

## Morbidity and Mortality Weekly Report (MMWR)

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# FDA Licensure of Quadrivalent Human Papillomavirus Vaccine (HPV4, Gardasil) for Use in Males and Guidance from the Advisory Committee on Immunization Practices (ACIP)

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## *Weekly*

**May 28, 2010 / 59(20);630-632**

On October 16, 2009, the Food and Drug Administration licensed quadrivalent human papillomavirus vaccine (HPV4; Gardasil, Merck & Co. Inc.) for use in males aged 9 through 26 years for prevention of genital warts caused by human papillomavirus (HPV) types 6 and 11. HPV4 had been licensed previously for use in females aged 9 through 26 years for prevention of HPV 6, 11, 16, and 18-related outcomes (i.e., vaginal, vulvar, and cervical precancers and cancers and genital warts). The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of females at age 11 or 12 years and catch-up vaccination for females aged 13 through 26 years (*1*). On October 21, 2009, ACIP provided guidance that HPV4 may be given to males aged 9 through 26 years to reduce their likelihood of acquiring genital warts; ACIP does not recommend HPV4 for routine use among males. This report presents the ACIP policy statement and summarizes background data. Issues reviewed by ACIP included efficacy, immunogenicity, and safety of the HPV4 vaccine in males, epidemiology of HPV and burden of HPV-associated diseases and cancers in males, cost-effectiveness of male vaccination, and programmatic considerations.

HPV types 6 and 11 cause approximately 90% of genital warts and most cases of recurrent respiratory papillomatosis. Approximately 500,000 cases of genital warts are estimated to occur each year in the United States among sexually active men and women (*2,3*). Direct medical costs related to genital warts are estimated at \$200 million per year (*2,3*); in addition, genital warts can have an adverse impact on quality of life (*4*). HPV-associated cancers in males include certain anal, penile, and oropharyngeal and oral cavity cancers caused primarily by HPV 16.

HPV4 has high efficacy for prevention of genital warts. The phase III efficacy study enrolled 4,065 males aged 16 through 26 years. Participants were enrolled from North America, South America, Europe, Australia, and Asia. The efficacy for prevention of genital warts related to HPV types 6, 11, 16, or 18 among males who received all 3 vaccine doses and were seronegative at day 1, and DNA negative day 1 through month 7 to the respective HPV type (per protocol population) was 89.4%; the efficacy for HPV 6 or 11-related genital warts alone was approximately the same (*Table*) (*5*). The efficacy for prevention of HPV 6, 11, 16, or 18-related genital warts among males who received at least 1 vaccine dose and regardless of baseline DNA or serology (intent to treat population), was 67.2%, and the efficacy for prevention of genital warts related to any HPV type was 62.1% (*Table*) (*5*). No evidence of efficacy was observed among males who were infected with the respective HPV type at baseline. The median duration of follow-up at the time of the study's interim analysis was approximately 2.3 years.

Data on immunogenicity in males are available from the phase III trial conducted among males aged 16 through 26 years, and from bridging immunogenicity studies conducted among males aged 9 through 15 years (*5*). Seroconversion rates were high for all four HPV types (HPV 6, 11, 16, or 18) targeted by HPV4, and postvaccination antibody titers were significantly higher in males aged 9 through 15 years compared with males aged 16 through 26 years (*5*).

As observed previously with females, in the clinical trials for males, the most common adverse events were injection-site reactions, most of which were mild or moderate in intensity (5). Headache and fever were the most commonly reported systemic adverse reactions in both treatment groups (5). Postlicensure data in females indicate that HPV4 adverse events are similar to adverse events reported following administration of other vaccines to adolescents (6).

Mathematical modeling suggests that adding male HPV vaccination to a female-only HPV vaccination program is not the most cost-effective vaccination strategy for reducing the overall burden of HPV-associated conditions in males and females when vaccination coverage of females is high (>80%) (7). When coverage of females is less than 80%, male vaccination might be cost-effective, although results vary substantially across models (7). Because the health burden is greater in females than males, and numerous models have shown vaccination of adolescent girls to be a cost-effective use of public health resources, improving coverage in females aged 11 and 12 years could potentially be a more effective and cost-effective strategy than adding male vaccination.

Men who have sex with men (MSM) are particularly at risk for conditions associated with HPV types 6, 11, 16, and 18; diseases and cancers that have a higher incidence among MSM include anal intraepithelial neoplasias, anal cancers, and genital warts (8,9). HPV4 has high efficacy for prevention of anal intraepithelial neoplasias in MSM (10); however, this information was not available before the October 2009 ACIP meeting and has not yet been reviewed by FDA.

## **Vaccine Guidance**

The 3-dose series of HPV4 may be given to males aged 9 through 26 years to reduce their likelihood of acquiring genital warts. HPV4 would be most effective when given before exposure to HPV through sexual contact.

## **Administration, Special Situations, Precautions, and Contraindications**

HPV4 is 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 the minimum interval 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 dosing interval that is shorter than recommended 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 HPV4 is permitted because HPV4 is not a live vaccine.

HPV4 can be administered to persons who are immunosuppressed (from disease or medications). However, the immune response and vaccine efficacy might be less than that in immunocompetent persons.

HPV4 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.

HPV4 is contraindicated for persons with a history of immediate hypersensitivity to any vaccine component. HPV4 is a recombinant vaccine produced in *Saccharomyces cerevisiae* (baker's yeast) and is contraindicated for persons with a history of immediate hypersensitivity to yeast.

## **References**

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**TABLE. Efficacy of quadrivalent human papillomavirus vaccine (HPV4) for prevention of genital warts in males aged 16 through 26 years**

Endpoint	Vaccine		Control		Vaccine efficacy	
	No.	Cases	No.	Cases	%	(95% CI*)
<b>Per protocol efficacy<sup>†,§</sup></b>						
HPV 6, 11, 16, and/or 18-related	1,397	3	1,408	28	89.4	(65.5--97.9)
<b>Intent to treat efficacy<sup>¶</sup></b>						
HPV 6, 11, 16, and/or 18-related	1,943	24	1,937	72	67.2	(47.3--80.3)
Any type-related	1,943	32	1,937	83	62.1	(42.4--75.6)

**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.

\* Confidence interval.

<sup>†</sup> Population included males who received all 3 vaccine doses, were seronegative at day 1, and DNA negative at day 1 through month 7 to the respective human papillomavirus (HPV) type, with case counting beginning after month 7.

<sup>§</sup> Efficacy for genital warts (HPV 6 and/or 11-related) was 89% (95% CI = 66--98). **Source:** Food and Drug Administration. Vaccine and Related Biological Products Advisory Committee meeting presentations. September 9, 2009. Available at <http://www.fda.gov/advisorycommittees/committeesmeetingmaterials/bloodvaccinesandotherbiologics/vaccinesandrelatedbiologicalproductsadvisorycommittee/ucm183835.htm> .

<sup>¶</sup> Population included all males who received at least 1 vaccine dose, regardless of baseline DNA or serology, with case counting beginning after day 1.

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Page last reviewed: May 28, 2010

Page last updated: May 28, 2010

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