FDA Licensure of Bivalent Human Papillomavirus Vaccine (HPV2, Cervarix) for Use in Females and Updated HPV Vaccination Recommendations from the Advisory Committee on Immunization Practices (ACIP)

On October 16, 2009, the Food and Drug Administration (FDA) licensed bivalent human papillomavirus vaccine (HPV2; Cervarix, GlaxoSmithKline) for use in females aged 10 through 25 years. Cervarix is the second human papillomavirus (HPV) vaccine licensed for use in females in the United States. Quadrivalent HPV vaccine (HPV4; Gardasil, Merck & Co, Inc.) was licensed in 2006 for use in females aged 9 through 26 years, and the Advisory Committee on Immunization Practices (ACIP) recommended routine HPV4 vaccination of females aged 11 or 12 years, and catch-up vaccination for females aged 13 through 26 years (*1*). This report provides updated recommendations for routine and catch-up vaccination of females with either HPV2 or HPV4.

Both HPV2 and HPV4 are composed of virus-like particles (VLPs) prepared from recombinant L1 capsid protein of HPV; the two vaccines are not live vaccines (Table 1). HPV2 is directed against two oncogenic types (HPV 16 and 18). HPV4 is directed against two oncogenic types (HPV 16 and 18) and two nononcogenic types (HPV 6 and 11). Both vaccines have high efficacy against HPV 16 and 18-related cervical precancer lesions. HPV4 also has high efficacy against HPV 6 and HPV 11-related genital warts and HPV 16 and 18-related vaginal and vulvar precancer lesions (Table 2) (*2*–*5*).

HPV 16 and 18 cause about 70% of cervical cancers; each of the other oncogenic HPV types accounts for a small percentage of all cervical cancers. Other HPV-associated cancers in females include a subset of vulvar, vaginal, anal, and oropharyngeal and oral cavity cancers, caused primarily by HPV 16. HPV 6 and 11 cause approximately 90% of genital warts and most cases of recurrent respiratory papillomatosis.

In anticipation of FDA licensure of HPV2, ACIP reviewed data on the immunogenicity, efficacy, and safety of HPV2, as well as information on HPV4. At its October 21, 2009, meeting, ACIP approved updated recommendations for use of HPV vaccines in females.

TABLE 1. Selected characteristics of quadrivalent human papillomavirus vaccine (HPV4) and bivalent human papillomavirus vaccine (HPV2)*

Characteristic	HPV4	HPV2
Manufacturer	Merck & Co, Inc.	GlaxoSmithKline
Vaccine composition (L1 protein)	20 μg HPV 6 40 μg HPV 11 40 μg HPV 16 20 μg HPV 18	20 μg HPV 16 20 μg HPV 18
Manufacturing	*Saccharomyces cerevisiae* (bread yeast), expressing L1	*Trichoplusia ni* insect cell line infected with L1 encoding recombinant baculovirus
Adjuvant	AAHS: 225 μg amorphous aluminum hydroxyphosphate sulfate	AS04: 500 μg aluminum hydroxide 50 μg 3-O-desacyl-4′ monophosphoryl lipid A
Preservatives	None	None
Other content	Sodium chloride, L-histidine, polysorbate 80, sodium borate, and water for injection	Sodium chloride and sodium dihydrogen phosphate dehydrate, and water for injection
Temperature storage	Store refrigerated at 36°–46°F (2°–8°C). Do not freeze.	Store refrigerated at 36°–46°F (2°–8°C). Do not freeze.
Volume per dose	0.5 mL	0.5 mL
Administration	Intramuscular	Intramuscular
Schedule/Intervals	3 doses Second and third doses 1 to 2 months and 6 months after first dose	3 doses Second and third doses 1 to 2 months and 6 months after first dose

* Both vaccines are composed of virus-like particles (VLPs) prepared from recombinant L1 capsid protein of human papillomavirus (HPV); the vaccines are not live vaccines.

TABLE 2. Efficacy of bivalent human papillomavirus vaccine (HPV2) and quadrivalent human papillomavirus vaccine (HPV4) in females

	Vaccine		Control		Vaccine efficacy	
Vaccine/Endpoint/HPV type	No.	Cases	No.	Cases	%	(CI*)
Bivalent vaccine (HPV2)†						(96.1% CI)
CIN2/3 or AIS§						
HPV 16 and/or 18	7,344	4	7,312	56	92.9	(79.9–98.3)
HPV 16	6,303	2	6,165	46	95.7	(82.9–99.6)
HPV 18	6,794	2	6,746	15	86.7	(39.7–98.7)
Quadrivalent vaccine (HPV4)¶						(95% CI)
CIN2/3 or AIS**						
HPV 6, 11, 16, and/or 18	7,864	2	7,865	110	98.2	(93.3–99.8)
HPV 16	6,647	2	6,455	81	97.6	(91.1–99.7)
HPV 18	7,382	0	7,316	29	100.0	(86.6–100.0)
VIN2/3 or VaIN2/3 **						
HPV 6, 11, 16, and/or 18	7,900	0	7,902	23	100.0	(82.6–100.0)
HPV 16	6,654	0	6,467	17	100.0	(76.5–100.0)
HPV 18	7,414	0	7,343	2	100.0	(<0–100.0)
Genital warts††						
HPV 6 and/or 11	6,932	2	6,856	189	99.0	(96.2–99.9)

Abbreviations: CIN2/3 = cervical intraepithelial neoplasia grade 2 or 3, AIS = adenocarcinoma in situ, VIN2/3 = vulvar intraepithelial neoplasia grade 2 or 3, VaIN2/3 = vaginal intraepithelial neoplasia grade 2 or 3, HPV = human papillomavirus.

* Confidence interval.

† Phase III trial. According to protocol efficacy analysis included females aged 15 through 25 years who received all 3 vaccine doses, were seronegative at day 1 and HPV DNA negative at day 1 through month 6 for the respective HPV type, and had normal or low grade cytology at day 1, with case counting beginning 1 day after third vaccine dose; mean duration of follow-up post first vaccine dose: 34.9 months.

§ **Source:** Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet 2009;374:301–14.

¶ Combined analysis of one phase II and two phase III trials. Per protocol efficacy analysis included females aged 16 through 26 years who received all 3 vaccine doses, were seronegative at day 1 and HPV DNA negative at day 1 through month 7 for the respective HPV type, with case counting beginning 1 month after third vaccine dose; mean duration of follow-up post first vaccine dose: 42 months.

** **Source:** Kjaer SK, Sigurdsson K, Iversen OE, et al. A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (Types 6/11/16/18) vaccine against high-grade cervical and external genital lesions. Cancer Prev Res 2009;2:868–78.

†† **Source:** Food and Drug Administration. Product approval-prescribing information [package insert]. Gardasil [human papillomavirus quadrivalent (types 6, 11, 16, and 18) vaccine, recombinant], Merck & Co, Inc: Food and Drug Administration 2009. Available at http://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm094042.htm. Accessed May 25, 2010.

HPV2 Clinical Trial Data

HPV2 efficacy was evaluated in two randomized, double-blind, controlled clinical trials in females aged 15 through 25 years, including a phase IIb study (*6,7*) and a phase III study (*4*). The phase III trial included 18,644 females, followed for a mean of 34.9 months. Efficacy against HPV 16 or 18-related cervical intraepithelial neoplasia grade 2 or 3 or adenocarcinoma in situ (CIN2+) was 92.9% in the according to protocol analysis (Table 2) (*4*). Among women who were HPV 16 or 18 DNA positive at study enrollment, the vaccine had no efficacy against CIN2+ due to that type. A subset of participants in the phase IIb study has been followed for up to 6.4 years (mean: 5.9 years) after dose one with high efficacy against HPV 16 or 18-related CIN2+ demonstrated throughout the follow-up period (*7*).

Protection against cervical lesions due to nonvaccine HPV types was evaluated. In an analysis limited to lesions without HPV 16 or 18 coinfection, efficacy against CIN2+ due to any of 12 nonvaccine oncogenic types (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) was 37.4% (96.1% confidence interval [CI] = 7.4–58.2). In a post hoc analysis, efficacy against HPV 31-related CIN2+ in the according to protocol population was 89.4% (99.7% CI = 29.0–99.7) (*5*).

In all studies, ≥99% of participants developed an HPV 16 and 18 antibody response 1 month after completing the 3-dose series. Bridging immunogenicity studies were conducted among 1,193 females aged 10 through 14 years; geometric mean titers (GMTs) 1 month after the third dose were noninferior to those in females aged 15 through 25 years (*5*). The antibody responses for all vaccine antigens were noninferior after concomitant administration of HPV2 with tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine and/or with meningococcal conjugate vaccine in females aged 11 through 18 years compared with those after administration at separate visits. Rates of solicited and unsolicited symptoms and events were similar in all study groups (*8*).

HPV2 vaccinees were evaluated for injection-site and systemic symptoms, medically significant conditions, new onset autoimmune disorders, new onset

chronic diseases, deaths, serious adverse events, and pregnancy outcomes. Safety was evaluated by pooling data from 11 clinical trials of bivalent vaccine in females aged 10 through 25 years (*9*), and by a meta-analysis of safety databases of bivalent vaccine as well as other vaccines with the same adjuvant (*10*). The pooled safety analysis included 23,713 females aged 10 through 25 years; approximately 12,000 females received at least 1 dose of HPV2. In an analysis of local and general adverse events, a larger proportion of persons reported at least one injection-site symptom in the HPV2 group compared with controls (*5*). In the HPV2 group, 92% reported injection-site pain, 48% redness, and 44% swelling compared with 64%–87%, 24%–28%, and 17%–21% in the control groups. Fatigue, headache, and myalgia were the most common general symptoms. No differences were observed in unsolicited symptoms within 30 days of vaccination between the vaccine group and control groups.

Serious adverse events and deaths were evaluated in a pooled safety analysis that included 29,953 females aged 10 through 72 years (16,142 received HPV2). Proportions of persons reporting a serious adverse event were similar in vaccine and control groups (5.3% and 5.9%, respectively), as were the types of serious adverse events reported (*5*). In the pooled safety analysis, including 12,533 women who received HPV2 and over 10,730 in the control groups, incidence of potential new autoimmune disorders did not differ (0.8% in both groups).

Clinical protocols excluded women who were pregnant, and participants were instructed to avoid pregnancy until 2 months after the last vaccination. However, 3,696 pregnancies occurred in the vaccine group and 3,580 in the pooled control groups. Overall, no differences were observed in rates of any specific pregnancy outcomes between groups (*5*). Among 761 pregnancies around the time of vaccination (defined as last menstrual period 30 days before to 45 days after vaccination), 13.6% of pregnancies ended in spontaneous abortion in the vaccine group compared with 9.6% in the control group. HPV2 has been classified as Category B on the basis of animal studies that revealed no evidence of impaired fertility or harm to the fetus. No data are available on use of HPV2 in lactating women.

Vaccine Recommendations for HPV2 and HPV4

ACIP recommends routine vaccination of females aged 11 or 12 years with 3 doses of either HPV2 or HPV4. The vaccination series can be started beginning at age 9 years.

Vaccination is recommended for females aged 13 through 26 years who have not been vaccinated previously or who have not completed the 3-dose series. If a female reaches age 26 years before the vaccination series is complete, remaining doses can be administered after age 26 years. Ideally, vaccine should be administered before potential exposure to HPV through sexual contact.

ACIP recommends vaccination with HPV2 or HPV4 for prevention of cervical cancers and precancers. Both vaccines might provide protection against some other HPV-related cancers in addition to cervical cancer, although there are currently only data sufficient to recommend HPV4 for protection against vulvar and vaginal cancers and precancers. HPV4 is recommended also for prevention of genital warts.

Dosage, Administration, and Schedules

The dosing and administration schedules are the same for HPV4 and HPV2. Each dose is 0.5 mL, administered intramuscularly, preferably in a deltoid muscle. The vaccines are administered in a 3-dose schedule. The second dose is administered 1 to 2 months after the first dose, and the third dose is administered 6 months after the first dose.

The minimum interval between the first and second dose of vaccine is 4 weeks and between the second and third dose is 12 weeks. The minimum interval between the first and third dose is 24 weeks. Doses received after a shorter-than-recommended dosing interval should be readministered. If the HPV vaccine schedule is interrupted, the vaccine series does not need to be restarted. Coadministration of a different inactivated or live vaccine, either simultaneously or at any time before or after HPV vaccine, is permitted because neither HPV vaccine is a live vaccine.

Whenever feasible, the same HPV vaccine should be used for the entire vaccination series. No studies address interchangeability of HPV vaccines. However, if the vaccine provider does not know or have available the HPV vaccine product previously administered, either HPV vaccine can be used to complete the series to provide protection against HPV 16 and 18. For protection against HPV 6 or 11-related genital warts, a vaccination series with less than 3 doses of HPV4 might provide less protection against genital warts than a complete 3-dose HPV4 series.

Special Situations

Females who have abnormalities on their cervical cancer screening results are likely to be infected with one or more genital HPV types. With increasing severity of Papanicolau (Pap) findings, the likelihood of infection with HPV 16 or 18 increases, and benefits of vaccination decrease. Vaccination is still recommended for such females, because vaccination can provide protection against infection with HPV vaccine types not already acquired. Females should be advised that vaccination will have no therapeutic effect on an existing HPV infection or abnormal Pap test.

Prevaccination assessments (e.g., Pap testing or screening for high-risk HPV DNA, type-specific HPV tests, or HPV antibody) to establish the appropriateness of HPV vaccination are not recommended at any age.

A history of genital warts or clinically evident genital warts indicates infection with HPV, most often HPV 6 or 11. Vaccination is still recommended for such females because vaccination can provide protection against infection with HPV vaccine types not already acquired. Females should be advised that vaccination will have no therapeutic effect on an existing HPV infection or genital warts.

Lactating women can receive HPV vaccine.

HPV2 and HPV4 are not live vaccines, and can be administered to females who are immunosuppressed (from disease or medications). However, the immune response and vaccine efficacy might be less than that in immunocompetent persons.

Precautions and Contraindications

HPV vaccines are not recommended for use in pregnant women. If a woman is found to be pregnant after initiating the vaccination series, the remainder of the 3-dose series should be delayed until completion of pregnancy. Pregnancy testing is not needed before vaccination. If a vaccine dose has been administered during pregnancy, no intervention is needed.

Patients and health-care providers should report any exposure to HPV4 during pregnancy to Merck at telephone, 800-986-8999, and any exposure to HPV2 during pregnancy to GlaxoSmithKline at telephone, 888-452-9622.

HPV vaccines can be administered to persons with minor acute illnesses. Vaccination of persons with moderate or severe acute illnesses should be deferred until after the patient improves.

Syncope can occur after vaccination and has been observed among adolescents and young adults. To avoid serious injury related to a syncopal episode, vaccine providers should consider observing patients for 15 minutes after they are vaccinated.

HPV vaccines are contraindicated for persons with a history of immediate hypersensitivity to any vaccine component. HPV4 is produced in *Saccharomyces cerevisiae* (baker's yeast) and is contraindicated for persons with a history of immediate hypersensitivity to yeast. Prefilled syringes of HPV2 have latex in the rubber stopper and should not be used in persons with anaphylactic latex allergy. HPV2 single dose vials contain no latex.

References

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