

## Human Papillomavirus (HPV) Vaccines

### Key Points

- Human papillomaviruses (HPVs) are a group of more than 150 related viruses, certain types of which can cause cancer.
- The Food and Drug Administration-approved vaccines Gardasil® and Cervarix® are highly effective in preventing infection with certain types of HPV.
- HPV vaccination has the potential to reduce cervical cancer deaths around the world by as much as two-thirds, and to prevent anal cancer in males and females. Gardasil can also prevent genital warts.

### 1. What are human papillomaviruses?

Human papillomaviruses (HPVs) are a group of more than 150 related viruses. They are called papillomaviruses because certain types may cause warts, or papillomas, which are benign (noncancerous) growths. Some types of HPV are associated with certain types of cancer. These are called "high-risk," oncogenic, or carcinogenic HPVs.

Of the more than 150 types of HPV, more than 40 types can be passed from one person to another through sexual contact. Transmission can occur in the genitals, anal, or oral 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. What kinds of cancer are related to HPV infection?

Infection with high-risk 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 2011, more than 12,000 women in the United States are expected to be diagnosed with cervical cancer and more than 4,000 are expected to die from it (1). Nearly half a million women develop cervical cancer each year worldwide, and more than a quarter of a million die from it.

High-risk HPV types also cause most anal cancers. Although anal cancer is uncommon, more than 5,000 men and women in the United States are expected to be diagnosed with the disease in 2011 and 770 people are expected to die because of it (1).

Infection with high-risk HPV is also known to cause some cancers of the oropharynx, vulva, vagina, and penis (2, 3).

### 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 (4).



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For those who are sexually active, a long-term, mutually monogamous relationship with an uninfected partner is the strategy most likely to prevent HPV infection (4). However, it is difficult to determine whether a partner who has been sexually active in the past is currently infected.

Research has shown that correct and consistent condom use can reduce the transmission of HPV between sexual partners (5). However, because areas not covered by a condom can be infected by the virus (4), they are unlikely to provide complete protection against transmission of infection.

The Food and Drug Administration (FDA) has approved two vaccines to prevent HPV infection: Gardasil® and Cervarix®. Both vaccines are highly effective in preventing infections with HPV types 16 and 18, two high-risk HPVs that cause about 70 percent of cervical and anal cancers. Gardasil also prevents infection with HPV types 6 and 11, which cause 90 percent of genital warts (6).

#### **4. What are Gardasil and Cervarix?**

The Gardasil vaccine is produced by Merck & Co., Inc. It 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 anal cancer and precancerous anal lesions caused by HPV types 16 and 18. Gardasil is also approved 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.

The Cervarix vaccine 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 NCI scientists. NCI 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, 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, nor do they 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. There could be some future changes in recommendations for vaccinated women.

#### **5. How do HPV vaccines work?**

The HPV vaccines work like other immunizations that guard against viral infections. 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.

The HPV surface components can interact with one another to form virus-like particles (VLP) that are not infectious, because they lack DNA. However, these VLPs can attach to cells and stimulate the immune system to produce antibodies that can prevent the complete papillomavirus, in future encounters, from infecting cells.

Although HPV vaccines can help prevent future 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. The vaccines have been shown to provide protection against persistent cervical HPV 16/18 infections for up to 8 years, which is the maximum time of research follow-up thus far. More will be known about the total duration of protection as research continues (7).

HPV vaccination has also been found to prevent nearly 100 percent of the precancerous cervical cell changes that would have been caused by HPV 16/18. The data so far show duration of protection for up to 6.4 years with Cervarix and for up to 5 years for Gardasil—in women who were not infected with HPV at the time of vaccination (7–10).

A recent analysis of data from a clinical trial of Cervarix found that this vaccine is just as effective at protecting women against persistent HPV 16 and 18 infection in the anus as it is at protecting them from these infections in the cervix (11).

Both Gardasil and Cervarix are designed to be given to people in three doses over a 6-month period. However, a recent study showed that women who received only two doses of Cervarix had just as much protection from persistent HPV 16/18 infection as women who received three doses, and the protection was observed through 4 years of follow up (12). Even one dose provided protection; however, these findings need to be evaluated with more research to determine whether fewer than three doses of the vaccine will provide adequate duration of protection. Nonetheless, this information may be helpful for public health officials who administer vaccination programs among groups of people unlikely to complete the three-dose regimen.

## **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 (13).

The other cancers caused by HPV are less common than cervical cancer. However, there are no formal screening programs for these cancers, so vaccination has the potential to greatly reduce deaths from these cancers also.

## **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 (14). 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>.

**9. 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 and males ages 9 to 26 and approved Cervarix for use in females ages 10 to 25.

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.

For females, ACIP recommends that Gardasil or Cervarix vaccination be given routinely at ages 11 or 12, and that the series may be started for girls as early as 9 years of age. Girls and women ages 13 to 26 who have not been vaccinated already, or who did not complete the three-dose series, can also be vaccinated against HPV. If a woman reaches the age of 26 before completing the three-dose series, ACIP recommendations say that she can still receive the remaining doses (15).

For males, ACIP allows vaccination with Gardasil between the ages of 9 and 26 to reduce the likelihood of genital warts. However, ACIP has not yet issued recommendations for use of Gardasil for preventing HPV-associated cancers in males (16).

The cost-benefit ratio of vaccinating males is under debate because HPV-related cancers are rarer in men than women. More information about the ACIP recommendations for vaccination against HPV can be found on the CDC's Web site at <http://www.cdc.gov/mmwr/pdf/rr/rr5602.pdf>.

In addition, states can decide whether or not to require vaccination 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/vaccines/state-requirements>.

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

Although Gardasil and Cervarix have been found to be generally safe when given to people who are already infected with HPV, the vaccines do not treat infection and they provide maximum benefit if a person receives them before he or she is sexually active (17).

It is possible that someone infected with HPV will still get residual benefit from vaccination, even if he or she has already been infected with one or more of the types included in the vaccines. However, this possibility is still under investigation.

At present, there is no generally available test to show whether an individual has been exposed to HPV. The currently approved HPV DNA test shows only whether a person has a current HPV infection, and it identifies the HPV type. But it does not provide information on past infections.

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

ACIP recommends that women who have abnormal Pap test results, which may indicate HPV infection, should still receive HPV vaccination if they are in the appropriate age group because the vaccine may protect them against high-risk HPV types that they have not yet acquired. However, these women should be told that the vaccination will not cure them of current HPV infections and that it will not treat the abnormal results of their Pap test (15).

**12. 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. There could be future changes in screening recommendations for vaccinated women.

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

The retail price of the HPV vaccines is approximately \$130 per dose (18). However, the actual cost for vaccination may be determined by the clinic that provides the service. Clinics may charge for staff time and the vaccination equipment, for example, or they may have sliding-scale fees that set the cost according to a person's level of income or insurance coverage.

The best way to know how much vaccination will cost is to contact the insurance plan or the clinic. Individual or group insurance plans are subject to state laws. These laws generally establish whether insurers should cover the cost of vaccination based on recommendations from the ACIP.

Medicaid covers HPV vaccination in accordance with the ACIP recommendations, 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, receiving immunizations through a Federally Qualified Health Center or Rural Health Clinic, or are Native American or Alaska Native. More information about this program is available at <http://www.cdc.gov/vaccines/programs/vfc/default.htm>.

The vaccine manufacturers also offer help for people who cannot afford HPV vaccination. GSK has the Vaccines Access Program, which provides Cervarix free of charge to women who do not have insurance and who have a low income, and who are ages 19 to 25 and therefore too old for the Medicaid Vaccines for Children Program. More information is available at <http://www.GSK-VAP.com> or by telephone at 1-877-822-2911.

Merck offers the Merck Vaccine Patient Assistance Program, which provides Gardasil for free to people over the age of 19 who do not have health insurance or cannot afford to pay for the vaccine. More information is available at <http://www.merck.com/merckhelps/vaccines/> or by telephone at 1-800-293-3881.

### 14. 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. Most of this research has focused on cervical cells in women, but researchers are now investigating these questions in other tissues in which HPV may cause cancer, such as the oropharynx and anus.

NCI is conducting a community-based clinical trial of Cervarix 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.

Another prevention strategy that is being explored is topical microbicides. Carrageenan, a compound that is extracted from a type of seaweed and used widely in foods and other products, has been found to inhibit HPV infection in laboratory studies. Clinical trials are under way to test whether a topical microbicide that contains carrageenan can prevent genital HPV infection.

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. 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.

The FDA-approved tests for HPV infection in women detect viral DNA in cervical cells that are collected during a Pap test. Researchers are trying to find other ways to test for HPV infection that may be faster, more accurate, and less expensive. These new tests may be especially useful in developing countries and medically underserved populations.

Researchers at NCI and elsewhere are also studying what people know and understand about HPV and cancer, the best way to communicate to the public the latest research results, and how doctors are talking with their

patients about HPV. This research will help to ensure that the public receives accurate information about HPV that is easily understood and will help people get access to the appropriate tests.

## 15. How can people learn more about HPV infection?

The following federal agencies can provide more information about HPV infection:

<b>Organization:</b>	National Institute of Allergy and Infectious Diseases
<b>Address:</b>	Office of Communications and Government Relations 6610 Rockledge Drive, MSC 6612 Bethesda, MD 20892-6612
<b>Telephone:</b>	301-496-5717 1-866-284-4107
<b>TTY:</b>	1-800-877-8339
<b>Web site:</b>	<a href="http://www.niaid.nih.gov">http://www.niaid.nih.gov</a>
<b>Organization:</b>	Centers for Disease Control and Prevention
<b>Address:</b>	1600 Clifton Road Atlanta, GA 30333
<b>Telephone:</b>	1-800-CDC-INFO (1-800-232-4636) 8:00 a.m. to 8:00 p.m. Eastern Time, Monday to Friday
<b>TTY:</b>	1-888-232-6348
<b>Web site:</b>	<a href="http://www.cdc.gov/std">http://www.cdc.gov/std</a> <a href="http://www.cdc.gov/hpv/">http://www.cdc.gov/hpv/</a>
<b>E-mail:</b>	<a href="mailto:cdcinfo@cdc.gov">cdcinfo@cdc.gov</a>

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#### Related NCI materials and Web pages:

- *Human Papillomaviruses and Cancer* Fact Sheet (<http://www.cancer.gov/cancertopics/factsheet/Risk/HPV>)
- *Pap Test* Fact Sheet (<http://www.cancer.gov/cancertopics/factsheet/Detection/Pap-test>)
- Cervical Cancer Home Page (<http://www.cancer.gov/cancertopics/types/cervical/>)
- HPV Vaccines for Cervical Cancer Digest Page (<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™ Cervical Cancer* (<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](mailto: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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