



## POLICY STATEMENT

## HPV Vaccine Recommendations

## abstract

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On October 25, 2011, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention recommended that the quadrivalent human papillomavirus vaccine (Gardasil; Merck & Co, Inc, Whitehouse Station, NJ) be used routinely in males. The American Academy of Pediatrics has reviewed updated data provided by the Advisory Committee on Immunization Practices on vaccine efficacy, safety, and cost-effectiveness as well as programmatic considerations and supports this recommendation. This revised statement updates recommendations for human papillomavirus immunization of both males and females. *Pediatrics* 2012;129:602–605

## INTRODUCTION

The American Academy of Pediatrics (AAP) recommends immunization against human papillomavirus (HPV) for all 11- through 12-year-old children as part of the adolescent immunization platform. Quadrivalent HPV vaccine (HPV4; Gardasil; Merck & Co, Inc, Whitehouse Station, NJ) is the only vaccine approved for males, and either HPV4 or bivalent HPV vaccine (HPV2; Cervarix; GlaxoSmithKline, Middlesex, UK) may be used in females. This brief policy statement supersedes the previous AAP “permissive recommendation” for use of HPV4 in males<sup>1</sup> and the retired 2007 policy statement.<sup>2</sup> A complete rationale is available in the statement from the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention.<sup>3</sup>

## BRIEF BACKGROUND AND RATIONALE

HPVs are the most common sexually transmitted viruses in the United States. The highest prevalence of HPV infection is found in sexually active adolescents and young adults. Most HPV infections are asymptomatic and resolve without complications within 2 years. However, persistent infection with high-risk HPV types is responsible for most cervical and anal cancers in females. In males, high-risk HPV types are responsible for a large proportion of cancers of the mouth and pharynx, which are increasing in recent years, and of anal and penile cancers. Each year in the United States, approximately 15 000 cases of cancer in females and 7000 cases of cancer in males are caused by HPV types 16 and 18. Of the cancers in males, the great majority are cancers of the oropharynx (approximately 5400), followed by anal cancer (approximately 1400) and penile cancer (approximately 300). The rationale for routine HPV immunization at 11 through 12 years of age is twofold. First, optimal vaccine efficacy is derived if the vaccine is

## COMMITTEE ON INFECTIOUS DISEASES

## KEY WORDS

human papillomavirus, HPV, vaccine, males, females, adolescents, immunization, cancer

## ABBREVIATIONS

AAP—American Academy of Pediatrics

HPV—human papillomavirus

HPV2—bivalent human papillomavirus vaccine

HPV4—quadrivalent human papillomavirus vaccine

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administered before onset of sexual activity. The vaccine is inactive against HPV types previously acquired by the vaccine recipient. Second, antibody responses are highest at ages 9 through 15 years. Immunization of males provides direct benefit to males, including prevention of genital warts and anal cancer. Prevention of oropharyngeal cancer has not been studied but is biologically plausible. In addition, immunization of males is expected to provide indirect benefit for females through herd immunity. Four years after the initial recommendation for immunization of females, uptake of the HPV vaccine lags behind other vaccines offered in adolescence; results of the 2010 National Immunization Survey indicated 32% of females 13 through 17 years have completed the 3-dose series. The cost-effectiveness of male immunization is sensitive to a range of assumptions, such as vaccine efficacy, vaccine coverage of females, and the effect of HPV-associated diseases on quality of life. Recognizing low vaccine uptake among females and the preponderance of heterosexual transmission in the epidemiology of HPV, immunization of males becomes a cost-effective intervention for preventing disease caused by vaccine types of HPV in both genders.

Other interventions to reduce HPV infection and HPV-associated genital warts and malignancies include counseling of adolescents regarding sexuality, including abstinence and proper use of condoms, and circumcision of males. HPV is transmitted skin to skin, so protection by condoms is imperfect.<sup>4-6</sup>

As a sidebar, there is precedent for vaccines recommended by the AAP and the Advisory Committee on Immunization Practices for prevention of sexually transmitted infections and cancer and for immunization of all children to minimize infectious complications

disproportionately affecting females during their reproductive years. Rubella vaccine (a component of the measles-mumps-rubella vaccine) is intended primarily to prevent fetal miscarriages and malformations after rubella infection during pregnancy, and hepatitis B virus vaccine prevents cirrhosis of the liver and hepatocellular carcinoma caused by hepatitis B virus acquired at time of birth or through later sexual exposure.

### HPV VACCINES

HPV4 contains no viral DNA and is not infectious. It consists of bioengineered viruslike particles produced from the major capsid protein of HPV types 16 and 18, which are responsible for 70% of cases of cervical, 87% of anal, 60% of oropharyngeal, and 31% of penile cancers. In addition, the vaccine includes capsid proteins of types 6 and 11, which are responsible for 90% of genital warts and almost all cases of juvenile recurrent respiratory papillomatosis. Clinical trials have revealed the vaccine to be highly immunogenic, safe, and well tolerated in males and females 9 through 26 years of age. Antibody responses are at least twice as high in individuals of both genders 9 through 15 years of age as in those 16 through 26 years of age. HPV4 was licensed for use in females in 2006; antibodies have been shown to persist for at least 9 years. HPV4 was licensed for use in males in 2009; the duration of vaccine-induced antibodies is still under investigation but is known to be at least 5 years.

In sexually active female subjects 16 through 26 years of age, protection has been demonstrated against persistent infection; precancerous lesions of the cervix, vulva, and vagina; and genital warts caused by HPV types contained in the vaccine. The vaccine was recommended for females in 2007. In sexually active male subjects 16 through

26 years of age, vaccine efficacy was demonstrated against genital warts caused by vaccine types. HPV4 was permitted in males in 2010. Also in 2010, the US Food and Drug Administration added a new indication of prevention of anal cancer in males and females on the basis of data from an efficacy study in males. In new data from a substudy of high-risk sexually active young men (men who have sex with men), protection has been demonstrated against precancerous lesions of the anus. These data contribute to the current recommendation. The study did not have adequate power (too few penile or perineal precancerous lesions) to support benefit in preventing these precancerous conditions. No studies of HPV4 vaccine protection against oropharyngeal cancers or recurrent respiratory papillomatosis have been conducted.

HPV2, directed at HPV types 16 and 18, was licensed for use in females in 2009. This vaccine is highly immunogenic, safe, and well tolerated in females 9 through 26 years of age. Antibody responses are highest in girls 9 through 15 years of age. HPV2 is not licensed for use in males.

The safety of HPV4 was evaluated in 2 large phase III clinical trials in females, 1 phase III clinical trial in males, and several immunogenicity studies in adolescents. There is continued surveillance of potential adverse effects of HPV vaccine through the Vaccine Adverse Effect Reporting System as well as real-time surveillance of large health maintenance organization practices via the Vaccine Safety Datalink. Several other countries or communities conduct similar surveillance for adverse effects of HPV vaccines. The Food and Drug Administration requires post-marketing surveillance by vaccine manufacturers. After more than 40 million doses have been administered in the first 5 years of routine

administration in American girls, no discernible, vaccine-specific adverse effect, with the exception of rare anaphylaxis to vaccine components, has been detected.

## RECOMMENDATIONS

1. Girls 11 through 12 years of age should be immunized routinely with 3 doses of HPV4 or HPV2, administered intramuscularly at 0, 1 to 2, and 6 months. The vaccines can be administered starting at 9 years of age at the discretion of the physician.
2. All girls and women 13 through 26 years of age who have not been immunized previously or have not completed the full vaccine series should complete the series.
3. Boys 11 through 12 years of age should be immunized routinely with 3 doses of HPV4, administered intramuscularly at 0, 1 to 2, and 6 months. The vaccine can be given starting at 9 years of age at the discretion of the physician.
4. All boys and men 13 through 21 years of age who have not been immunized previously or have not completed the full vaccine series should receive HPV4 vaccine.
5. Men 22 through 26 years of age who have not been immunized previously or have not completed the full vaccine series may receive HPV4 vaccine. Cost-efficacy models do not justify a stronger recommendation in this age group.
6. Special effort should be given to immunizing men who have sex with men up to 26 years of age who have not been immunized previously or have not completed the full vaccine series.
7. Previous sexual activity is not a contraindication to HPV immunization or completion of the immunization series. Patients infected with 1 HPV type may still benefit from protection against remaining HPV types in the vaccine. Testing for previous exposure to HPV is not recommended. HPV vaccine can be administered when a female patient has an abnormal or equivocal Papanicolaou test result. There is no known therapeutic (as opposed to prophylactic) benefit from the HPV vaccines.
8. HIV-infected people of either gender, 9 through 26 years of age, who have not been immunized previously or have not completed the full vaccine series should receive or complete their series with HPV4.
9. HPV vaccines can be administered at the same visit as all other recommended vaccines.
10. HPV vaccine can be administered in these special circumstances:
  - a. when a patient is immunocompromised because of disease or medication
  - b. when a female patient is breastfeeding
11. HPV vaccine is not recommended during pregnancy. The practitioner should inquire about pregnancy in sexually active female patients, but a pregnancy test is not required before starting the immunization series. If a vaccine recipient becomes pregnant, subsequent doses should be postponed until completion of the pregnancy. It is recommended that women who become pregnant while receiving HPV vaccine be reported to registries that have been developed to record data on outcomes (HPV2: 1-888-452-9622; HPV4: 1-800-986-8999).
12. Because HPV vaccine will not prevent infection attributable to all high-risk HPV types, cervical cancer screening recommendations

(ie, Papanicolaou testing) should continue to be conducted in women who have received HPV vaccine.

13. Administration of HPV vaccine does not change current counseling recommendations for use of barrier methods for the prevention of HPV and other sexually transmitted infections as well as discussion about healthy choices about sexual activity, including condoms and abstinence.
14. HPV immunization of children 9 years of age and older should be covered by all public and private health insurers.

## CONTRAINDICATIONS

HPV4 should not be given to people with a history of immediate hypersensitivity to yeast or to pregnant women.

## PRECAUTIONS

Immunizations should be deferred for people with moderate or severe acute illness. Because syncope can occur in adolescents after injections and has been reported after HPV vaccine, vaccine recipients should sit or lie down for 15 minutes after administration.

## IMPLEMENTATION

These updated recommendations for HPV immunization will have considerable operational and fiscal effect on pediatric practice. Therefore, the AAP has developed implementation guidance on supply, payment, coding, and liability issues; these documents can be found at [www.aapredbook.org/implementation](http://www.aapredbook.org/implementation).

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