. Currently, commercially available HPV vaccines utilize virus-like particles (VLPs) of the L1 major capsid protein, the injection of which induces high titers of systemic antibodies that ultimately prevent the HPV virus from infecting the host cell.

There are 3 main types of HPV

vaccines on the global market: 1) a bivalent vaccine, Cervarix (GSK), composed of HPV-16/18 VLPs and the proprietary adjuvant AS04; 2) a quadrivalent vaccine, Gardasil (Merck), containing HPV-6/11/16/18 VLPs, and an aluminum salt adjuvant; and 3) a 9-valent (nonavalent) vaccine, Gardasil 9 (Merck), based on the quadrivalent vaccine but containing VLPs of 5 additional oncogenic HPV serotypes: 31, 33, 45, 52, and 58. The 9-valent HPV vaccine was introduced with the goal of preventing 90% of cervical cancer cases globally. In 2016, the 9-valent vaccine was approved by the FDA with a 2-dose schedule in girls and boys aged 9 to 14 years, and it has since become the only HPV vaccine available in the United States (Table 1).⁴



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Safety

Despite almost 2 decades of high-quality research demonstrating that HPV vaccines have excellent safety profiles, a worrisome trend has developed: Many patients or their parents cite concerns about vaccine safety as the reason for declining HPV vaccination. A recent cross-sectional study that investigated HPV vaccination trends in the United States noted that the percentage of caregivers for unvaccinated adolescents who cited vaccine safety as the primary reason to defer vaccination rose from 13% in 2015 to 23.4% in 2018.⁵ Exposure to vaccine misinformation, particularly through social media, could be a contributing factor to vaccine hesitancy. Therefore, it is of paramount importance that clinicians effectively address these safety concerns and dispel misinformation about HPV vaccines.

Since their licensure, more than 135 million doses of HPV vaccines have been distributed in the United States (with more than 270 million doses distributed worldwide).^{6,7} HPV vaccines are considered extremely safe. The most common adverse events (AEs) associated with HPV vaccines are minor and transient: local AEs (pain, itchiness, swelling, and redness at the injection site) and mild systemic symptoms (headache, nausea).⁶ Rarely, patients experience dizziness and syncope, although syncope has been found to be more common in adolescents after receiving any vaccine.⁶ The incidence of severe allergic reaction (anaphylaxis) is exceedingly low (0.3-3 per million).^{6,7} Prelicensure clinical trials of HPV vaccines established their favorable safety profiles, and in recent years, more population-based studies have supported these findings. A Cochrane review in 2018 showed that although

TABLE 1. Characteristics of Selected HPV Vaccines⁴

Brand name and manufacturer	Cervarix*	Gardasil*	Gardasil 9
	GSK	Merck	Merck
Valency	2	4	9
HPV types protected against	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Recombinant system	Purified L1 VLPs from <i>Trichoplasia ni</i> cells infected with recombinant baculovirus	Purified L1 VLPs from recombinant <i>Saccharomyces cerevisiae</i>	Purified L1 VLPs from recombinant <i>S. cerevisiae</i>
Adjuvant	AS04 adjuvant system: aluminum hydroxide and 3-O-desacyl-4'-monophosphoryl lipid A	Amorphous aluminum hydroxyphosphate sulfate	Amorphous aluminum hydroxyphosphate sulfate
Recommended for	Females aged 9-25 years	Routine immunization: 11-12 years old (can start as early as 9 years) Catch-up immunization (have not been adequately vaccinated): 13-26 years old	Routine immunization: 11-12 years old (can start as early as 9 years) Catch-up immunization (have not been adequately vaccinated): 13-26 years old Shared decision-making about immunization: 27-45 years old
Recommended administration schedules	Two doses: 0 and 6-12 months in individuals initiating vaccination at ages 9-14 years, except immunocompromised persons OR Three doses: 0, 1-2, and 6 months in individuals initiating vaccination at ages ≥ 15 years and immunocompromised persons		

HPV, human papillomavirus; VLP, virus-like particle.

*No longer commercially available in the United States

local AEs were more common in vaccinated subjects than in placebo recipients, there was no significant difference in mild and serious systemic AEs between vaccinated subjects and placebo recipients.⁷ Additionally, since 2007, the Global Advisory Committee on Vaccine Safety (GACVS; established by the World Health Organization) periodically reviews new safety data on HPV vaccines. GACVS has found no significantly increased risk of the any of following conditions: Guillain-Barre

syndrome, autoimmune conditions, or venous thromboembolic AEs.⁸⁻¹¹ Additionally, GACVS has found no causal association between HPV vaccine and conditions including complex regional pain syndrome and postural orthostatic tachycardia syndrome.

Although HPV vaccination is not recommended during pregnancy per the American Academy of Obstetricians and Gynecologists (ACOG), routine pregnancy testing is not recommended prior to vaccination.¹² According to

TABLE 2. Selected HPV Vaccine Prelicensure Efficacy Trial Data³⁰

Vaccine (trial age and sex)	Trial	HPV vaccine type—attributable end points	Per-protocol group		Control group		Vaccine efficacy (95% CI)
			Number of participants	Participants with outcome	Number of participants	Participants with outcome	
Cervarix							
Females aged 15-25 years	PATRICIA ³¹ NCT00122681	CIN 2+	7338	5	7305	97	94.9% (87.7%-98.4%)
Females aged >25 years	VIVIANE ³² NCT00294047	Incidence of persistent infection or CIN 1+	1852	7	1818	71	90.5% (78.6%-96.5%)
		CIN 2+	1852	1	1818	6	83.7% (46.5%-99.7%)
Gardasil							
Females aged 15-26 years	FUTURE I ³³ NCT00092521 FUTURE II ³⁴ NCT00092534	CIN 2+	7864	2	7865	110	98.2% (93.3%-99.8%)
		Anogenital warts	7665	2	7669	190	99.0% (95.8%-99.7%)
Females aged 24-45 years	FUTURE III ³⁵ NCT00090220	Incidence of persistent infection, CIN 1+, or external genital lesions	1581	10	1584	86	88.7% (78.1%-94.8%)
		CIN 2+	1581	1	1584	6	83.3% (37.6%-99.6%)
Gardasil 9							
Females aged 16-26 years	NCT00543543 ²⁶	HPV-31, -33, -45, -52, -58 CIN 2+, VIN 2+, VAIN 2+	6016	1	6017	38	97.4% (85.0%-99.9%)

1+, grade 1 or higher; 2+, grade 2 or higher; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; VAIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia.

research findings, inadvertent exposure to HPV vaccine during pregnancy was not associated with increased rates of spontaneous abortion or adverse birth outcomes.^{13,14} HPV vaccine is safe and recommended for breastfeeding women who have not been previously vaccinated.¹²

More recent population-based studies focusing on the 9-valent HPV vaccine continue to demonstrate its excellent safety profile, which is similar to that reported in prelicensure trials and in trials with the quadrivalent HPV vaccine.^{15,16}

Many claims surrounding the HPV vaccine are not based in evidence and should be refuted accordingly. A concern

sometimes voiced by parents is that their adolescent children are “not sexually active” and that receiving the HPV vaccine would promote unsafe sexual behaviors among adolescents.⁵ However, research has shown no significant association between legislation to increase HPV vaccination and changes in adolescent sexual behavior.¹⁷ Additionally, HPV vaccination was not associated with increased rates of sexually transmitted infection in a large population of female subjects.¹⁷ These data provide evidence that the claims that HPV vaccination encourages unsafe sexual activity are unfounded. Another concern has been raised regarding whether the HPV vaccine causes decreased fertility. Two

studies have found no evidence that the vaccine is associated with either primary ovarian insufficiency or increased infertility.^{18,19}

Efficacy

Natural infection with HPV triggers an immune response both by formation of neutralizing antibodies and by cell-mediated immunity via cytotoxic T lymphocytes; however, this response is slow and titers of antibodies from natural infection are much lower compared with those seen after HPV vaccination.^{20,21} Currently, immunogenicity is determined by evaluating seropositivity, geometric mean titer, and

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- In patients undergoing hemorrhoidectomy, a total of 266 mg (20 mL) of EXPAREL was diluted with 10 mL of saline, for a total of 30 mL, divided into six 5 mL aliquots, injected by visualizing the anal sphincter as a clock face and slowly infiltrating one aliquot to each of the even numbers to produce a field block.

Local Analgesia via Infiltration Dosing in Pediatric Patients

The recommended dose of EXPAREL for single-dose infiltration in pediatric patients, aged 6 to less than 17 years, is 4 mg/kg (up to a maximum of 266 mg), and is based upon two studies of pediatric patients undergoing either spine surgery or cardiac surgery.

Regional Analgesia via Interscalene Brachial Plexus Nerve Block Dosing in Adults

The recommended dose of EXPAREL for interscalene brachial plexus nerve block in adults is 133 mg (10 mL), and is based upon one study of patients undergoing either total shoulder arthroplasty or rotator cuff repair.

Compatibility Considerations

Administering EXPAREL with drugs other than bupivacaine HCl prior to administration is not recommended.

- Non-bupivacaine based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more.
- Bupivacaine HCl administered together with EXPAREL may impact the pharmacokinetic and/or physicochemical properties of EXPAREL, and this effect is concentration dependent. Therefore, bupivacaine HCl and EXPAREL may be administered simultaneously in the same syringe, and bupivacaine HCl may be injected immediately before EXPAREL as long as the ratio of the milligram dose of bupivacaine HCl solution to EXPAREL does not exceed 1:2. The toxic effects of these drugs are additive and their administration should be used with caution including monitoring for neurologic and cardiovascular effects related to local anesthetic systemic toxicity.²⁰
- When a topical antiseptic such as povidone iodine (e.g., Betadine®) is applied, the site should be allowed to dry before EXPAREL is administered into the surgical site. EXPAREL should not be allowed to come into contact with antiseptics such as povidone iodine in solution.

Studies conducted with EXPAREL demonstrated that the most common implantable materials (polypropylene, PTFE, silicone, stainless steel, and titanium) are not affected by the presence of EXPAREL any more than they are by saline. None of the materials studied had an adverse effect on EXPAREL.

Non-Interchangeability with Other Formulations of Bupivacaine

Different formulations of bupivacaine are not bioequivalent even if the milligram dosage is the same. Therefore, it is not possible to convert dosing from any other formulations of bupivacaine to EXPAREL and vice versa.

Liposomal encapsulation or incorporation in a lipid complex can substantially affect a drug's functional properties relative to those of the unencapsulated or nonlipid-associated drug. In addition, different liposomal or lipid-complexed products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect functional properties of these drug products. Do not substitute.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Administration of EXPAREL results in significant systemic plasma levels of bupivacaine which can persist for 96 hours after local infiltration and 120 hours after interscalene brachial plexus nerve block. In general, peripheral nerve blocks have shown systemic plasma levels of bupivacaine for extended duration when compared to local infiltration. Systemic plasma levels of bupivacaine following administration of EXPAREL are not correlated with local efficacy.

PATIENT COUNSELING

Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis); headache; rapid heart rate; shortness of breath; lightheadedness; or fatigue.



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Patent Numbers:
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antibody stability. In a study of young women who received the 9-valent HPV vaccine (NCT00543543), seropositivity to HPV-16/18 approached 100%, and most participants (77.5%-100%) remained seropositive after 60 months.²² Variations in antibody titers have been observed according to age, sex, vaccine type, and vaccine dosage, and multiple studies have suggested that vaccine-induced antibody titers are significantly higher in younger recipients.^{20,23} It is important to note that the relationship between immunogenicity from HPV vaccine and the vaccine's efficacy is not clearly characterized. For all HPV vaccines, no minimum level of antibody titer has been established as a threshold for efficacy.

Regardless of vaccine type or population, HPV vaccination has been shown to generate a durable, long-term immunogenic response, with studies showing stable antibody levels even 10 years after the initial vaccination.^{21,24,25} Results of a recent study in women in Costa Rica (NCT00128661) showed that a single dose of HPV vaccine achieved near 100% seropositivity and generated antibody titers that were 9-fold higher than those provoked by natural infection and that persisted for more than 7 years.²⁶ It is worth noting that a single dose of vaccine produces antibody titers lower than those produced by 2 or 3 doses, thus precluding noninferiority studies. Large studies with long follow-up times are needed to evaluate the true efficacy of single-dose vaccination regimens.

The efficacy of 2-, 4-, and 9-valent HPV vaccines against oncogenic HPV infection has been extensively evaluated through clinical trials. The most critical measure of HPV vaccine efficacy is prevention of invasive cancer. However, cervical cancer develops over many years after initial HPV infection and is often preceded by persistent cervical dysplasia, which is detected via routine screening. Therefore, prevention of invasive cancer was replaced by surrogate end points in HPV vaccine efficacy studies. These end points included 6-month persistent vaccine type-specific HPV infection, cervical intraepithelial neoplasia grade 2 or higher (CIN 2+), cervical adenocarcinoma in situ (AIS), and anogenital warts. All 3 vaccines demonstrated similarly high efficacy (summarized in **Table 2**).³⁰ The initial clinical trials were conducted in women 16 to 26 years old using a 3-dose vaccination schedule. Later studies also included adult women 26 to 45 years old, adolescents using the 2-dose schedule, and women who received only a single dose of vaccine. Analysis was performed in women without previous HPV infection (HPV-naïve population) and in the overall population (regardless of prior HPV infection status). Across HPV vaccine

types, higher efficacy was observed in the HPV-naïve population.^{8,20,22,24,27-29}

For the quadrivalent vaccine, the overall efficacy against persistent HPV-6/11/16/18 infection was 87% in the HPV-naïve group. In the same group, efficacy against external genital lesions as well as CIN 2+ associated with vaccine-type HPV was greater than 98%.^{8,36,37} For women 24 to 45 years old, vaccination efficacy against persistent type-specific HPV infection, CIN 1+, and external genital lesions was still above 89% in the HPV-naïve group, and efficacy in the overall population was 67%.³⁵ It is worth noting that cross-protection against other HPV serotypes has been observed for both bi- and quadrivalent vaccines. This is not surprising, given that the additional oncogenic HPV serotypes are genetically related to HPV-16/18. The bivalent vaccine has been shown to provide higher efficacy against HPV-31, -33, and -45 through cross-protection compared with the quadrivalent vaccine.^{38,39} The 9-valent vaccine has the added benefit of providing coverage against additional oncogenic HPV serotypes. The efficacy of the 9-valent vaccine in preventing persistent infection with the 5 additional oncogenic HPV serotypes was 95% in both HPV-naïve women and the overall population. Efficacy against high-grade disease was 97% in HPV-naïve women and 81% in the overall population.^{8,22,29}

Early clinical trials also demonstrated high vaccine efficacy even in women who failed to complete the full vaccination series and received only 1 to 2 doses of vaccine. This finding led to trials that evaluated the noninferiority of a 2-dose vaccination schedule in young adolescents (9 to 14 years old).

In a surprising finding, mean antibody titers were significantly higher in adolescents who received 2 doses of vaccine than in women aged 16 to 26 years who received 3 doses.^{40,41} In women older than 26 years, all 3 vaccines continue to demonstrate efficacy against persistent HPV infection and precancerous lesions, although efficacy is more pronounced in HPV-naïve women.⁸ Given that vaccine efficacy is highest in young women who are HPV naïve, the current recommendation is to start vaccination for all individuals at ages 11 to 12 years (and as early as 9 years) with a 2-dose schedule. Individuals older than 15 years would benefit from a 3-dose regimen.¹²

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Real-World Effectiveness

More than 15 years has passed since the introduction of the first HPV vaccine, and studies focusing on the real-world effectiveness of the vaccine and possible herd protection have been conducted. These studies examine the long-term impact of HPV vaccines, especially at the population level. Early data show that HPV vaccines are effective in preventing HPV infection, precancerous cervical lesions, genital warts, and cervical cancer in the community. Importantly, these studies show a reduction in HPV prevalence not only in the vaccinated population but also in the unvaccinated population. A recent US study reported that in the 11 years

after the introduction of HPV vaccines, detection of quadrivalent vaccine-type HPV in vaccinated women was reduced by approximately 80%, from 35% to 6.7%. Additionally, a decrease in the prevalence of 9-valent vaccine-type HPV was also observed in vaccinated women. Moreover, among unvaccinated women, the prevalence of quadrivalent vaccine-type HPV was also reduced by 40%, suggestive of herd protection.⁴²

Along with the decline in HPV-6/11 infections, a decrease in the prevalence and incidence of genital warts has been observed. A Danish study found that the overall incidence of genital warts, which had been increasing in the country until 2007, started to decline shortly after initiation of HPV vaccination, with the most significant decrease observed in young women with high HPV vaccination rates.⁴³

Additional studies have investigated the association between HPV vaccination and the incidence of HPV-attributable cancers. A retrospective, population-based, cross-sectional study showed that after vaccine approval, the rate of decrease in annual cervical cancer incidence in 20- to 24-year-olds grew to 9.5% compared with 2.3% prior to vaccine initiation. This finding suggests that the accelerated decrease in cervical cancer incidence in younger women may be related to HPV vaccination.⁴⁴ Another Swedish study that examined the relationship between HPV vaccination and risk of invasive cervical cancer demonstrated that the incidence rate of cervical cancer in vaccinated women younger than 31 years was significantly lower than that in unvaccinated women, with the lowest incidence rate among women vaccinated before age 17.⁴⁵

Lastly, as HPV vaccines become more prevalent worldwide, public health research has been using modeling studies to predict the long-term effectiveness and impact of HPV vaccination in the community. Early data suggest that even in models where only girls are vaccinated, and with a low vaccination rate of 20%, herd effects could be achieved. In models where high coverage of HPV vaccination is achieved in both boys and girls, data suggest that it may even be possible to eliminate high-risk HPV types.⁴⁶⁻⁴⁸

Special Topics

Although a therapeutic HPV vaccine that can treat HPV-associated precancerous lesions or cervical cancer is not yet available, several clinical trials are currently under way. More importantly, emerging evidence has

suggested that there may be benefits for women undergoing surgical treatment for HPV-related disease in receiving adjuvant vaccination with the currently available prophylactic HPV vaccine after primary treatment. For this population, studies have revealed a reduction in risk of recurrent lesions (CIN 2+) caused by HPV-16/18 after adjuvant vaccination.^{46,47}

Currently, ACOG and the Centers for Disease Control and Prevention have recommended that the HPV vaccine could be offered to those aged 27 to 45 years who had not been previously vaccinated based on shared clinical decision-making.¹² Although vaccine efficacy and effectiveness are lower in women in this age group, HPV vaccination may still offer benefits for specific populations.

Conclusion

In May 2018, the World Health Organization Director-General announced a global call for action to eliminate cervical cancer.⁴⁷ The HPV vaccine, shown to be safe and highly effective, especially when administered at an early age prior to initiation of sexual activity, is a critical component of the strategy to achieve this goal. High rates of HPV immunization will also have important effects on other HPV-associated cancers. In addition to continued investigation into the efficacy and effectiveness of single-dose vaccines, efforts to address vaccine hesitancy and improve access to HPV vaccination are critical to achieve the goal of lowering barriers to vaccination worldwide. ■

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