



The Quadrivalent Human Papillomavirus Vaccine

Anna Wheat

The human papillomavirus (HPV) is a group of over 100 viruses, 40 of which can be transmitted through mucosal cells during vaginal or anal intercourse, thereby infecting genital areas. Different HPVs infect the body in distinctive ways. In many cases there are no obvious symptoms (until late sequelae such as cervical cancer manifest themselves), but some of the viruses cause genital warts, genital lesions (abnormal cells), and some of the viruses cause cancers of the cervix, vulva, vagina, anus, or penis. Most people's immune systems will clear HPV within two years,¹ but sometimes the virus persists, and if untreated, may eventually cause cancer.

HPV is the most common sexually transmitted disease. According to the Centers for Disease Control and Prevention (CDC), 20 million Americans are currently infected with HPV, and 6.2 million are newly infected every year. At least 50% of sexually active men and women will become infected with HPV at some point in their lives.¹ At any given time, about 1% of the population is infected with genital warts caused by HPV.²

THE QUADRIVALENT HPV VACCINE

Gardasil[®], manufactured by Merck and Co, is a quadrivalent HPV vaccine approved for administration to females between the ages of 9 and 26. It confers immunity against four of the most common types of HPV – types 6, 11, 16 and 18. HPV types 6 and 11 are responsible for 90 percent of genital warts; types 16 and 18 are responsible for 70 percent of cervical cancers. The vaccine is a bioengineered, component vaccine made up of virus-like particles produced from the surface proteins of HPV types 6, 11, 16 and 18. The vaccine contains no viral DNA and is not infectious.³ Approved by the FDA in June 2006, it does not contain antibiotics or mercury compounds such as thimerosal⁴ (the vaccine preservative alleged – without supportive data – to cause autism).

HPV vaccine should be used to prevent HPV infection in women who are not infected. Vaccination before sexual debut is recommended, as early as age 9 at the discretion of the physician. Routine vaccination is recommended for girls ages 11-12. "Catch-up" vaccinations are recommended for girls and young women ages 13 - 26. The FDA has not approved the vaccine for males.

ADMINISTRATION

Gardasil[®] is administered in three independent 0.5 ml doses at 0, 2, and 6 months. The vaccine is available as a sterile suspension for injection in a single-dose vial or a pre-filled syringe.⁴ The vaccine should be stored at 2°C–8°C (36°F–46°F) and should not be frozen or exposed to light; its shelf life is 36 months. Side effects include soreness at the injection site, headache, fatigue, or vague feeling of discomfort after injection. Persons should not receive the vaccine if (1) they have

ever had a life threatening allergic reaction to yeast, any other component of the vaccine, or a previous dose of the vaccine, (2) they are pregnant, or (3) they are suffering from a moderate or severe illness. The vaccine retails for \$120 per dose for a total of \$360, not including the price of the office visit.

EFFECTIVENESS

Four clinical trials have been completed to test HPV vaccine; one evaluated a monovalent (HPV 16) vaccine — a phase II study; three evaluated the quadrivalent vaccine — one phase II and two phase III studies.⁴ As reported in 2007 by the Advisory Committee on Immunization Practices,⁴ the quadrivalent vaccine was shown to be quite effective:

"Various endpoints were assessed in the different studies, including vaccine type-related persistent HPV infection, cervical intraepithelial neoplasia (CIN), vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VaIN), and genital warts. The primary endpoint and the basis for licensure was the combined incidence of HPV 16- and 18-related CIN 2/3 or AIS. These endpoints served as surrogate markers for cervical cancer. Studies using an invasive cervical cancer endpoint were not feasible because the standard of care is to screen for and treat CIN 2/3 and AIS lesions to prevent invasive cervical cancer. Furthermore, the time from acquisition of infection to the development of cancer can exceed 20 years. ... Quadrivalent HPV vaccine has a high efficacy for prevention of vaccine HPV type HPV 6-, 11-, 16-, and 18-persistent infection, vaccine type-related CIN, CIN 2/3, and external genital lesions (genital warts, VIN and VaIN) when analyses were restricted to participants who received all 3 doses of vaccine, had no protocol violations, and no evidence of infection with the relevant vaccine HPV type (seronegative and HPV PCR-negative through 1 month after dose 3). ... Participants infected with one or more vaccine HPV types before vaccination were protected against disease caused by the other vaccine HPV types. No evidence exists that the vaccine protects against disease caused by non-vaccine HPV types."⁴

RECOMMENDATIONS

The CDC⁴, The American Academy of Pediatrics (AAP)³, The Society for Adolescent Medicine (SAM)⁵, The American College Health Association (ACHA)⁶, The American Cancer Society (ACS)⁷, and The American College of Obstetricians and Gynecologists (ACOG)⁸ have developed recommendations for the use of quadrivalent HPV vaccine. The following consensus has emerged in the scientific literature:

1. Routine vaccination is recommended for girls 11-12 years old, ideally before sexual debut. Vaccination can be administered as young as age 9 at the discretion of the physician.
2. Catch-up vaccination is recommended for girls 13-26 years old who have not been vaccinated or who have not completed the three-dose vaccination series.
3. Quadrivalent HPV vaccine is administered in a 3-dose schedule. The second and third doses should be administered 2 and 6 months after the first dose.
4. The minimum interval between the first and second doses of vaccine is 4 weeks. The minimum recommended interval between the second and third doses of vaccine is 12 weeks. Inadequate doses of quadrivalent HPV vaccine or vaccine doses received after a shorter-than-recommended dosing interval should be re-administered.
5. Quadrivalent HPV vaccine can be administered at the same visit as other age appropriate vaccines, however each vaccine should be administered using a separate syringe at a different anatomic site.
6. Lactating as well as immunosuppressed females can receive the vaccine.
7. Pregnant women, females with moderate to severe acute illness, or anyone allergic to any part of the vaccine (such as yeast) should not get the vaccine.
8. Regular cervical cancer screenings should ensue despite vaccination status.

Several additional recommendations are well worth noting:

CDC: If the quadrivalent HPV vaccine schedule is interrupted, the vaccine series does not need to be restarted. If the series is interrupted after the first dose, the second dose should be administered as soon as possible, and the second and third doses should be separated by an interval of at least 12 weeks. If only the third dose is delayed, it should be administered as soon as possible.⁴

ACOG: Testing for HPV is currently not recommended before vaccination.⁸

ACOG: Sexually active women can receive the quadrivalent HPV vaccine. Women with previous abnormal cervical cytology or genital warts also can receive the quadrivalent HPV vaccine. The quadrivalent vaccine can be given to patients with previous CIN, but practitioners need to emphasize that the benefits may be limited, and cervical cytology screening and corresponding management based on ACOG recommendations must continue.⁴

CURRENT HPV VACCINE CONTROVERSIES

Expected Impacts vs. Unanswered Questions

Dr. Anne Schuchat, Director of CDC's National Center for Immunization and Respiratory Diseases, notes that the quadrivalent HPV vaccine "has been tested in thousands of women around the world and has been found to be safe and effective in providing protection against the two types of HPV that cause most cervical cancers."⁹ Projected clinical gains include decreased incidence of

genital warts, cervical lesions, cervical dysplasia, and cervical cancer. Furthermore, the quadrivalent vaccine has the potential to be cost-effective if administered to females of the appropriate ages. For example, a study done by the Department of Health Policy and Management at the Harvard school of Public Health demonstrated the potential monetary savings of large-scale immunization. Assuming that the vaccination gives lifelong immunity, savings will be seen to the highest degree when girls are vaccinated in preadolescence (before age 14), theoretically allowing the delay of initial cervical cancer screening, and allowing longer intervals between subsequent screenings. Both outcomes would produce substantial savings¹⁰ for those vaccinated as well as third-party payers.

Despite the potential advantages of quadrivalent HPV vaccine, the medical world has been cautious in its adoption, primarily because the vaccine is new, and the usual questions attendant at the time of vaccine roll-out have arisen. Will the vaccine actually decrease the burden of cervical cancer and death? For how long will effective immunity be conferred by the three-dose series?¹¹ Will boosters be needed? (When? How frequently? At what cost?) Will use of the vaccine create selective pressure on particular HPV types, causing other types to become dominant in cervical lesions, genital warts, and other conditions? Given the current price of the quadrivalent HPV vaccine, will it be accessible in the developing world?¹² Will the price decline, and how soon? Will developing nations have access to vaccine at reduced cost? And most importantly, will use of the vaccine strengthen or weaken the existing (highly effective) infrastructure for cervical cancer screening in the U.S. and internationally? Resolving these questions will require decades of use and careful observation.¹³

Parental Consent vs. Child's Sexuality

Adolescents under 18 years of age represent a group that can be targeted before the initiation of sexual activity, but do not have the authority to vaccinate themselves against the virus.¹⁴ Currently, if a parent opposes the HPV vaccine because they see it as a "go ahead" for their child to engage in sexual activity, a teenager under the age of 18 can be denied permission to receive the vaccine, even though they *do not* need such permission to access birth control and testing for sexually transmitted infections. Assuming that the use of HPV vaccine becomes the *community standard of practice* throughout the United States, the issue of parental permission will undoubtedly be addressed.

DISCUSSION

The most important question remains: "Do the benefits of HPV vaccine outweigh the unknowns?" On the one hand, there is considerable evidence that the vaccine is safe and effective in preventing HPV types 6,11,16 and 18, and nothing has been published to discredit either the safety or the efficacy of the vaccine. On the other hand, the duration of immunity conferred by the vaccine is unknown, and concerns have arisen that receipt of the vaccine may cause some women to eschew regular pelvic examinations and Pap smears. As well, suppression of current dominant oncogenic serotypes may cause other types to become dominant, with unknown results. At five-year follow-up the vaccine is 100%¹⁵ effective; there is no indication of diminished efficacy. Time will tell whether a booster is indicated, when, and for whom. Nonetheless, five years of protection (and counting) during the early, high-risk years of sexual

activity (ages 15-24) is good protection. Public health must advocate for the continued use of pelvic examinations and Pap smears; HPV vaccine promises to reduce disease burden, but is *not* a cure-all for cervical cancer. As for the “type spreading” phenomenon, the quadrivalent HPV vaccine is no different than any other vaccine. Suppressing specific microorganisms creates selective pressure for the emergence of formerly insignificant genetic variants, and “new” genetic variants, as well. Only careful monitoring and cost-benefit analysis can determine if the intervention is worthwhile, despite its unintended but predictable consequences.

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The author has no financial interests to disclose.

Letters To the Editor

Dear Dr. Friedman,

Thank you for writing about electronic medical records in *Medicine & Health/Rhode Island* [September 2008]. I am writing this letter to inform you of the best-kept secret in electronic medical records (EMR): the VA Medical Center.

I always enjoy your articles, and this one was no exception. In my own internist's office I often feel like my doctor does not even know the color of my eyes. I always feel nervous when my one-word answers lead to a half-minute interlude of typing. Just recently the Rhode Island Free Clinic, where I volunteer, switched over to EMR, and the frustrations from those scroll-down boxes may have led to our losing some of our invaluable volunteer providers.

The advantages of EMR, as you listed, are numerous. At the VA, where I am currently on my medicine clerkship, they have had EMR since 1995. When a patient is admitted to the hospital, I can immediately see everything from a cardiology consult note 10 years ago to his last five EKGs. I can see his most recent CT scan of the head as well as his outpatient neurologist's recommendations based on those findings. With a simple double-click I can see a patient's weight over the last 15 years displayed as a line graph. Labs and pending orders appear on the computer screen. I can start a note in the morning and finish it later in the day. Clinical reminders such as “colonoscopy due” pop up on the screen when the patient meets preventative medicine guidelines for these procedures.

I would argue that EMR not only offer numerous advantages, they are crucial to how medicine should be practiced. Handwriting at Rhode Island Hospital, where I was a student

on the psych consult service, made me feel like an archeologist deciphering hieroglyphics. Medicine teams make recommendations, but the assessment and plan could be impossible to read. Health care workers seem to accept these limitations as “the way things are.” Instead of deciding that electronic medical records are a middle ground, we should figure out how to maximize our abilities with the best technology that is available.

Doctors at the VA have taken advantage of this system. They write notes faster than they would if writing them by hand. They make good eye contact with patients and show them x-rays and lab values as they pop up on the screen. They show the patients trends in their weight, blood pressure, and cholesterol to improve health education. Some primary care physicians do look at the screen more than they talk to the patient, but I believe that it is our medical training that will need to adapt, rather than EMR.

Please visit the VA in Providence and see how wonderful electronic medical records can be.

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The author has no financial interests to disclose.