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<< Back to Home Page.

Gardasil Continues to Stir Heavy Controversy

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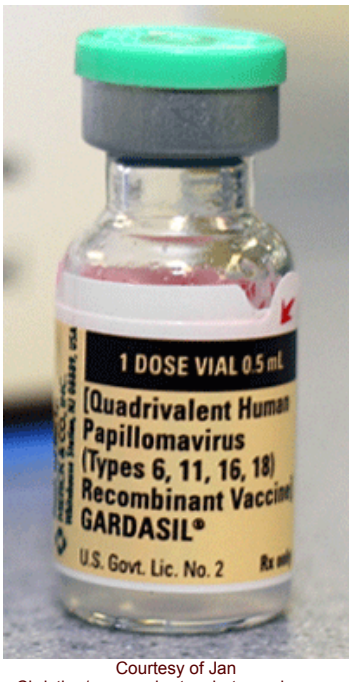
What is Gardasil?

Gardasil is the first available vaccine against genital human papillomavirus (HPV), the most common sexually transmitted virus in the United States. There are various strains of HPV. Made by the company Merck Inc., the vaccine protects against HPV types 6, 11, 16 and 18 in both males and females (Centers for Disease Control and Prevention, "Human Papillomavirus"; Cerner Multum, Inc.). Gardasil protects both males and females from anal cancer and precancerous lesions caused by those four HPV types. In girls and young women of ages 9 to 26, this vaccine protects against HPV types 16 and 18 that are the cause of nearly 75% of cervical cancer cases, 70% of vaginal cancer cases, and 50% of vulvar cancer cases. In females, Gardasil also protects against types 6 and 11 that are the cause of 90% of genital warts cases. In boys and men of ages 9 to 26, the FDA approved Gardasil for the prevention of genital warts caused by HPV types 6 and 11, which constitute 90% of genital warts cases (Cerner Multum, Inc.; U.S. Food and Drug Administration, "Gardasil").

It is important to note that Gardasil may not completely protect anyone, nor has it been shown to protect against diseases associated with the other 26 or more sexually transmitted HPV types or against diseases not caused by HPV. This vaccine does not prevent all cervical cancer cases, making it crucial for women who have (or have not) been vaccinated to continue routine cervical cancer screenings, such as annual pap smears. In addition, Gardasil is not a treatment for cancer or genital warts and is not effective for those who already been infected with HPV (Cerner Multum, Inc.).



Courtesy of Jan Christian/www.ambrotosphotography.com

Figure 1: The Gardasil vaccine, developed by Merck, protects against HPV types 6, 11, 16, and 18 and is administered in three doses.

Gardasil Administration

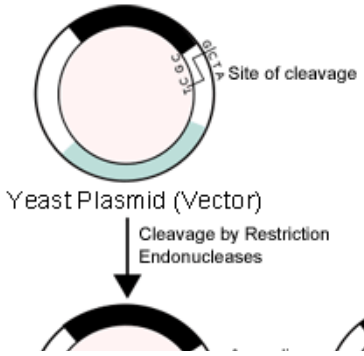
Gardasil (see Figure 1) is injected into the upper arm or upper thigh muscle and is administered in three doses of injection that must be given within a one year period. Any person in the age group of 9 to 26 can receive the first dose. The second dose is typically given two months after the first, and the final dose is given six months after the first (Drug Information Online; Net Doctor).

Clinical researchers have discovered that giving three doses of Gardasil allow women's antibody levels against those HPV strains to progressively increase with each dose. They believe this may provide women with greater immunity for a longer duration than could be provided with only one dose (Gostout). However, since some studies have been finding that higher antibody levels do not correlate with greater immunity from HPV infection, this three dosage schedule may be changed in the future (McCormack and Joura).

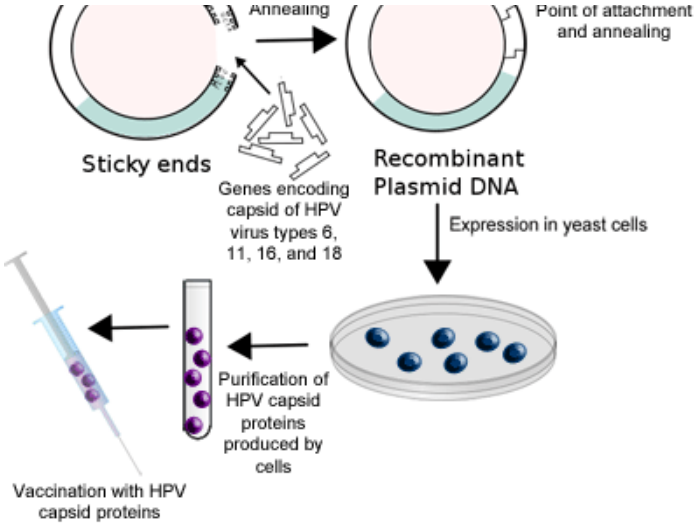
The Science Behind Gardasil: A Recombinant Vaccine

There are different types of vaccines, including inactivated; live, attenuated; toxoid; conjugate; subunit; DNA; and recombinant vector vaccines (U.S. Department of Health and Human Services of National Institutes of Health).

Gardasil is a type of recombinant vaccine, as shown in Figure 2. The Gardasil recombinant vaccines are made by taking genes that encode for capsid proteins of HPV types 6, 11, 16, and 18 and inserting them into yeast expression vectors, which are circular DNA pieces containing specific sequences that allow translation of those genes into proteins. The HPV protein-encoding genes are expressed in the yeast vectors to create large amounts of protein, which are then purified and used in the vaccine (McCormack and Joura; U.S. Food and Drug Administration, "Gardasil").



When a person is vaccinated with Gardasil, the immune system develops acquired immunity against those four HPV strains. Immune system cells called naïve B-lymphocytes recognize the inactivated extracts and proteins in the vaccine as foreign, triggering the lymphocytes to divide into memory B-lymphocytes and plasma B-lymphocytes. The plasma cells provide short-term immunity by producing sets of antibodies specific to



Adapted from Minestrone Soup/Wikimedia Commons

Figure 2 *(Click here to view enlarged image.)*: Gardasil is a recombinant vaccine made by taking capsid-encoding genes from HPV types 6, 11, 16, and 18 and expressing them in yeast cells. The proteins made by the yeast cells are purified and used in the vaccination. Since the vaccine contains only HPV proteins and not the entire virus, it does not cause infection and allows the body to develop acquired immunity to those specific HPV strains.

the protein extracts from those four HPV strains, allowing the antibodies to attack those foreign organisms. The memory B-lymphocytes, however, provide long-lasting immunity by developing B-cell receptors with a high affinity for the antigens present on the capsid proteins in the vaccine (Kaiser; Robinson). Consequently, if this person is exposed to the activated forms of HPV types 6, 11, 16 or 18 through natural means in the future, the memory B cells will recognize them and trigger production of those antibodies to combat the virus (Kaiser). Since Gardasil contains only the proteins from the virus and not the whole HPV virus, the vaccine does not cause HPV infection (U.S. Food and Drug Administration, "Gardasil").

Concerns Regarding Safety of Gardasil

The Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) have created the Vaccine Adverse Event Reporting System (VAERS) to monitor adverse side effects to Gardasil and other vaccines. Any patient who experiences an adverse side effect after receiving a vaccination may report this side effect through VAERS. This allows the CDC and the FDA to gather information about adverse or minor side effects of vaccines so that this information can be revealed to the public (Vaccine Adverse Event Reporting System).

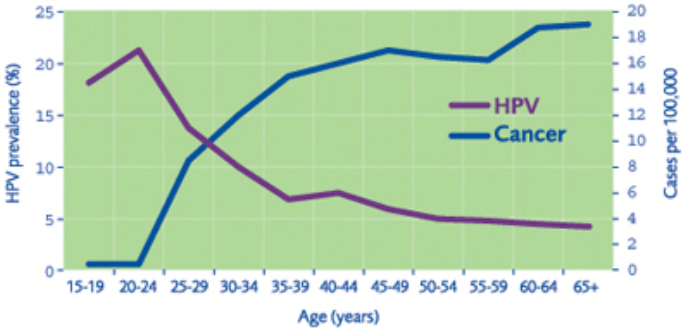
From the time that the FDA approved Gardasil in June 2006 to February 2011, 33 million doses of Gardasil have been injected in the U.S., and 18,354 reports of adverse side effects were reported to VAERS. About 92% of those were non-serious, including syncope (fainting), pain, swelling, headaches, nausea, and fever; and 8% were serious, meaning that they resulted in death, were life-threatening, caused a disability, resulted in a birth defect, and caused or prolonged a hospitilization. There have been 51 VAERS reports of deaths among girls or women vaccinated with Gardasil, 32 of which have been confirmed. However, it is believed that not all of these deaths and other adverse side effects were caused by the vaccine. For example, of the females who reported blood clots after receiving the vaccine, most already had a high risk of blood clots, such as obesity, smoking, or use of oral contraceptives (Centers for Disease Control and Prevention, "Reports of Health Concerns Following HPV Vaccination"). As a result, some physicians are reluctant to blame Gardasil for all of the reported side effects (Chitale).

Opinions regarding the safety of Gardasil vary among physicians, with many urging for more studies of its side effects. Since the vaccine has been available for about 5 years, there have not been published studies reporting long term side effects of Gardasil. In accordance with the FDA's recommendations, Merck is conducting a study of 44,000 subjects to uncover the short- and long-term side effects of the vaccine (U.S. Food and Drug Administration, "FDA Approves Expanded Uses for Gardasil to Include Preventing Certain Vulvar and Vaginal Cancers").

Some physicians, including Dr. Joseph Zanga at the Columbus Regional Healthcare System in Georgia and Dr. Jacques Moritz, the director of gynecology at St. Luke's Roosevelt Hospital, believe that current cervical cancer screening techniques (such as the pap smear) and treatment options obviate the need for Gardasil, especially since it does not protect against all HPV strains. However, others, including Dr. Kevin Ault, the associate professor Gynecology and Obstetrics at Emory University, believe that the benefits of Gardasil outweigh its risks and that the reported adverse side effects are likely not caused by the vaccine (Chitale).

A 2009 editorial in the *Journal of the American Medical Association (JAMA)* pointed out several flaws of Gardasil that should be considered. Of the 15 oncogenic, or cancer-causing, HPV strains, Gardasil only protects from infection by two of them (HPV types 16 and 18). Consequently, receiving the vaccination does not preclude someone from being infected with a HPV strain and developing cancer (Haug, 2009). Furthermore, since genital warts and lesions are not solely caused by HPV strains 6 and 11, Gardasil does not provide complete immunity from those lesions. For example, a 2011 editorial published in the *New England Journal of Medicine* reported that in a medical institute in Germany, of 347 men with genital lesions, 38% of them were not infected with HPV strains 6 and 11, indicating that Gardasil most likely would not have protected them from infection (Wieland and Kreuter, 2011). These reports indicate that Merck should try to improve Gardasil to provide immunity against a greater spectrum of HPV strains.

Even if a person receives the Gardasil vaccination at a young age, it has not been shown that this will prevent development of cervical cancer during adulthood. Even though girls and women of ages 9 to 26 can receive the vaccine, cervical cancer is rare in females younger than 30 years of age, as shown in Figure 3; the median age of cervical cancer diagnosis is 47 years (Centers for Disease Control and Prevention, "Cervical Cancer Rates by Race and Ethnicity"). However, Merck has not of yet demonstrated whether receiving Gardasil at an age between 9 and 26 can reduce cervical cancer rates in women of that age group. Furthermore, of the 79% of women who will be infected with HPV, about 90% of women will not develop cervical cancer due to the strength of their natural immune response; as of now, it has not been determined who will actually benefit from the Gardasil vaccination, making it necessary to conduct clinical studies



National Cancer Institute, SEER data, 1990-1994

vaccination), making it necessary to conduct clinical studies that involve a long-term follow up with those who get vaccinated (Centers for Disease Control and Prevention, "Genital HPV Infection – Fact Sheet"; Haug, 2009).

Figure 3: Even though HPV infection prevalence is higher in females younger than 26 years of age, cervical cancer rates are higher in older female populations.

Comparison with Cervarix

In 2009, the FDA approved GlaxoSmithKline's vaccine Cervarix for the prevention of cervical cancer in girls and women of ages 10 to 25, making Cervarix the second available vaccine against HPV. Cervarix protects against HPV types 16 and 18, as does Gardasil, in addition to types 31, 33, and 45, the next most common cervical cancer-causing HPV strains. A study funded by GlaxoSmithKline and published in *The Lancet* found that even though Cervarix was constructed to provide immunity only to HPV types 16 and 18, the vaccine also provides cross-protection against types 31, 33, and 45 (Paavonen et al., 2009).

According to Diane Harper, M.D. from the University of Missouri-Kansas City School of Medicine, Cervarix is more effective in preventing against cervical cancer than Gardasil since Cervarix provides immunity from 5 HPV strains for 6.4 years while Gardasil provides immunity from 4 strains for 5 years. However, while Gardasil also protects against 90% of genital warts cases by providing immunity to types 6 and 11, Cervarix does not (Chusteka). Nevertheless, both vaccines have been approved by the FDA, although Gardasil is the only one approved for both females and males (GlaxoSmithKline).

Future Goals

Physicians and the general public are currently awaiting studies indicating the long-term effects of Gardasil, in terms of its long term side effects and its potential to reduce cervical cancer rates among those vaccinated. There is hope that in the future, improvements in Gardasil or Cervarix or development of new vaccines could provide greater immunity to all HPV strains, thereby lowering cervical and other HPV-associated cancer rates substantially.

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<< Back to Home Page.