

Human Papillomavirus (HPV) Vaccines

Key Points

- Human papillomaviruses (HPVs) are a group of more than 100 related viruses. Certain types of HPV are the major cause of cervical cancer (see Questions 1 and 2).
- The U.S. Food and Drug Administration (FDA) has approved Gardasil[®] and Cervarix[®], vaccines that are highly effective in preventing infection with some types of HPV (see Question 3).
- Complete vaccination has the potential to reduce cervical cancer deaths around the world by as much as two-thirds (see Question 7).
- The vaccines are proven to be effective only if given before an individual is infected with HPV (see Question 11).
- It is important for both vaccinated and unvaccinated women to continue to undergo cervical cancer screening (see Questions 4 and 14).

1. What are human papillomaviruses?

Human papillomaviruses (HPVs) are a group of more than 100 related viruses. They are called papillomaviruses because certain types may cause warts, or papillomas, which are benign (noncancerous) tumors. The HPVs that cause the common warts that grow on hands and feet are different from those that cause growths in the throat or genital area. Some types of HPV are associated with certain types of cancer. These are called "high-risk," oncogenic, or carcinogenic HPVs.

Of the more than 100 types of HPV, over 30 types can be passed from one person to another through sexual contact. Transmission can occur in the genitals, anal, or mouth regions. Although HPVs are usually transmitted sexually, doctors cannot say for certain when infection occurred. About 6 million new genital HPV infections occur each year in the United States. Most HPV infections occur without any symptoms and go away without any treatment over the course of a few years. However, HPV infections sometimes persist for many years, with or without causing detectable cell abnormalities.

2. Do HPV infections cause cancer?

Infection with certain types of HPV is the major cause of cervical cancer. Almost all women will have an HPV infection at some point, but very few will develop cervical cancer. The immune system of most women will usually suppress or eliminate HPVs. Only HPV infections that are persistent (do not go away over many years) can lead to cervical cancer. In 2009, more than 11,000 women in the United States will be diagnosed with this type of cancer and about 4,000 will die from it. Cervical cancer strikes nearly half a million women each year worldwide, claiming more than a quarter of a million lives. Studies have found that HPV infection is also a strong risk factor for oropharyngeal cancer (cancer that forms in tissues of the oropharynx, which is the middle part of the throat and includes the soft palate, the base of the tongue, and the tonsils) (1, 2). Studies also suggest that HPVs may play a role in cancers of the anus, vulva, vagina, and penis.

3. Can HPV infection be prevented?

The surest way to eliminate risk for genital HPV infection is to refrain from any genital contact with another individual.



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For those who choose to be sexually active, a long-term, mutually monogamous relationship with an uninfected partner is the strategy most likely to prevent genital HPV infection. However, it is difficult to determine whether a partner who has been sexually active in the past is currently infected.

It is not known how much protection condoms provide against HPV infection, because areas not covered by a condom can be infected by the virus. Although the effect of condoms in preventing HPV infection is unknown, condom use has been associated with a lower rate of cervical cancer, an HPV-associated disease.

The U.S. Food and Drug Administration (FDA) has approved two vaccines to prevent HPV infection: Gardasil® and Cervarix®. Both vaccines are highly effective in preventing persistent infections with HPV types 16 and 18, two high-risk HPVs that cause most (70 percent) cervical cancers. Gardasil also prevents infection with HPV types 6 and 11, which cause virtually all (90 percent) genital warts (3). In addition, there is some initial evidence that Cervarix provides partial protection against a few other HPV types that can cause cancer, but further evaluation is required before the magnitude and impact of this effect is understood.

4. What are Gardasil and Cervarix?

The Gardasil vaccine, which is produced by Merck & Co., Inc. (Merck), is called a quadrivalent vaccine because it protects against four HPV types: 6, 11, 16, and 18. Gardasil is given through a series of three injections into muscle tissue over a 6-month period. The FDA has approved Gardasil for use in females for the prevention of cervical cancer, and some vulvar and vaginal cancers, caused by HPV types 16 and 18 and for use in males and females for the prevention of genital warts caused by HPV types 6 and 11. The vaccine is approved for these uses in females and males ages 9 to 26.

Cervarix is produced by GlaxoSmithKline (GSK). It is called a bivalent vaccine because it targets two HPV types: 16 and 18. This vaccine is also given in three doses over a 6-month period. The FDA has approved Cervarix for use in females ages 10 to 25 for the prevention of cervical cancer caused by HPV types 16 and 18.

Both Gardasil and Cervarix are based on technology developed in part by National Cancer Institute (NCI) scientists. NCI, a component of the National Institutes of Health, licensed the technology to two pharmaceutical companies—Merck and GSK—to develop HPV vaccines for widespread distribution.

Neither of these HPV vaccines has been proven to provide complete protection against persistent infection with other HPV types, although some initial results suggest that both vaccines might provide partial protection against a few additional HPV types that can cause cervical cancer. Overall, therefore, about 30 percent of cervical cancers will not be prevented by these vaccines. Also, in the case of Gardasil, 10 percent of genital warts will not be prevented by the vaccine. Neither vaccine prevents other sexually transmitted diseases, and they do not treat HPV infection or cervical cancer.

Because the vaccines do not protect against all HPV infections that cause cervical cancer, it is important for vaccinated women to continue to undergo cervical cancer screening as recommended for women who have not been vaccinated.

5. How do HPV vaccines work?

The HPV vaccines work like other immunizations that guard against viral infection. The investigators hypothesized that the unique surface components of HPV might create an antibody response that is capable of protecting the body against infection and that these components could be used to form the basis of a vaccine. These surface components can interact with one another to form virus-like particles (VLP) that are noninfectious and stimulate the immune system to produce antibodies that can prevent the complete papillomavirus from infecting cells. They are thought to protect primarily by causing the production of antibodies that prevent infection and, consequently, the development of cervical cell changes (as seen on Pap tests) that may lead to cancer (4). Although these vaccines can help prevent HPV infection, they do not help eliminate existing HPV infections.

6. How effective are the HPV vaccines?

Gardasil and Cervarix are highly effective in preventing infection with the types of HPV they target. Studies have shown that both Gardasil and Cervarix prevent nearly 100 percent of the precancerous cervical cell

changes caused by the types of HPV targeted by the vaccine for up to 4 years after vaccination among women who were not infected at the time of vaccination (5, 6, 7).

7. Why are these vaccines important?

Widespread vaccination has the potential to reduce cervical cancer deaths around the world by as much as two-thirds, if all women were to get the vaccine and if protection turns out to be long-term. In addition, the vaccines can reduce the need for medical care, biopsies, and invasive procedures associated with follow-up from abnormal Pap tests, thus helping to reduce health care costs and anxieties related to abnormal Pap tests and follow-up procedures (4).

8. How safe are the HPV vaccines?

Before any vaccine is licensed, the FDA must determine that it is both safe and effective. Both Gardasil and Cervarix have been tested in tens of thousands of people in the United States and many other countries. Thus far, no serious side effects have been shown to be caused by the vaccines. The most common problems have been brief soreness and other local symptoms at the injection site. These problems are similar to ones commonly experienced with other vaccines. The vaccines have not been sufficiently tested during pregnancy and, therefore, should not be used by pregnant women.

A recent safety review by the FDA and the Centers for Disease Control and Prevention (CDC) considered adverse side effects related to Gardasil immunization that have been reported to the Vaccine Adverse Events Reporting System since the vaccine was licensed (8). The rates of adverse side effects in the safety review were consistent with what was seen in safety studies carried out before the vaccine was approved and were similar to those seen with other vaccines. However, a higher proportion of syncope (fainting) and venous thrombotic events (blood clots) were seen with Gardasil than are usually seen with other vaccines. Falls after syncope may sometimes cause serious injuries, such as head injuries. These can largely be prevented by keeping the vaccinated person seated for up to 15 minutes after vaccination. The FDA and CDC have reminded health care providers that, to prevent falls and injuries, all vaccine recipients should remain seated or lying down and be closely observed for 15 minutes after vaccination. More information is available on the CDC's Web site at <http://www.cdc.gov/vaccinesafety/Vaccines/HPV/Index.html> on the Internet.

9. How long do the vaccines protect against infection?

The duration of immunity is not yet known. Research is being conducted to find out how long protection will last. Phase III clinical trials have shown that Gardasil and Cervarix can provide protection against HPV16 for 4 years. Smaller studies have suggested that protection is likely to last for longer than 4 years, but it is not known if protection conferred through vaccination will be lifelong.

10. Will booster vaccinations be needed?

Studies are under way to determine whether booster vaccinations (supplementary doses of a vaccine, usually smaller than the initial dose or doses, that are given to maintain immunity) are necessary.

11. Who should get these vaccines?

Both Gardasil and Cervarix are proven to be effective only if given before infection with HPV, so it is recommended that they be given before an individual is sexually active. The FDA's licensing decision includes information about the age and sex for recipients of the vaccine. The FDA approved Gardasil for use in females ages 9 to 26 and approved Cervarix for use in females ages 10 to 25.

Data from Merck show high efficacy of Gardasil in males for preventing genital warts associated with HPV6 and HPV11, the two HPV types that cause most genital warts. The FDA approved Gardasil for use in males ages 9 to 26 to prevent genital warts caused by HPV6 and HPV11.

In addition to the benefits that exist for cervical cancer prevention in females and the prevention of warts in both males and females, there may be additional benefits to vaccination. These include a possible reduction in risk of anal and oropharyngeal cancers in males and females, as well as penile cancer in males, although clinical trials have not directly evaluated these possibilities.

After a vaccine is licensed by the FDA, the Advisory Committee on Immunization Practices (ACIP) makes additional recommendations to the Secretary of the U.S. Department of Health and Human Services and the Director of the CDC on who should receive the vaccine, at what age, how often, the appropriate dose, and situations in which it should not be administered. ACIP is made up of 15 experts in fields associated with immunization. ACIP provides advice on the most effective ways to use vaccines to prevent diseases. ACIP recommends that Gardasil be given routinely to girls ages 11 to 12. The recommendations also allow for the vaccination of girls beginning at 9 years of age and the vaccination of girls and women ages 13 to 26. An ACIP policy for Cervarix is expected within the next few months. It is also expected that ACIP will make recommendations about use of the vaccine in males. The cost-benefit ratio of vaccinating males is under debate because HPV-associated cancers are rarer in men than women. More information about the ACIP recommendations for vaccination against HPVs can be found on the CDC's Web site at <http://www.cdc.gov/mmwr/pdf/rr/rr5602.pdf> on the Internet.

In addition, states can decide whether or not to require vaccinations of children prior to their enrollment in schools or child care. Each state makes this decision individually. Information about specific state vaccine decisions is available from the National Network for Immunization Information Web site at <http://www.immunizationinfo.org/vaccineInfo/> on the Internet.

12. Should the vaccines be given to people who are already infected with HPV?

Although the preventive vaccines currently under study have been found to be generally safe when given to women who are already infected with HPV, it is important for women to know that the vaccines protect against infection, and provide maximum benefit, for a woman who is vaccinated before she is sexually active. This is because these vaccines do not treat infections. For example, one recent study found that Cervarix was not effective in helping women who are already infected to clear the infection (9). However, because very few young women have been infected with all HPV types that are included in the vaccines, it is possible that women may still get residual benefit from vaccination even if they have been infected with one or more of the types included in the vaccines. This possibility has not yet been formally studied.

It is not feasible to prescreen all women to see who has been exposed to the HPV types in the vaccines. At present, there is no generally available test to tell whether an individual has been exposed to HPV. The currently approved HPV DNA test shows only whether a woman has a current HPV infection and identifies the HPV type. It does not provide information on past infections. The decision to vaccinate or not, based on likelihood of prior exposure to these HPV types, is being discussed by ACIP and other advisory groups.

13. Should women who already have cervical cell changes get the vaccines?

Gardasil and Cervarix appear to be safe in women who have cervical abnormalities, but it is not expected that the vaccine would help clear the abnormalities because it has been shown that the vaccine does not treat established infections. Women should talk with their health care providers about treatment for abnormal cervical cell changes.

14. Do women who have been vaccinated still need to have Pap tests?

Yes. Because these vaccines do not protect against all HPV types that can cause cancer, Pap tests continue to be essential to detect cervical cancers and precancerous changes. In addition, Pap tests are critically important for women who have not been vaccinated or who are already infected with HPV.

15. How much do these vaccines cost, and will insurance pay for it?

The retail price of Gardasil is approximately \$120 per dose and \$360 for the full series. Individual or group insurance plans are subject to state laws, which generally establish coverage based on recommendations from the ACIP. Medicaid coverage is in accordance with the ACIP standard, and immunizations are a mandatory service under Medicaid for eligible individuals under age 21. Medicaid also includes the Vaccines for Children Program, which provides immunization services for children 18 and under who are Medicaid eligible, uninsured, underinsured, and receiving immunizations through a Federally Qualified Health Center or Rural Health Clinic, or who are Native American or Alaska Native.

16. What research is being done on HPV?

Researchers at NCI and elsewhere are studying how high-risk HPV types cause precancerous changes in normal cells and how these changes can be prevented or managed most efficiently. NCI is conducting a community-based clinical trial of the Cervarix HPV vaccine in Costa Rica, where cervical cancer rates are high. This study is designed to obtain information about the vaccine's longer-term safety, the extent and duration of protection, the immune mechanisms of protection, and the natural history of infection with HPV types other than the types included in the vaccine. NCI is also collaborating with other researchers on second-generation preventive vaccines and on therapeutic HPV vaccines, which would prevent the development of cancer among women previously infected with HPV. The ideal vaccine strategy would combine a preventive and therapeutic vaccine.

Laboratory research has indicated that HPVs produce proteins known as E5, E6, and E7. These proteins interfere with the cell functions that normally prevent excessive growth. For example, HPV E6 interferes with the human protein p53, which acts to keep tumors from growing. A better understanding of how these proteins interact may help researchers develop ways to interrupt the process by which HPV infection can lead to the growth of abnormal cells.

Researchers at the NCI and elsewhere are also studying what people know and understand about HPVs and cervical cancer, the best way to communicate to the public about the latest research results, and how doctors are talking with their patients about HPVs. This research will help to ensure that the public receives accurate information about HPVs that is easily understood and will facilitate access to appropriate tests for those who need them.

17. How can people learn more about HPV infection?

The following Federal Government agencies can provide more information about HPV infection:

The NCI's Digest Page on HPV (Human Papillomavirus) Vaccines for Cervical Cancer provides links to NCI materials about HPV vaccines as well as general information about HPVs, cancer vaccines, and cervical cancer. This Web site can be found at <http://www.cancer.gov/cancertopics/hpv-vaccines> on the Internet.

The National Institute of Allergy and Infectious Diseases (NIAID), a part of the National Institutes of Health, supports research on HPV infection and offers printed materials. NIAID can be contacted at:

Organization: National Institute of Allergy and Infectious Diseases

Address: Office of Communications and Government Relations
6610 Rockledge Drive, MSC 6612
Bethesda, MD 20892-6612

Telephone: 301-496-5717 or 1-866-284-4107 (toll-free)

TTY: 1-800-877-8339

Web site: <http://www.niaid.nih.gov>

The CDC-INFO Contact Center provides information on sexually transmitted infections, including HPVs, and how to prevent them. The center can be reached by calling toll-free 1-800-CDC-INFO (1-800-232-4636). Both English- and Spanish-speaking specialists are available 24 hours a day, 7 days a week, 365 days a year. Staff provide information about sexually transmitted diseases (STDs) and referrals to free or low-cost clinics nationwide. Free educational literature about sexually transmitted infections and prevention methods is also available. More information from the CDC about sexually transmitted infections is available at <http://www.cdc.gov/std> on the Internet.

The CDC's Division of STD Prevention Web site also has information about HPVs, including treatment guidelines and surveillance statistics. This Web site can be found at <http://www.cdc.gov/hpv/> on the Internet.

Selected References

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8. Slade BA, Leidel L, Vellozzi C, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *Journal of the American Medical Association* 2009; 302(7):750–757.
9. Hildesheim A, Herrero R, Wacholder S, et al. Effect of human papillomavirus 16/18 L1 viruslike particle vaccine among young women with preexisting infection: A randomized trial. *Journal of the American Medical Association* 2007; 298(7):743–753.

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Related NCI materials and Web pages:

- National Cancer Institute Fact Sheet 3.20, *Human Papillomaviruses and Cancer: Questions and Answers* (<http://www.cancer.gov/cancertopics/factsheet/Risk/HPV>)
- National Cancer Institute Fact Sheet 5.16, *Pap Test* (<http://www.cancer.gov/cancertopics/factsheet/Detection/Pap-test>)
- Cervical Cancer Home Page (<http://www.cancer.gov/cancertopics/types/cervical/>)
- Digest Page on HPV (Human Papillomavirus) Vaccines for Cervical Cancer (<http://www.cancer.gov/cancertopics/hpv-vaccines>)
- *Understanding Cervical Changes: A Health Guide for Women* (<http://www.cancer.gov/cancertopics/understandingcervicalchanges>)
- *What You Need To Know About™ Cancer of the Cervix* (<http://www.cancer.gov/cancertopics/wyntk/cervix>)

How can we help?

We offer comprehensive research-based information for patients and their families, health professionals, cancer researchers, advocates, and the public.

- **Call** NCI's Cancer Information Service at 1–800–4–CANCER (1–800–422–6237)
- **Visit** us at <http://www.cancer.gov/> or <http://www.cancer.gov/espanol>
- **Chat** using LiveHelp, NCI's instant messaging service, at <http://www.cancer.gov/livehelp>
- **E-mail** us at cancergovstaff@mail.nih.gov
- **Order** publications at <http://www.cancer.gov/publications> or by calling 1–800–4–CANCER
- **Get help** with quitting smoking at 1–877–44U–QUIT (1–877–448–7848)

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