



The Potential of Human Papillomavirus Vaccines

Robert Steinbrook, M.D.

The anticipated licensure within the next three months of a vaccine against human papillomavirus (HPV) would represent a major public health advance against cervical cancer and other, less common

cancers, including those of the anus, penis, vagina, and vulva. The Food and Drug Administration (FDA) is conducting a six-month priority review of Merck's investigational HPV vaccine and should announce its licensing decision by June 8. Questions remain, however, about the potential behavioral consequences of routinely vaccinating adolescents against a sexually acquired infection, and the public reaction is uncertain.

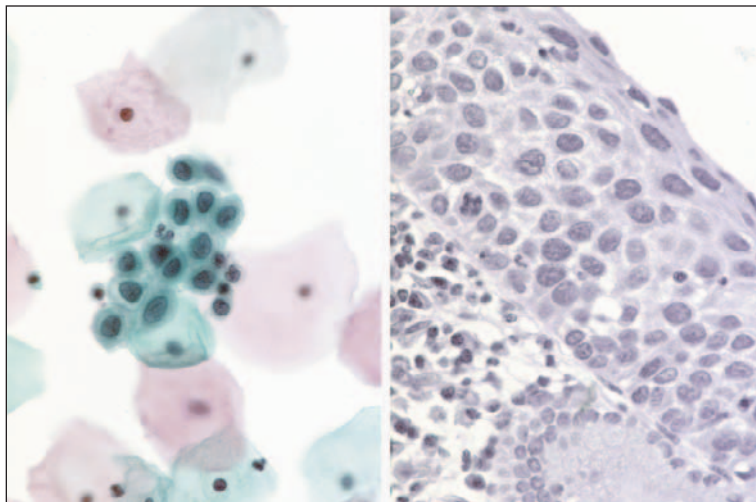
Genital HPV infection is common, with an estimated 6.2 million new infections each year in the United States. Although most infections are asymptomatic and transient, persistent infection with oncogenic HPV types is a serious health issue. Cervical cancer is the 11th most common cancer among women in the United States — with an estimated 10,370 new cas-

es and 3710 deaths in 2005. There are racial and socioeconomic disparities; more than half of all cases occur in women who have never or rarely been screened. Among women in developing countries, where effective screening programs are often lacking (see page 1110), cervical cancer is the second most common cancer, and a leading cause of cancer-related death.

The two investigational HPV vaccines are based on technology invented at the National Institutes of Health and licensed for commercial development.^{1,2} Merck has made a quadrivalent vaccine for use in men and women that is administered in three doses (at 0, 2, and 6 months). A key reason for vaccinating men is to prevent them from transmitting HPV to women or to other men. The vaccine is designed to protect against HPV

types 16 and 18, which are responsible for an estimated 70 percent of cases of cervical, anal, and genital cancers, and HPV types 6 and 11, which cause an estimated 90 percent of cases of genital warts. The latter two types also cause an estimated 90 percent of cases of recurrent respiratory papillomatosis, a rare but debilitating disease that can occur in infants as well as adults, in which papillomas obstruct the airway; patients may require many surgical procedures to remove the obstructions.

GlaxoSmithKline is testing, for use in women, a bivalent vaccine against HPV types 16 and 18 that is also administered in three doses (at 0, 1, and 6 months). Both vaccines consist of papillomavirus-like particles, which are empty shells of viral structural proteins. They are thought to protect against HPV infection primarily by inducing the production of neutralizing antibodies, thereby preventing the development of cervical intraepithelial neoplasia — the precursor lesion of invasive cervical carcinoma.



High-Grade Squamous Dysplasia and an Intraepithelial Lesion Due to HPV Infection of the Cervical Squamous Epithelium.

ma — and other precancerous lesions.

HPV vaccines will not prevent infection with other sexually transmitted diseases, nor will their introduction eliminate the need for cervical-cancer screening; screening will continue to be essential to detect cancers and precancerous changes caused by other HPV types, as well as any cancer in women who have not been vaccinated or are already infected with HPV. If the vaccines' promise is fulfilled, however, they will markedly reduce the need for medical care, biopsies, and invasive procedures associated with the follow-up of abnormal Pap tests, as well as alleviating the associated anxieties and health care costs.

The pivotal efficacy and safety data for the HPV vaccines remain unpublished, and some are still being collected, particularly for the GlaxoSmithKline vaccine. Nonetheless, the data presented by the companies in public meetings of the federal Advisory Committee on Immunization Practices (ACIP) show that the vaccines have a high degree of efficacy and that the immune response is strongest in persons who are vaccinated at

younger ages. The Merck vaccine has high efficacy against cervical intraepithelial neoplasia and external genital lesions in women 16 to 26 years of age, according to Lauri Markowitz of the Centers for Disease Control and Prevention (CDC), who reviewed the data for the committee. The Merck vaccine has remained effective for 2.5 to 3.5 years after a three-dose series, and it appears to be safe, the main adverse reaction being pain at the injection site.

After the companies' February presentations to the ACIP, Jon Abramson, chairman of the committee, said in an interview that he "had never before seen vaccines that in the prelicensure studies have close to 100 percent efficacy. The data are absolutely stunning." Abramson, who also chairs the department of pediatrics at the Wake Forest University School of Medicine, added: "The problem is that we don't know how long the protection will last. The worst that should happen is that a booster vaccine will be needed."

In December 2005, Merck submitted to the FDA an application for a biologics license for its HPV vaccine. The application covers

the vaccination of girls and boys 9 to 15 years of age and of women 16 to 26 years of age. The FDA is expected to set the age range for the vaccine and decide whether it will be licensed for use in boys as well as girls and women. Although Merck has not revealed the price it intends to charge for a three-dose series, a company cost-effectiveness analysis assumes a cost of \$300 to \$500, according to a presentation to the ACIP. Glaxo-SmithKline is expected to submit its licensing application to the FDA before the end of 2006.

The ACIP plays a critical role in advising the CDC and the Department of Health and Human Services about the use of vaccines, and the government usually follows its recommendations. The committee is also influential in determining which vaccines will be paid for by state and federal programs and private insurance companies.

If Merck's HPV vaccine is licensed, the ACIP will probably vote at a June meeting on whether to recommend routine vaccination at 11 to 12 years of age, in an effort to confer immunity before adolescents become sexually active. HPV infection is usually acquired soon after sexual activity begins, with a cumulative incidence of about 40 percent within 16 months. According to 2003 data from the Youth Risk Behavior Surveillance System, 7.4 percent of adolescents initiate sexual activity before 13 years of age, about one third of them by ninth grade, and about two thirds by the end of high school. If people are vaccinated before they have had sex, they should benefit irrespective of when they become sexually active.

The ACIP may also decide whether the vaccine should be recommended for older adolescents and young adults who have

not been previously vaccinated and — depending on the FDA's licensing criteria — whether it should be recommended for boys as well as girls and women. Although a recommendation for routine HPV vaccination should lead to widespread use, it would be substantially different from mandating vaccination. According to Abramson, the committee is not considering the latter approach, nor does it have authority to make such recommendations. Mandating vaccination requires action by individual states.

In addition to the outcome of the FDA review, there are many unknowns about HPV vaccination. One is the duration of immunity, which will have to be determined through follow-up studies. Another is the effect on sexual behavior, which should be learned through monitoring efforts. Nonetheless, Nicole Liddon, a sociologist at the CDC, told the committee in February that it is “unlikely” that routine HPV vaccination will change adolescent sexual behavior: the initiation of sexual activity reflects many factors, including parental and community influences; fear of sexually transmitted diseases has not been a major motivation

for adolescents to abstain from sex; and the availability of condoms and emergency contraception has not had measurable effects on the frequency of unsafe behavior.

The acceptance of the HPV vaccine — by physicians, parents, pre-teens, and the public at large — is also uncertain. As with many issues related to sex, people may have strong views. Increased acceptance is likely to require ongoing discussion and educational efforts. At the February ACIP meeting, the conservative Family Research Council, which promotes abstinence before marriage and fidelity within marriage as the best way to prevent sexually transmitted diseases, distanced itself from suggestions that it opposed HPV vaccines.³ Calling such reports “false,” the council said it “would oppose any measures to legally require vaccination or to coerce parents into authorizing it” and that “there is no justification for any vaccination mandate as a condition of public school attendance. However, we do support the widespread distribution and use of vaccines against HPV.”

Finally, the epidemiology of

cervical cancer highlights the need to provide HPV vaccines to persons who may never or rarely be screened, as well as to improve cervical-cancer prevention programs so that they will reach the women with the highest risk of disease.^{4,5} The HPV vaccine is likely to be considerably more expensive than many recommended vaccines, and its benefits will not be fully apparent for decades. It will be far easier to recommend routine vaccination than to provide the resources for its routine use, in the United States and throughout the world.

Dr. Steinbrook is a national correspondent for the *Journal*.

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3. Goodman E. Good news on cancer? Not for everyone. *Boston Globe*. November 12, 2005:A11.
4. Blumenthal PD, Gaffikin L. Cervical cancer prevention making programs more appropriate and pragmatic. *JAMA* 2005;294:2225-8.
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BECOMING A PHYSICIAN

Heart Sounds

Katharine Treadway, M.D.

The second-year students are learning about the cardiac exam today. They file into a large classroom, where they will first learn about heart murmurs — their location, quality, and meaning. Then, as part of their session, they will have the opportunity to work in small groups examining several patients who have good examples of “classic” murmurs. As they listen to each patient, they

will be guided by a fellow in cardiology. They are excited to be able to listen to real patients' hearts instead of just each others'.

Over the years, I have watched my students examine these patients, many of whom are my own, who have so kindly offered their hearts for an afternoon of student education. When the students are introduced to their first patient, they are unfailingly po-

lite, concerned about the patient's comfort, grateful for the opportunity to listen to a real heart. Then they settle into the process of performing the exam: observing the chest wall, feeling for the apical impulse, trying to understand its character and what it might tell them about the heart they are about to hear. Finally, using their stethoscopes, they listen to the sounds beneath. They are awk-

CORRECTION

The Potential of Human Papillomavirus Vaccines

The Potential of Human Papillomavirus Vaccines . On page 1109, in the middle column, lines 12 through 16 should have read, "The two investigational HPV vaccines are based in part on technology developed at the National Institutes of Health," rather than "The two investigational HPV vaccines are based on technology invented at the National Institutes of Health," as printed.