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The case for HPV immunization

HPV4 is now available for boys, and a second vaccine to protect against HPV-associated cancer has been approved. Should you be using these vaccines in your practice?

HPV4 has proven highly effective in women ages 15 to 26 who have not been previously infected with the HPV types in the vaccine.

The first quadrivalent human papillomavirus vaccine (HPV4) was licensed in the United States in 2006 (Gardasil, Merck & Co., Inc.).[1] It contains viral proteins from HPV types 18, 16, 11, and 6, the types currently responsible for 70% of cervical cancers and 90% of anogenital warts.[2] The vaccine is licensed for use in females ages 9 to 26 years for the prevention of cervical, vulvar, and vaginal precancerous lesions and cancer, and for the prevention of anogenital warts.[1] It was recently licensed in the United States for the prevention of anogenital warts in males, as it has been in other countries.[2,3]

HPV and cancer: Quantifying the threat

Human papillomavirus (HPV) is responsible for cancers at several anatomical sites, including the cervix, anus, oral mucosa, vulva, vagina, and penis.[1] The rate of cervical cancer in the United States has declined markedly since the introduction of screening programs using cervical cytology testing.[1] This decline has been predominantly in squamous cell carcinomas, not adenocarcinomas, which are located in the endocervix and harder to detect.[1]

There are still around 12,000 cases of cervical cancer diagnosed each year in the United States, for an incidence of 8.1/100,000 women, and 3924 cervical cancer-related deaths.[1] In addition, 7% to 10% of the 50 million cervical cytology tests done each year require some form of follow-up. Of these, 2 million to 3 million findings requiring follow-up are atypical squamous cells of undetermined significance (ASC-US) and 1.25 million are low-grade squamous intraepithelial lesions.[1]

There were more than 4000 cases of anal cancer recorded in 2003, a rate of 1.6/100,000 in women and 1.3/100,000 in men. In contrast to the trend in cervical cancer rates, anal cancer rates are increasing.[4] It is not known how many incident cases of genital and anal warts there are annually, but some estimates place the number as high as 1 million. Lifetime cumulative risk has been estimated at 10%.[5]

Global morbidity and mortality from HPV is considerable, with 500,000 cases of cervical cancer and 260,000 cervical cancer-related deaths reported worldwide in 2005.[2] Rates are highest in developing countries in Latin America, Africa, and Asia.[2]

The vaccine is effective in women

HPV4 has proven to be highly effective in women ages 15 to 26 who have not been previously infected with the HPV types in the vaccine. Effectiveness has been 98% to 100% after 3 to 5 years in these women, using such end points as moderate and severe cervical intraepithelial neoplasia (CIN2 and CIN3), endocervical adenocarcinoma in situ (AIS), anogenital warts, and vulvar and vaginal intraepithelial neoplasia.[1,2,6] These trials are ongoing.

Efficacy among women with current or past HPV infection is less certain. Studies of this question have included only small numbers and the confidence intervals have been

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TABLE 1

ACIP HPV4 recommendations[1]

• Routinely vaccinate girls between the ages of 11 and 12 years with 3 doses of the HPV4 vaccine. The series can start in those as young as 9 years.
• Provide catch-up vaccination of females between the ages of 13 and 26 who have not been previously vaccinated.
• Avoid unnecessary testing: Neither Pap testing nor HPV screening is needed before vaccination.
• Don't hesitate to administer the HPV4 vaccine with other age-appropriate vaccines.
• Follow the vaccine recommendations even if your patient has an abnormal Pap test, a positive HPV DNA test, or genital warts. Keep in mind that vaccination does not change recommendations for cervical cancer screening.

ACIP, Advisory Committee on Immunization Practices.

large and included 0. In intention-to-treat studies, efficacy has been 39% to 46% for prevention of CIN2 or 3 and AIS caused by HPV 16 and 18, 69% for prevention of HPV 16/18-related vaginal intraepithelial neoplasia, and 68.5% for vaccine type-related warts.[1]

Who should be vaccinated?

According to the June 2006 recommendations of the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC), immunization with 3 doses of HPV4 should be routine for girls between the ages of 11 and 12. Vaccination may be started in girls as young as age 9 and can also be done for females between the ages of 13 and 26.[1] The ACIP recommendations are summarized in **TABLE 1**.

The World Health Organization (WHO) qualifies its recommendations a bit. "Routine HPV vaccination," notes WHO, "should be included in national immunization programs *provided* that:

- prevention of cervical cancer or other HPV-related diseases, or both, constitutes a public health priority,
- vaccine introduction is programmatically feasible,
- sustainable financing can be secured, and
- the cost effectiveness of vaccination strategies in the country or region are considered."[2]

WHO also says the vaccine is most effective prior to HPV infection and that, based on the age of initiation of sexual activity, the target population is most likely to be females 9 to 13 years of age. WHO does not recommend vaccination in males.[2]

In the United States, most professional organizations, including the American Academy of Family Physicians, have adopted recommendations in line with those of ACIP. One exception is the American Cancer Society (ACS), which takes issue with ACIP's recommendations for the 19- to 26-year age group. The ACS position is that the evidence is insufficient to recommend for or against routine use of the HPV vaccine for this age group.[7]

Some doubts among parents and physicians

Recent national vaccine survey data show that only 25% of females ages 13 to 17 had received 1 or more doses of HPV4 vaccine.[8] Young women appear to be interested in the vaccine and in possibly receiving it, but they tend to underestimate their risk of contracting HPV.[9,10] Some parents are concerned that the vaccine may encourage risk-taking behavior.[11] Physicians report that some parents fear the vaccine is too new to be fully evaluated and are concerned that insurance may not cover the cost of the 3-shot series.[12]

Physician attitudes toward the vaccine are generally positive. Close to 90% of family physicians and 98% of pediatricians administer the vaccine in their practices.

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Close to 90% of family physicians and 98% of pediatricians administer the HPV4 vaccine in their practices.

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TABLE 2

HPV4 systemic adverse events in females, ages 9-23 years[1]

Adverse events occurring 1 to 15 days post-vaccination	HPV4 recipients (N=5088)	Placebo recipients (N=3790)
Pyrexia	13.0%	11.2%
Nausea	6.7%	6.6%
Nasopharyngitis	6.4%	6.4%
Dizziness	4.0%	3.7%
Diarrhea	3.6%	3.5%
Vomiting	2.4%	1.9%
Myalgia	2.0%	2.0%
Cough	2.0%	1.5%
Toothache	1.5%	1.4%
Upper respiratory tract infection	1.5%	1.5%
Malaise	1.4%	1.2%
Arthralgia	1.2%	0.9%
Insomnia	1.2%	0.9%
Nasal congestion	1.1%	0.9%

The approved age range for HPV4 in women may be expanded above 26 years.

Eighty percent strongly recommend it to 13- to 15-year-olds, and 50% recommend it to 11- to 12-year-olds.

A small minority of family physicians has misconceptions regarding the vaccine:

- 15% believe an HPV test should be ordered before vaccination
- 19% believe the vaccine should not be given to those diagnosed with HPV
- 31% believe a pregnancy test should be ordered before administering the vaccine.[12]

Safety concerns, minor and major

Clinical trials conducted by the vaccine manufacturer demonstrated slightly higher rates of some systemic adverse reactions in the vaccinated group compared with placebo groups (**TABLE 2**). Data on adverse reactions at the injection site also showed somewhat higher percentages in the vaccine group. These trials were not large enough to detect severe, rare adverse reactions.

The CDC and the US Food and Drug Administration (FDA) collaboratively operate a passive reporting system, the Vaccine Adverse Events Reporting System (VAERS), as a way of conducting surveillance for these rare events. The manufacturer is required to report suspected adverse events to VAERS, but providers and consumers can also report any suspected adverse events.

There are problems with VAERS. Because it is a passive system, some adverse events may not be reported. At the same time, some events reported by consumers and physicians may be coincidental occurrences not caused by the vaccine. To complicate matters further, patients often receive more than 1 vaccine at the same time, so that attributing any particular adverse reaction to a single vaccine is problematic. These imperfections in VAERS should lead to caution in interpreting reports received on any 1 vaccine.

A recent article published in the *Journal of the American Medical Association* (*JAMA*) described the reports on the HPV4

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vaccine received by the VAERS for the first 2½ years after licensure.[13] Slightly more than 23 million doses had been distributed during this time, and 12,424 adverse events were reported. The most common were syncope (1847), dizziness (1763), nausea (1170), headache (957), and injection site reactions (926). Of all these reported events, 772 reactions were classified as serious, and 32 vaccine recipients died. Investigation of the deaths revealed that the mean time from vaccine to the death was 47 days, the deaths were caused by a variety of underlying conditions, and 4 deaths remained unexplained.

The only 2 serious adverse events that appeared to occur more frequently than background rates were venous thrombotic events, at 1 per 500,000 doses, and syncope, at a rate of 8.2 per 100,000 doses. The syncopal events were concentrated among the 11- to 18-year-olds and resulted in 293 falls and 200 head injuries. The authors of the *JAMA* article caution about attributing any cause and effect to the venous thromboembolism findings because of the high rates of oral contraceptive use in this age group, which increases the risk of this condition. Studies are ongoing to try to sort out these issues.

New developments: HPV4 for boys, licensing a bivalent vaccine

At its meeting in October 2009, ACIP decided to approve HPV4 for the prevention of anogenital warts in boys and young men ages 9 to 26.[14] The potential benefits of using the HPV vaccine in males include reduced incidence of anogenital warts, possible reduction in HPV-related cancers, and reduced transmission of the HPV viruses in the vaccine to women and other men. The ACIP panel did not recommend routine immunization, however, leaving it up to physicians and patients to decide whether the vaccine is worthwhile. The advisory group said it would take up the question of the vaccine's effectiveness in preventing HPV-related male cancers at future meetings.

At the same meeting, ACIP also voted to recommend Cervarix, the bivalent HPV vaccine from GlaxoSmithKline, for routine use in girls 11 and 12 years of age for the prevention of cancer and precancerous lesions.[14] This vaccine contains antigens against HPV types 16 and 18 and does not provide protection against genital warts. Cervarix has been licensed in other countries and, to date, has demonstrated effectiveness comparable to that of the HPV4 against HPV 16- and 18-related outcomes.[1,2,6]

The availability of 2 HPV vaccines, 1 against both warts and cervical cancer and the other against cervical cancer only, will present some challenging ethical and practical issues for ACIP, as well as for states and physicians.

Unresolved issues

Some critics of the vaccine have pointed out that neither HPV vaccine has yet been proven to prevent cervical cancer. Because the amount of time it takes HPV infection to progress to cervical cancer is, on average, 10 to 20 years, vaccine trials will need to be continued for years to establish this point. However, high-grade cervical lesions and genital warts are outcomes important to patients on their own and are associated with considerable morbidity. It is unknown how continued use of the vaccine will affect the epidemiology of HPV infection and the incidence of HPV types not affected by the vaccine.

Safety monitoring of the vaccine continues. At this time it appears that syncopal episodes occur at increased rates shortly after administration of the HPV4 vaccine, and vaccine providers are encouraged to follow ACIP recommendations of a 15-minute waiting period after the administration of the vaccine.[13] Ongoing studies will continue to look at potential rare adverse reactions and determine if the vaccine is truly a cause of venous thromboembolic events.

The approved age range for the use of HPV4 in women for the prevention of cancer, precancerous lesions, and warts may be expanded above 26 years. The benefit among women of this age will be less than for younger women, because of the higher probability of previous exposure to HPV. ACIP will need to decide on whether the vaccine should be routinely or selectively recommended above age 26. JFP

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Syncopal episodes occur at increased rates after HPV4 vaccination. That's why it's wise to allow a 15-minute waiting period after administration of the vaccine.

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