Gardasil HPV Vaccination Series

In 2006, United States pharmaceutical company Merck released the Gardasil vaccination series, which protected recipients against four strains of Human Papillomaviruses, or HPV. HPV is a sexually transmitted infection which may be asymptomatic or cause symptoms such as genital warts, and is linked to cervical, vaginal, vulvar, anal, penile, head, neck, and face cancers. In 2006, based on research conducted by researchers Ian Frazer and Jian Zhou in the 1990s, Merck released a four-strain version of Gardasil, which protected boys and girls aged nine and older against the major HPV strains HPV-6, HPV-11, HPV-16, and HPV-18. In 2014, Merck released Gardasil 9, a nine-strain version that protected from the original four HPV strains plus strains HPV-31, HPV-33, HPV-45, and HPV-58. Gardasil is a preventative measure and reduces the risk of contracting HPV and HPV-related cancers by up to ninety-seven percent.

Gardasil protects males and females from contracting HPV. HPV is a sexually transmitted infection primarily transmitted through genital skin contact. It infects the epithelial cells of the body, or the cells that line organs and body cavities. HPV often results in no symptoms or in symptoms such as genital warts. Strains HPV-16 and HPV-18 link to eighty percent of cervical cancer instances in females, while strains HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58 link to twenty percent of cervical cancer occurrences. Malignant strains of HPV infect the body's cells, and as those infected cells reproduce, they reproduce with the virus's cancerous genetic information, leading to the production of abnormal, cancerous cells.

Between 1980 and 1984, Harald zur Hausen, a scientist at the German Cancer Research Center in Heidelberg, Germany, discovered that HPV can cause cervical cancer while working with cervical cancer tumor samples. In 1967, prior to his discovery of HPV, zur Hausen discovered that Epstein-Barr virus, a type of virus that causes infectious mononucleosis, or mono, can mutate healthy cells into cancer cells, one of the first discoveries of viruses causing cancer in humans. In zur Hausen's work with HPV, he looked at cervical tumor and genital wart samples to see if there was a similar viral link between those types of disease processes. Zur Hausen and his team isolated what they later identified as a malignant strain of HPV from genital wart samples in 1980. Following that initial discovery, zur Hausen's team discovered three more HPV strains after analyzing cervical cancer tumor cells, linking HPV with cervical cancer for the first time with confidence. In 2008, zur Hausen shared The Nobel Prize in Physiology or Medicine for his work on strains of HPV that caused cervical cancer with Françise Barré Sinoussi and Luc Montagnier for their work on human immunodeficiency virus.

In the early 1990s, Frazer and Zhou began developing technology that would eventually be used to produce an HPV vaccine that could help protect people from contracting cervical cancer. The two scientists met in 1989 while Frazer was visiting the University of Cambridge, in Cambridge, England, and Zhou was visiting a nearby lab. At the time, Frazer claimed there was nothing in the scientific literature that answered how the human immune system reacted to HPV, a phenomenon that Frazer wanted to study, according to his article "The HPV Vaccine Story." Zhou, on the other hand, wanted to study how HPV transformed human cells, according to Frazer. Frazer writes that in order to study either of these phenomena, the researchers would need to synthesize infectious HPV viruses. To do so, in 1990, Zhou moved to Brisbane, Australia, to work at Frazer's lab at the University of Queensland. There, the two researchers began working on synthesizing virus-like particles, or VLPs, for HPV. VLPs are protein structures that resemble the original virus but lack the viral genetic information that actually makes an organism sick. Thus, VLPs essentially trick the body into initiating an immune response, or the bodily response to fight against pathogens and viruses, by exposing the body to the virus's proteins without actually making the organism sick.

After Frazer and Zhou successfully produced VLPs for HPV, they described their findings and the process of producing the VLPs in the 1991 publication, "Expression of Vaccinia Recombinant HPV 16 L1 and L2 ORF Proteins in Epithelial Cells is Sufficient for Assembly of HPV Virion-Like Particles." There, they claim that their technology could be used to create a vaccine against HPV.

That same year, Frazer and Zhou filed a patent application for the rights to the vaccine technology in Australia, suspecting that the VLPs they developed would be used in any HPV vaccine produced. However, various other research teams around the world were also researching technology to produce an HPV vaccine, and also filed patents in other countries for the rights to the vaccine. In 2007, in the case Frazer v. Schlegel, the United States Court of Appeals finally awarded the rights to the HPV vaccine to Frazer and Zhou over other research parties, deciding that they were the first team to accurately develop the vaccine technology.

As the legal battle over the international patent rights went on between the various parties, the pharmaceutical company Merck licensed the technology from multiple researchers to begin producing a vaccine. After a series of trials, in 2006, the United States Food and Drug Administration, or the FDA, approved the use of Merck's vaccine Gardasil, which protects against four-strains of HPV for use in females. The FDA approves all vaccines administered in the US and tests all vaccines extensively to ensure their safety and efficacy. Then, in 2007, Australia and Europe approved the HPV vaccine Cervarix from the pharmaceutical company GlaxoSmithKline, and in 2009, the FDA also approved it for use in the US. Cervarix only protected females from the two most virulent strains of HPV, HPV-16 and HPV-18. In 2011, the FDA approved Gardasil's use in males, and in 2014, approved the use of Gardasil 9, a nine-strain version of Gardasil that works in both females and males. As of 2021, three separate HPV vaccines exist, including Gardasil, Gardasil 9 and Cervarix.

In 2019, the American Academy of Pediatrics recommended that children receive an HPV vaccine between ages nine and fourteen. Children between those ages generally have not yet engaged in sexual activity. Merck recommends that the recipient of the vaccine not yet be sexually active because the vaccines are protective measures against HPV, commonly transmitted by sexual contact. There is a chance that in sexually active recipients, the vaccine may be ineffective against any strain the recipient has already come in contact with. However, as of October 2018, the FDA expanded the use of Gardasil for people up to age forty-five, citing a study that found that the HPV vaccination may be helpful in preventing persistent HPV infection in those already infected with one or more strains of the virus. Additionally, even though only females can get cervical cancer, Gardasil is administered to both males and females. Gardasil protects against two HPV strains that cause genital warts in both males and females. Additionally, Gardasil is recommended for males to promote herd immunity against HPV, which is a population's collective resistance to a disease when a high proportion of individuals are immune to the disease, and results in fewer occurrences of the disease in unvaccinated people.

Doctors and nurses administer Gardasil to males and females in three doses. Three doses ensure long-lasting protection against the most malignant strains of HPV. Doctors administer the first dose, the second does three months later, and the third dose three months after the second. Merck recommends that children vaccinated before the age of fourteen receive all three doses, but states that two doses will provide a moderate level of protection.

While the American Cancer Society recommends immunizing people against HPV using vaccines like Gardasil to prevent cancers related to the virus, some recipients noted certain side effects. Vaccination recipients reported injection-site swelling, redness, pain, bruising and reports of nausea, fever, headache, and dizziness. According to Merck, there is an increased risk of fainting after recipients receive the vaccine. Therefore, Merck recommends observing the patient for fifteen minutes following inoculation to reduce any fainting-based injury. The United States Vaccine Injury Compensation Program states that adverse effects associated with the vaccine include anaphylaxis, or severe allergic reactions, fainting, and potential shoulder injury where doctors inject the vaccination. Merck also released the required pamphlet, called an insert, to prescribers detailing their investigation into the vaccine's safety.

In order to investigate the potential risks and symptoms associated with the vaccine, Merck evaluated the safety of Gardasil 9, the nine-strain version of Gardasil. Merck conducted seven clinical

trials, which involved 15,703 individuals who received at least one dose of Gardasil 9, and released the results as an insert. The overseeing trial staff monitored injection-site and systemic adverse reactions as safety variables in the trial. The trial staff found that the rates of injection site pain remained approximately the same for the participants across each of the three injections. They also found that swelling at the patient's injection site increased at each successive vaccination. They concluded that there were numerically higher rates of injection-site reactions in the nine-strain version of Gardasil than there were in the four-strain version. Pain, redness and swelling are normal reactions in the area of the shot, as any antigen molecule injected is a foreign object, and these reactions indicate that the vaccine is working. Trial staff also monitored serious adverse effects among trial participants and found that 2.3 percent of trial participants reported a serious adverse effect during the elapsed time of study. Of those reports, Merck claimed that there were only four serious adverse effects actually linked to the vaccine, including headache, fever, asthmatic crisis, and anaphylaxis. The trials concluded by stating that the vaccine was not responsible for any deaths or any increased occurrences of autoimmune disorders.

Early estimates of the vaccination's efficacy found that the four-strain vaccines were up to ninety percent effective against genital and cervical cancers. The nine-strain version prevents females from the cancer-causing strains included in the vaccine ninety-eight percent of the time. The nine-strain vaccine also has a hundred percent efficacy in preventing vulvar cancer and a seventy-five percent efficacy in preventing anal cancer. The additional five strains of HPV which are included in the nine-strain version of Gardasil, strains HPV-31, HPV-33, HPV- 45, HPV-52, and HPV-58, further protect recipients from additional, rarer forms of HPV-caused cancers, including cervical, vulvar, and vaginal cancers.

Gardasil continued to be present in the US news throughout the late 2010s. According to the Centers for Disease Control, or CDC, more and more US teenagers are getting the HPV vaccine. In 2016, over sixty percent of US teenagers had obtained at least one dose of the HPV vaccine, which was a four percent increase from 2015. That same article found that protection among teenagers was lower among teenagers in rural areas of the United States. The journalist cites that the discrepancy could be due to a lack of resources in rural areas, or political or religious beliefs among parents. A 2015 study by Leah Smith and colleagues found that some parents feared that allowing vaccination against HPV for their children may promote promiscuous behavior. However, the same study found that there were no increased instances of sexual behavior regardless of vaccination status. Other factors such as cost and dosage play a role in lack of HPV vaccination.

A large study of childhood immunizations in 2014 concluded that some vaccines have a 94.7 per cent rate of adherence to vaccination schedules, but that other vaccines such as Hepatitis A, which had a 57.5 percent adherence to schedule, are much lower. The study found that the main factors causing low adherence to vaccine schedules were cost and reservations from parents and providers about too many vaccinations. For the HPV vaccine, reasons for lack of adherence to vaccination schedule may be cost, as the HPV vaccine costs approximately 300 US dollars per dose and is often not covered by health insurance, and reservation from parents over the need for three doses.

Since the introduction of Gardasil in 2006, the CDC reports that HPV HPV-6, HPV-11, HPV-16 and HPV-18 prevalence has decreased by fifty-six percent in female teenagers around the ages of fourteen through nineteen. In addition, according to research conducted by Merck, Gardasil provides up to a ninety-seven percent efficacy rate in protecting females from cervical cancer. While Gardasil protects against the nine strains of HPV, other HPV vaccines such as Cervarix only protects females from the two strains most commonly associated with HPV, strains HPV-16 and HPV-18. Researchers continue to look for less expensive means to administer the vaccine and ways to administer the HPV vaccine in fewer doses. The introduction of HPV vaccines has reduced instances of various HPV-linked cancers among males and females and has opened up the possibility of developing additional vaccinations against cancer-causing viruses.

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