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# Human *papillomavirus* (HPV) vaccine: Gardasil reactions

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## Abstract

The World Health Organization (WHO) as well as public health officials in Australia, Canada, Europe, and the United States recommend vaccination of young women against HPV to prevent cervical cancer, and to reduce the number of treatments for cervical cancer precursors. The death rate from cervical cancer in the United States is 3 per 100,000 and in 2011, about 12,000 women were diagnosed with cervical cancer and 4,000 died. In 2009, there were about 34,000 deaths from car accidents in the U.S. for a death rate of 11 per 100,000. HPV infection is extremely common; most sexually active people will be infected with HPV at some point in life. HPV infection usually causes no symptoms, but can cause genital warts and anal cancer in both women and men. The HPV vaccine prevents infection by the HPV types responsible for most cervical cancers. There are two available forms of the HPV vaccine: Cervarix; prevents infection by HPV-16 and HPV-18 and Gardasil; prevents infection by HPV-16, HPV-18, and also HPV-6 and HPV-11. There are many side events may cause by HPV vaccines such as; seizures, fatigue, strokes, dizziness, weakness, headaches, stomach pains, vomiting, muscle pain and weakness, joint pain, auto-immune problems, chest pains, hair loss, appetite loss, shortness of breath, heart problems, personality changes, insomnia, hand/leg tremors, arm/leg weakness, paralysis, itching, rashes, swelling, aching muscles, pelvic pain, nerve pain, menstrual cycle changes, fainting, swollen lymph nodes, night sweats, nausea, temporary vision/hearing loss. This topic review focused mainly on the side effects and health serious problems with Gardasil vaccine.

**Key words:** HPV vaccine, Cervical cancer, Cervarix, Gardasil

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## Introduction

The World Health Organization (WHO) as well as public health officials in Australia, Canada, Europe, and the United States recommend vaccination of young women against HPV to prevent cervical cancer, and to reduce the number of treatments for cervical cancer precursors. The death rate from cervical cancer in the United States is 3 per 100,000 and in 2011, about 12,000 women were diagnosed with cervical cancer and 4,000 died. In 2009, there were about 34,000 deaths from car accidents in the U.S. for a death rate of 11 per 100,000 [1].

Research Article doi: 10.18081/2333-5106/014-04/136–146

HPV infection is extremely common; most sexually active people will be infected with HPV at some point in life. HPV infection usually causes no symptoms, but can cause genital warts and anal cancer in both women and men [2].

The HPV vaccine prevents infection by the HPV types responsible for most cervical cancers. There are two available forms of the HPV vaccine: Cervarix; prevents infection by HPV-16 and HPV-18 and Gardasil; prevents infection by HPV-16, HPV-18, and also HPV-6 and HPV-11. There are many side events may cause by HPV vaccines such as; seizures, fatigue, strokes, dizziness, weakness, headaches, stomach pains, vomiting, muscle pain and weakness, joint pain, auto-immune problems, chest pains, hair loss, appetite loss, shortness of breath, heart problems, personality changes, insomnia, hand/leg tremors, arm/leg weakness, paralysis, itching, rashes, swelling, aching muscles, pelvic pain, nerve pain, menstrual cycle changes, fainting, swollen lymph nodes, night sweats, nausea, temporary vision/hearing loss [3].

Current HPV vaccines are based on virus-like particles, and are composed of self-assembled pentamers of the larger protein of the L1 capsid. HPV vaccines are prophylactic and are not therapeutic. The goal of prophylactic HPV vaccination is to avoid persistent infections that will progress to an invasive carcinoma. HPV vaccination would not be appropriate to elicit an anti-cancer response, since the tumor cells do not express significant levels of L1 protein.

For treatment of cancers originating from HPV there is immunotherapy, which focuses on generating a cellular immune response against antigens associated with cellular transformation [4]. The HPV vaccine does not modify the cellular immunity that is responsible for eliminating the infected cells, rather it induces the production of antibodies against the L1 protein in blood. The two main HPV vaccines, Gardasil (Merck) and Cervarix (GSK), were approved in 2006 and in 2009, respectively, so it is still difficult to predict its long-term efficacy [5].

## Available vaccines

Three different vaccines, which vary in the number of HPV types they contain and target, have been clinically developed, although not all are available in all locations:

- Quadrivalent HPV vaccine (Gardasil) targets HPV types 6, 11, 16, and 18.
- 9-valent vaccine (Gardasil 9) targets the same HPV types as the quadrivalent vaccine (6, 11, 16, and 18) as well as types 31, 33, 45, 52, and 58.
- Bivalent vaccine (Cervarix) targets HPV types 16 and 18.

In the United States, only the 9-valent vaccine is available. Practitioners in other locations should confirm vaccine availability locally [6].

## Rationale

### Females

Vaccination with 9-valent, quadrivalent, or bivalent HPV vaccine provides a direct benefit to female recipients by safely protecting against cancers that can result from persistent HPV

Research Article doi: 10.18081/2333-5106/014-04/136–146

infection. This preventive effect is most notable and best studied with cervical cancer, which is one of the most common female cancers worldwide. HPV types 16 and 18, which are targeted by all three HPV vaccines, cause approximately 70 percent of all cervical cancers worldwide, and HPV types 31, 33, 45, 52, and 58, which are additionally targeted by the 9-valent vaccine, cause an additional 20 percent [7].

HPV types 16 and 18 also cause nearly 90 percent of anal cancers and a substantial proportion of vaginal, vulvar, and oropharyngeal cancers. Vaccination with the quadrivalent or 9-valent HPV vaccine also protects against anogenital warts (90 percent of which are caused by HPV types 6 and 11); although they are benign lesions, they are associated with physical and psychological morbidity and have a high rate of treatment failure. The adverse effects of HPV vaccination are generally limited to mild local reactions [8].

Various modeling studies have outlined the potential benefits of HPV vaccination, which appear to be cost effective for the recommended age range [9]. One study suggested that vaccination of the entire United States population of 12-year-old girls would annually prevent more than 200,000 HPV infections, 100,000 abnormal cervical cytology examinations, and 3300 cases of cervical cancer if cervical cancer screening continued as currently recommended [10]. In settings where there has been high uptake of vaccine among females there is also evidence of herd immunity among males of similar age, reflected by a reduction in genital warts [11].

**Males**

HPV vaccination provides a direct benefit to male recipients by safely protecting against cancers that can result from persistent HPV infection. HPV types 16 and 18 cause nearly 90 percent of anal cancers and substantial proportion of oropharyngeal and penile cancers. Vaccination with 9-valent or quadrivalent vaccine also protects against anogenital warts (90 percent of which are caused by HPV types 6 and 11). The overall burden of HPV-associated cancers and precancers among males is less than the burden of cervical cancer in females. Nevertheless, despite a smaller direct absolute benefit of HPV vaccination in males compared with females, the overall benefit of vaccinating males outweighs its potential risks because of additional population benefits from herd immunity and the documented safety of HPV vaccines [12].

Various models have indicated that vaccinating both males and females is more beneficial in reducing HPV infection and disease than by vaccinating only females, although male vaccination is less cost effective than female vaccination [13]. However, cost-effectiveness analyses are limited by uncertainty regarding different variables that affect the impact of male vaccination. These include vaccine efficacy and duration of protection, vaccine coverage of females, the effect of herd immunity, the range of health outcomes included, and the effect of HPV-associated diseases on quality of life [14].

In particular, models have found that the cost-effectiveness of male vaccination is higher in the setting of lower levels of female coverage. This is because there would be less herd protection

Research Article doi: 10.18081/2333-5106/014-04/136–146

from female vaccination, and thus males would have more direct benefit from vaccination. In one study that used population data from the Netherlands, the burden of HPV-associated cancers in men could be reduced by an estimated 37 and 66 percent if vaccine uptake among girls and young women reached 60 and 90 percent, respectively, but vaccine uptake among females is considerably less than 60 percent in many locations [14]. Furthermore, even if vaccine uptake were sufficiently high among females to confer protection against males, this would have minimal effect on men who have sex with men, who have substantially higher rates of HPV-associated anal cancer and precursor lesions than heterosexual males [15].

In resource-limited settings, expert groups recommend that public health efforts focus primarily on vaccinating young females, the group in which the absolute benefit and cost-effectiveness of HPV vaccination is the highest.

## Administration

### Indications and age range

In accordance with the Advisory Committee on Immunization Practices (ACIP) in the United States, we recommend routine HPV vaccination for all females and males in the following age ranges [`9]:

- Routine HPV vaccination is recommended at 11 to 12 years. It can be administered starting at 9 years of age.
- For adolescents and adults aged 13 to 26 years who have not been previously vaccinated or who have not completed the vaccine series, catch-up vaccination is recommended.
- For adults 27 years and older, catch-up vaccination is not routinely recommended; the ACIP notes that the decision to vaccinate people in this age group should be made on an individual basis.

The likelihood of prior exposure to HPV vaccine types increases with age, and thus the population benefit and cost-effectiveness of HPV vaccination is lower among older patients [11]. However, for some individuals in this age group, such as those with no prior sexual experience or with a limited number of prior sexual partners, the risk of prior HPV exposure may be very low. We offer HPV vaccination to such individuals if they are deemed to have a future risk of HPV exposure (eg, expected new sexual partners); studies have suggested that HPV vaccination is immunogenic, efficacious, and safe in women older than 25 years [16]. However, clinicians and patients should be aware that HPV vaccination of individuals older than 26 years may not be covered by insurance providers or other payers, and this may affect the decision to vaccinate.

In the United States, the HPV vaccine is approved through age 45. It is possible that some individuals over the age of 45 years may also benefit from vaccination, but the benefit has not been well studied, and reimbursement for vaccination of such individuals is even less likely [17].

Research Article doi: 10.18081/2333-5106/014-04/136–146

These recommendations are consistent with other expert groups in the United States and Europe, including the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), the American College of Obstetricians and Gynecologists (ACOG), the American Cancer Society (ACS), and the International Papillomavirus Society [18]. These are also largely consistent with recommendations for resource-rich settings from the American Society of Clinical Oncology (ASCO) guidelines on cervical cancer prevention [19].

Recommendations from other expert groups for resource-limited settings are somewhat different. The World Health Organization (WHO) recommends that the primary target of HPV vaccination programs be females aged 9 to 14 years and that local public health programs should recommend vaccination of older females only if it is affordable and cost effective and does not divert resources from vaccinating the primary target population or screening for cervical cancer [12]. ASCO recommendations for resource-limited settings are similar [20].

**Optimal timing**

Within the recommended age range, the optimal time for HPV immunization is prior to an individual's sexual debut. Clinical trial data of vaccine efficacy in males and females suggest that immunization with HPV vaccine is most effective among individuals who have not been infected with HPV (eg, patients who are "HPV-naïve"). None of the available HPV vaccines treat or accelerate the clearance of preexisting vaccine-type HPV infections or related disease. Individuals who are sexually active should still be vaccinated consistent with age-specific recommendations. A history of an abnormal Papanicolaou test, genital warts, or HPV infection is NOT a contraindication to HPV immunization [21]. However, immunization is less beneficial for those who have already been infected with one of more of the HPV vaccine types.

**Choice of vaccine**

Not all HPV vaccines are available in all locations. If cost and availability are not an issue, we recommend the 9-valent vaccine. The greater HPV-type coverage provided by the 9-valent compared with the quadrivalent and bivalent vaccines protects against additional cervical cancers. Although it is not clear that greater HPV-type coverage by vaccinating males with the 9-valent rather than quadrivalent vaccine would substantially improve male cancer prevention, it would likely further reduce the risk of cervical cancer in women indirectly through herd immunity [22].

In general, the same formulation should be used to complete the series, if possible. However, if the HPV vaccine formulation initially used is unknown or unavailable, or if the 9-valent vaccine is being introduced into the formulary, a different HPV vaccine formulation can be used to complete the series [23].

Research Article doi: 10.18081/2333-5106/014-04/136–146

**Immunization schedule**

In the United States, the recommended dosing schedule depends on the age of the patient at vaccine initiation [24].

**Individuals initiating the vaccine series before 15 years of age**

Two doses of HPV vaccine should be given at 0 and at 6 to 12 months.
If the second dose was administered less than five months after the first, the dose should be repeated a minimum of 12 weeks after the second dose and a minimum of five months after the first.

**Individuals initiating the vaccine series at 15 years of age or older**

Three doses of HPV vaccine should be given at 0, 1 to 2 (typically 2), and 6 months.The minimum intervals between the first two doses is four weeks, between the second and third doses is 12 weeks, and between the first and third dose is five months. If a dose was administered at a shorter interval, it should be repeated once the minimum recommended interval since the most recent dose has passed.

**Immunocompromised patients**

Three doses of HPV vaccine should be given at 0, 1 to 2, and 6 months regardless of age.
This ACIP recommended vaccination schedule is the same as that recommended by the Strategic [25]. The two-dose series is similarly recommended in many other countries. Practitioners outside the United States should consult local guidelines for the recommended immunization schedule in their country.
HPV vaccine can be safely administered at the same time as other age-appropriate vaccines at a different anatomic site. Administering HPV vaccine at the same time as certain other vaccines (ie, tetanus, acellular pertussis, and diphtheria vaccine and inactivated poliovirus vaccine) does not appear to adversely affect the immune response to either the HPV vaccine or the concomitant vaccine [26].
Although the initial clinical efficacy studies evaluated a three-dose schedule, subsequent studies found that two vaccine doses in young individuals have similar or greater immunogenicity compared with three doses in older females (the group in whom vaccine efficacy was established in clinical trials) [27]. Observational evidence additionally suggests that fewer than three doses are still associated with reductions in cervical neoplasia [28]. For the quadrivalent vaccine, furthermore, two doses appear comparably effective as three doses for prevention of genital warts [29]. Three doses of HPV vaccine are still recommended for individuals 15 and older because of the lower immunologic response to HPV vaccination in this population.

Research Article doi: 10.18081/2333-5106/014-04/136–146

As an example of supportive evidence for the two-dose schedule, a trial of 1518 participants randomly assigned to receive the 9-valent vaccine at different dosing schedules demonstrated that antibody titers for HPV vaccine types were consistently higher among females and males aged 9 to 14 years who received two vaccine doses spaced 6 or 12 months apart compared with females aged 16 to 26 years who received three vaccine doses over six months [30].

One cohort of females aged 9 to 14 years in this trial was also assigned to receive three vaccine doses; among females in this age group, antibody responses were generally comparable with two- versus three-vaccine doses, and many vaccine-type titers trended higher with two doses.

While no efficacy trials have been conducted to directly evaluate a two-dose schedule, a post hoc analysis of data from two trials of the bivalent HPV vaccine in young women (aged 15 to 25 years) who had no HPV type 16 or 18 infection at baseline suggests that two vaccine doses can effectively protect against HPV infection [31].

Of those with at least 12 months of follow-up, vaccine efficacy against six-month persistent infection with HPV types 16 and 18 was no different in women who received the intended three doses compared with those who received only two (89 and 90 efficacies, respectively) [11].

Observational studies have examined effectiveness by number of doses, but are difficult to evaluate primarily because of a number of unmeasured confounders.

In a large nationwide cohort from Denmark that included over 590,000 females, receipt of one, two, or three doses of quadrivalent vaccine (initiated at age 14 years or younger in the majority of participants) were each associated with similar reductions in the risk of CIN3 or worse compared with no vaccination [21]. Similarly, one observational study of over one million Swedish females suggested that two quadrivalent vaccine doses provided substantial protection against genital warts, although completion of three doses was slightly superior (128 versus 174 events per 100,000 person-years with two doses, compared with 528 events per 100,000 years without vaccination) [33].

**Missed doses**

Patients often do not follow up for their immunizations on schedule [12]. The ACIP recommends that if the vaccination series is interrupted for any length of time, it can be resumed without restarting the series.

**Postvaccination instructions**

Because of a potential for syncope with any vaccine, and particularly with the HPV vaccine, a routine 15-minute waiting period in a sitting or supine position following HPV vaccination is recommended [32]. This may decrease the risk of syncope with subsequent injury.

Research Article doi: 10.18081/2333-5106/014-04/136–146

**Adverse reactions to the HPV vaccine**

According to HPV vaccine manufacturers, the most common adverse reactions to Gardasil include pain, swelling, redness, stinging, bruising, bleeding at the injection site, and headache, fever, nausea, diarrhea, abdominal pain, and syncope). For Cervarix, local adverse reactions occurring in ≥ 20% of subjects are pain, redness, and swelling at the site of injection. The most common general adverse events in ≥ 20% of the subjects are fatigue, headache, myalgia, gastrointestinal symptoms, and arthralgia (FDA) [31].

While most frequent reported symptoms of HPV Gardasil vaccination are chronic pain with paresthesia, headaches, fatigue, and orthostatic intolerance [30]. Small series and isolated cases of complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), and fibromyalgia, have been reported after vaccination against HPV. These conditions are often difficult to diagnose, and show similar clinical characteristics [30].

Apparently, dysfunction of the sympathetic nervous system plays an important role in the pathogenesis of these syndromes [23]. Ninety-three percent of affected subjects continue to have disabled symptoms for more than four years, unable to return to school or work [21]. Other studies, nevertheless, have shown a lack of evidence of an association between HPV vaccine and CRPS. It should be mentioned that chronic arthropathy has also been observed with other vaccines, such as the rubella vaccine.

This topic review focused mainly on the side effects and health serious problems with Gardasil vaccine.

**Competing interests**

The authors declare that they have no competing interests.

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