NIH NATIONAL CANCER INSTITUTE

Human Papillomavirus (HPV) Vaccines

What are HPV vaccines?

HPV vaccines are vaccines that protect against infection with human papillomaviruses (HPV). HPV is a group of more than 200 related viruses, of which more than 40 are spread through direct sexual contact. Among these, two HPV types cause genital warts, and about a dozen HPV types can cause certain types of cancer—cervical, anal, oropharyngeal, penile, vulvar, and vaginal.

Three vaccines that prevent infection with disease-causing HPV types are licensed for use in the United States: Gardasil®, Gardasil® 9, and Cervarix®. All three vaccines prevent infection with HPV types 16 and 18, two high-risk HPVs that cause about 70% of cervical cancers and an even higher percentage of some of the other HPV-caused cancers (1, 2). Gardasil also prevents infection with HPV types 6 and 11, which cause 90% of genital warts (3). Gardasil 9 prevents infection with the same four HPV types plus five additional cancer-causing types (31, 33, 45, 52, and 58) that together account for 10 to 20% of cervical cancers.

Gardasil 9 is now the only HPV vaccine available for use in the United States. Cervarix and Gardasil are still used in other countries.

Who should get HPV vaccination?

The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) develops recommendations regarding all vaccination in the United States, including HPV vaccination. The current ACIP (CDC) recommendations for HPV vaccination are as follows (4):

- **Children and adults ages 9 through 26 years.** HPV vaccination is routinely recommended at age 11 or 12 years; vaccination can be started as early as age 9 years. HPV vaccination is recommended for all persons through age 26 years who were not adequately vaccinated earlier.
- **Adults ages 27 through 45 years.** Although the HPV vaccine is Food and Drug Administration (FDA) approved to be given through age 45 years, HPV vaccination is not recommended for all adults ages 27 through 45 years. Instead, ACIP recommends that clinicians consider discussing with their patients in this age group who were not adequately vaccinated earlier whether HPV vaccination is right for them. HPV vaccination in this age range provides less benefit because more people have already been exposed to the virus.

- **Persons who are pregnant.** HPV vaccination should be delayed until after pregnancy, but pregnancy testing is not required before vaccination. There is no evidence that vaccination will affect a pregnancy or harm a fetus.

How many doses of the HPV vaccine are needed?

The HPV vaccine is given as a series of shots. ACIP specifies different dosing schedules, depending on the age of the individual (5). Children who start the vaccine series before their 15th birthday need only two doses to be fully protected. People who start the series at age 15 or older and people who have certain conditions that weaken the immune system need three doses to be fully protected.

Researchers are currently investigating whether a single dose of HPV vaccine might be effective. See **What research is being done on strategies to prevent HPV infection?**

How do HPV vaccines work?

Like other immunizations that guard against viral infections, HPV vaccines stimulate the body to produce antibodies that, in future encounters with HPV, bind to the virus and prevent it from infecting cells.

The current HPV vaccines are based on virus-like particles (VLPs) that are formed by HPV surface components. VLPs are not infectious because they lack the virus's DNA. However, they closely resemble the natural virus, and antibodies against the VLPs also have activity against the natural virus. The VLPs have been found to be strongly immunogenic, which means that they induce high levels of antibody production by the body. This makes the vaccines highly effective.

The vaccines do not prevent other sexually transmitted diseases, nor do they treat existing HPV infections or HPV-caused disease.

How effective are HPV vaccines?

HPV vaccines are highly effective in preventing infection with the types of HPV they target when given before initial exposure to the virus—which means before individuals begin to engage in sexual activity.

In the trials that led to the approval of Gardasil and Cervarix, these vaccines were found to provide nearly 100% protection against persistent cervical infections with HPV types 16 and 18 and the cervical cell changes that these persistent infections can cause. Gardasil 9 is as effective as Gardasil for the prevention of diseases caused by the four shared HPV types (6, 11, 16, and 18), based on similar antibody responses in participants in clinical studies. The trials that led to approval of Gardasil 9 found it to be nearly 100% effective in preventing cervical, vulvar, and vaginal disease caused by the five additional HPV types (31, 33, 45, 52, and 58) that it targets (6). In a 2017 position paper, the World Health Organization stated that the HPV vaccines have equivalent efficacy (7). The Cervarix vaccine has been found to provide partial protection against a few additional HPV types not included in the vaccine that can cause cancer, a phenomenon called cross-protection (8).

A 2019 meta-analysis of girls-only HPV vaccination programs in 14 countries that included more than 60 million vaccinated people showed strong evidence of the vaccine's effectiveness (9). For example, compared with the period before vaccination began,

- infections with HPV 16 and 18 decreased by 83% among girls aged 15–19 years and by 66% among women aged 20–24 years at up to 8 years after vaccination began
- diagnoses of anogenital warts decreased by 67% among girls aged 15–19 years and by 54% among women aged 20–24 years at up to 9 years after vaccination began
- the prevalence of precancerous lesions that can lead to cervical cancer decreased by 51% among girls aged 15–19 years and by 31% among women aged 20–24 years at up to 9 years after vaccination began.

To date, protection against the targeted HPV types has been found to last for at least 10 years with Gardasil (10), at least 9 years with Cervarix (11), and at least 6 years with Gardasil 9 (12). Long-term studies of vaccine efficacy that are still in progress will help scientists better understand the total duration of protection.

A clinical trial of Gardasil in men indicated that it can prevent anal cell changes caused by persistent infection and genital warts (13). Analyses of data from women participating in a clinical trial of Cervarix found that this vaccine can protect women against persistent HPV 16 and 18 infections in the anus (14) and the oral cavity (15).

Why is it important for people to follow HPV vaccination recommendations?

The combination of HPV vaccination and cervical screening can provide the greatest protection against cervical cancer. Also, vaccination is the approved public health intervention for reducing the risk of developing HPV-associated cancers at sites other than the cervix.

It is important that as many people as possible in the recommended age group get vaccinated. Not only does vaccination protect vaccinated individuals against infection by the HPV types targeted by the respective vaccine, but also vaccination of a significant proportion of the population can reduce the prevalence of the vaccine-targeted HPV types in the population, thereby providing some protection for individuals who are not vaccinated (a phenomenon called herd immunity). For example, in Australia, where a high proportion of girls are vaccinated with Gardasil, the incidence of genital warts went down during the first 4 years of the vaccination program among young males—who were not being vaccinated at the time—as well as among young females (16).

Further evidence that large-scale HPV vaccination confers protection for unvaccinated individuals comes from a 2019 meta-analysis of girls-only HPV vaccination programs in 14 high-income countries that included 60 million vaccinated people (9). That analysis showed that, up to 8 years after the start of vaccination, diagnoses of anogenital warts decreased by 31% among women aged 25–29 years, by 48% among boys aged 15–19 years, and by 32% among men aged 20–24 years, compared with the period before vaccination began.

Widespread HPV vaccination has the potential to reduce cervical cancer incidence around the world by as much as 90% (8, 12). In addition, the vaccines may reduce the need for screening and subsequent medical care, biopsies, and invasive procedures associated with follow-up from abnormal cervical screening, thus helping to reduce health care costs and anxieties related to follow-up procedures (17).

Until recently, the other cancers caused by HPV were less common than cervical cancer. However, the incidence of HPV-positive oropharyngeal cancer and anal cancer has been increasing in the United States (18) while the incidence of cervical cancer has declined, due mainly to highly effective cervical cancer screening programs. Therefore, in the United States, non-cervical cancers caused by HPV are now as common as cervical cancers. In addition, most of the HPV-positive non-cervical cancers arise in men. There are no formal screening programs for the non-cervical cancers, so universal vaccination could have an important public health benefit.

How safe are HPV vaccines?

Before they could be licensed, all three HPV vaccines were tested for safety and efficacy in tens of thousands of people in the United States and many other countries. Since licensure, millions of individuals have been vaccinated and, 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 those commonly experienced with other vaccines.

A safety review by the FDA and the 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 (19–21). 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 thromboembolic events (blood clots) were seen with Gardasil than are usually seen with other vaccines. The patients who developed blood clots had known risk factors for developing them, such as taking oral contraceptives. A safety review of Gardasil in Denmark and Sweden did not identify an increased risk of blood clots (20). The most recent safety data review for HPV vaccines continues to indicate that these vaccines are safe (22).

Falls after fainting may sometimes cause serious injuries, such as head injuries. These can largely be prevented by keeping the 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 from the CDC at http://www.cdc.gov/vaccinesafety/Vaccines/HPV/Index.html.

Should HPV vaccines be given to women who are already infected with HPV or have cervical cell changes?

ACIP recommends that women who have an HPV infection and/or an abnormal Pap test result that may indicate an 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 or treat the abnormal results of their Pap test (23).

Although HPV vaccines have been found to be safe when given to people who are already infected with HPV, the vaccines do not treat infection. They provide maximum benefit if a person receives them before he or she is sexually active (24, 25).

It is likely that someone exposed to HPV will still get some residual benefit from vaccination, even if he or she has already been infected with one or more of the HPV types included in the vaccines.

Do women who have been vaccinated still need to be screened for cervical cancer?

Yes. Because HPV vaccines do not protect against all HPV types that can cause cancer, women who have been vaccinated are advised to follow the same screening recommendations as unvaccinated women. There could be future changes in screening recommendations for vaccinated women.

How much does HPV vaccination cost, and will insurance pay for it?

The best way to know how much vaccination will cost is to contact the insurance plan or the clinic.

Most private insurance plans cover HPV vaccination. The federal Affordable Care Act (ACA) requires most private insurance plans to cover recommended preventive services (including HPV vaccination) with no copay or deductible.

Medicaid covers HPV vaccination in accordance with ACIP recommendations, and immunizations are a mandatory service under Medicaid for eligible individuals under age 21. In addition, the federal Vaccines for Children Program 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/index.html.

Merck, the manufacturer of Gardasil 9, offers the Merck Vaccine Patient Assistance Program, which provides Gardasil 9 for free to people aged 19 to 26 who live in the United States, do not have health insurance, and have an annual household income less than a certain amount. More information is available at https://www.merckhelps.com/GARDASIL%209 or by telephone at 1–800–293–3881.

What research is being done on strategies to prevent HPV infection?

If a single dose of HPV vaccine were effective, that would be an important advance. An analysis of data from a community-based clinical trial of Cervarix in Costa Rica, where cervical cancer rates are high, found than even one dose of the vaccine caused the body to produce approximately nine times more antibodies against HPV than the body produces in response to a natural HPV infection, and those antibody levels persisted for at least 7 years (26). In addition, the rates of HPV infection remain low for at least 7 years (27). A large study using national data from women across Australia, where vaccination rates are high, found that one dose of HPV vaccine was as effective as two or three doses in preventing high-grade cervical lesions (28). A randomized clinical trial is currently under way in Costa Rica to evaluate if a single dose of HPV vaccine is sufficient to protect against HPV infection (29, 30).

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. An interim analysis of data from a randomized clinical trial showed that consistent use of a lubricant gel that contains carrageenan reduced the risk of genital HPV infection in healthy women (31).

Researchers are working to develop therapeutic HPV vaccines, which instead of preventing HPV infection would prevent cancer from developing among women previously infected with HPV (32–35). These vaccines work by stimulating the immune system to specifically target and kill infected cells. Ongoing clinical trials are testing the safety and efficacy of a therapeutic DNA vaccine to treat HPV-related cervical and vulvar lesions.

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Reviewed: September 9, 2019
