



**TOURO COLLEGE &
UNIVERSITY SYSTEM**

The Science Journal of the Lander
College of Arts and Sciences

Volume 8
Number 1 *Fall 2014*

1-1-2014

The Efficacy and Safety of the Human Papillomavirus Vaccine

Gail Tessler
Touro College

Follow this and additional works at: <https://touro scholar.touro.edu/sjlcas>

 Part of the [Therapeutics Commons](#), and the [Virus Diseases Commons](#)

Recommended Citation

Tessler, G. (2014). The Efficacy and Safety of the Human Papillomavirus Vaccine. *The Science Journal of the Lander College of Arts and Sciences*, 8(1). Retrieved from <https://touro scholar.touro.edu/sjlcas/vol8/iss1/9>

This Article is brought to you for free and open access by the Lander College of Arts and Sciences at Touro Scholar. It has been accepted for inclusion in The Science Journal of the Lander College of Arts and Sciences by an authorized editor of Touro Scholar. For more information, please contact touro.scholar@touro.edu.

The Efficacy and Safety of the Human Papillomavirus Vaccine

By: Gail Tessler

Gail graduated in June 2014 with a B.S. in biology. She is currently attending the Physician Assistant program at SUNY Downstate Medical Center.

Abstract

The HPV virus is said to be the cause of many infections, warts, and cancers. In addition to the fact that the treatment for HPV is not always successful, not every individual knows that s/he is infected and is very likely to infect his or her partner, too. This is one factor that explains why 14 million people each year in America alone contract HPV and makes cervical cancer so threatening to many people worldwide. In light of this and the known dangers of cervical, anal, vaginal and penile cancers, the HPV vaccine was created to prevent an infection of HPV from developing into a cancer. Within the past decade, two vaccines, Gardasil, manufactured by Merck, and Cervarix, manufactured by GSK, have been produced to help prevent 70 percent of the Human Papillomavirus strains in order to reduce the chances of contracting the various cancers and infections that are connected to HPV. (However, since the idea of cancer vaccines is so new to the health world, questions and wariness remain: Are Gardasil and Cervarix effective? Are they safe and not counterproductive? Should everybody in the age bracket of 10 until 25 be vaccinated? If so, because it is unusual for there to be two vaccines targeting the same goal, which company's make is preferred?) Many studies have been conducted on the new HPV vaccines within the past decade. The results are positive and the vaccines seem to get a 100% efficacy rate when administered correctly to the proper population. The difference of the vaccines is noted in their targeted strains. Therefore it is the patient's choice for which vaccine she would want to be administered.

Introduction

Prevalence of cervical cancer

Cervical cancer is the third-most common cancer in the world and the second-most fatal in women, causing about 274,000 deaths annually (Vici, 2014; de Noronha, 2013). Cervical cancer is a resilient cancer that is hard to eliminate. Screening programs are beneficial, even in young to middle-adult ages, when it leads to early detection and treatment, increasing chances of survival (de Noronha, 2013). Possible but unpleasant and not always successful treatments are monotherapy, radiation, chemotherapy, and drugs like Bevacizumab (Vici, 2014). Researchers are also concerned with quality of life, since the pelvic floor is affected after cancer has developed (de Noronha, 2013). For these reasons, researchers decided to focus on the preventive aspect so fewer treatment options will be necessary. An individual can check for cervical cancer with a Papanicola test which detects precancerous lesions that may eventually develop into cancer. Because of the increase of Papanicola testing recommended and performed, more people are aware of their cervical wellbeing (Markowitz et al., 2007). Many researchers noted that when they studied the pathogenesis of cervical cancer, 99% of cases and over 90% of squamous intra-epithelial lesions that appear before the cancer fully appears are actually caused by a virus, Human Papillomavirus (HPV) (Monie et al., 2008). In fact, the biggest widespread sexually transmitted infection (STI) in the world is HPV; About 79 million people in the US currently are infected with HPV and about 14 million people become infected each year (Markowitz et al., 2007). The cases increase with age until the mid-thirties age group, where the number of cases of HPV begins to decrease. HPV can

cure itself, as it actually does in about 90% of cases. However, if an individual's cervix does not heal, then she becomes at high risk for developing cervical cancer (Basu et al., 2013). Besides cervical cancer, HPV can also cause vaginal and vulvar cancer in women, penile cancer in men, and some oropharyngeal cancers and genital warts in both genders. Every year, about 26,200 new cancers are linked to HPV, and two-thirds of them affect women (Markowitz et al., 2007).

Pathogenesis of HPV

Of the 200 HPV genotypes, the majority of them can cause infections that may result in "benign or self-limited tumors (warts) in the skin or in the genitals." Those genotypes of HPV that do form warts are the oncogenic category of HPV (Wang & Roden, 2013). There are about 13 high-risk HPV strains and another seven probable high-risk strains. The most common HPV strains worldwide are HPV 16, 18, 31, 52 and 58 (Tachezy et al., 2013). The HPV virus can lead to cervical, vaginal, anal, pelvis, vulvar and oropharyngeal cancers (Wang & Roden, 2013). The two most common HPV strains that are related to cervical cancer are HPV 16 (50% of all cases) and HPV 18 (20% of all cases). However, in anatomic locations other than the cervix that can be infected by HPV, such as the head and neck centers, HPV 16 is the cause of cancer 90% of the time (Monie et al., 2008). During intercourse, the epithelial cells of the cervix and vagina might acquire some abrasions, which raise the possibility of undifferentiated basal cells being exposed to a strain of HPV. If HPV is present, the cells might differentiate with the viral genome and begin to replicate (Wang & Roden, 2013).

Replication of HPV

HPV's genome "encodes two classes of genes – early and late. The early genes control replication (E1, E2), transcription (E2), reorganization (E4), and transformation (E5, E6, E7). The late proteins are structural components of the viral capsid." However, the expression is controlled by the differentiation of the host – now infected – cell. When development occurs, the HPV genome mixes into the host's genome, causing E2, which is the main regulator of the virus's genes, and L1 and L2 to be suppressed (Monie et al., 2008). That allows E6 and E7 to overregulate. E7 would lead the cell into the S-phase of uncontrollable replication and the cell cycle will be disrupted. Eventually a thickened epithelial lesion will form. Its cells will flow from the epithelium and a virus will spread. HPV will then evolve into an HPV-related neoplasia and develop into warts or cancer if the immune system fails to protect the body (Basu et al., 2013).

Genital warts are the largest cause of sexually transmitted infection in the Western world. Their treatment is excruciating and also not permanent, as the warts commonly recur. Besides the high costs of treatments for genital warts, the recurrence is also nerve-racking and frustrating to a patient's mental state. Genital warts generally come about from HPV 6 and 11 – two low risk HPV strains – but more research is needed to test for the presence of other strains, like the high risk HPV 16 and 18 (Szarewski et al., 2013).

Development of a vaccine

Because it takes years for an HPV infection to become a cancer, it is probably going to take years before researchers will be able to see the full results of the vaccines (Markowitz et al., 2007). Two vaccines over the past decade were created to prevent the "grave outcomes of a long-lasting HPV infection and HPV-related anogenital malignancies, high grade cervical intraepithelial neoplasia (CIN), VIN, VaIN, and AIN" (Wang & Roden, 2013). The development of vaginal, vulvar, and anal cancer is not yet fully understood. Unlike cervical cancer, there is no routine screening developed yet for vaginal and vulvar cancer. Vaginal and vulvar are not common cancers; 1,070 and 3,507 cases were reported in the US, respectively (Markowitz et al., 2007).

The vaccines to prevent HPV are created by the use of virus-like particles (VLP) as the antigens needed to combat in the vaccines which come from the L1 surface protein of the precise types of HPV used in that specific vaccine (Basu et al., 2013). These VLPs are assisted by monoclonal antibodies (mAbs) for correctly folding into epitopes, virus typing and activating the proper immune response (Vidyasagar et al., 2014). The vaccine is considered dead as the VLPs are non-pathogenic and cannot cause other cells to become infected. Most importantly, the VLPs lack the viral genome. When a person is injected with the vaccine, the body responds and develops a high concentration of serum immunoglobulin

G antibody against those specific HPV types. Those antibodies are released in the cervico-vaginal secretion, and are also released when the epithelium acquires micro-abrasions. In this case, the antibodies will fight off any hint of infection before the virus has a chance to penetrate the basal keratinocytes in the vagina and cervix and infect them with HPV (Basu et al., 2013).

CIN usually precedes HPV and can be graded from CIN 1 through CIN 3, with CIN 3 being the most severe. CIN 2 and CIN 3 are dangerous and are believed to be "pre-malignant lesions, as over time CIN 3 has a 30 to 50 percent chance of becoming cancerous." Screening for cancerous cells in the cervix is generally observed during the CIN 2 and CIN 3 stages and with treatment, the cells may be stopped from developing into a cancer. Vaccines can stop CIN 2 and CIN 3 from developing altogether by preventing the infection of the common HPVs which eliminates the chance of cancer growth of those specific strains. The goal of the HPV vaccine is to prevent at least CIN 2 (Basu et al., 2013).

Because the vaccine is made from VLPs, it is considered a dead vaccine, since no live HPV ever enters the body in order to produce antibodies. Cervarix and Gardasil are based on insect and yeast cells, yielding a high cost for the vaccinations compared to those that are based on *Escherichia Coli*. The vaccines are actually from virus-like particles (VLPs) that can be created by expressing the recombinant L1 from mammals, insects, yeast, and bacteria. VLPs are similar to the virions in structure and immunology. Studies have shown that these VLPs can cause high concentrations of serum antibodies (IgG) and can also protect against papillomavirus in the outside body layers. When trials began for the L1 vaccines, it was noted that they caused a 40 times increase in concentration of antibodies in the serum in the average person (Basu et al., 2013).

Vaccine coverage

Both vaccines prevent the two most common HPV strains, HPV 16 and HPV 18. Gardasil is a quadrivalent vaccine, preventing against four different types of HPV – HPV 6, 11, 16, and 18. However, HPV 6 and HPV 11 are low-risk HPV strains which are the main causes of "genital warts and laryngeal papillomas." This creates Gardasil's ability to prevent cervical cancer and genital warts. Gardasil is prepared using VLPs from recombinant yeast (Basu et al., 2013).

Cervarix is bivalent, meaning it can only inhibit two types of HPV, which are the most potent types, HPV 16 and HPV 18. The vaccinated population remain at risk of developing cervical cancer that is caused by other strains of HPV, yet the chances of this happening are much lower. Nevertheless, recent studies show that Cervarix also protects against HPV 31 and HPV 45 because of its close genotype, making Cervarix's protection rate of all HPVs close to 80 percent (Basu et al., 2013). It has also been proven that these vaccinations "inhibit HPV-associated neoplasia in the vagina,

vulvar, anus, in addition to HPV 16 detection in oral rinses” (Wang & Roden, 2013). Cervarix is also different from Gardasil in that it is made from insect cells, allowing those with yeast allergies to be vaccinated.

Another important difference between the two vaccines is the adjuvant used. Because synthetic antigens and pure recombinant do not yield sufficient antigens in the body to build a strong response of antibodies, a new idea of adjuvants, something added to a vaccine to promote the antibodies’ response to the antigen, began to spread in the immunological world. Merck uses an alum-based adjuvant for Gardasil. Alum-based adjuvant is actually the most accepted adjuvant worldwide because of its effective Th2 response and its side effects – local and systemic effects like myofascitis and eosinophilia are atypical and infrequent (Petrovsky & Aguilar, 2004). Vaccines also have an adjuvant to help expose the antigen to the body for long periods of time so that the body can build a complete adaptive response for future use. The adjuvant used for Cervarix is ASO4, but not much is known its effects (Monie et al., 2008).

Who should be vaccinated

Cervarix and Gardasil are the first vaccine pair in history that focus on the same objective the same way just made by different companies. However, they are not interchangeable. Besides that Gardasil is a quadrivalent vaccine and prevents more than cervical cancer, it can also be used on the male population, while Cervarix cannot.

Gardasil is approved for males and females ages nine through twenty-six. However, the recommended age of HPV vaccination is ages 10-25. Based on studies performed on various ages, the pre-teens (10-15 years old) contained a higher “anti-HPV neutralizing antibodies response” than the group of 16- to 23-year-old females. Also, for maximum vaccine effect, it should be administered before the person engages in sexual activity (Basu et al., 2013). Pregnant women should not be vaccinated (Gardasil.com, 2013; Cervarix.com, 2013). It is recommended that boys also receive the vaccine during their teenage years. The vaccine seems to be less effective for boys than for girls. The fact that boys may depend on the girls being vaccinated also downplays the urgency of all boys getting vaccinated. Gardasil recommends boys and men to be vaccinated from ages nine through twenty-six to prevent anal cancer caused by HPV 16 and 18, genital warts caused by HPV 6 and 11, and anal intraepithelial grades 1, 2, and 3. Cervarix has not yet been approved in the US for males as more studies are needed to decide whether it is potent.

Administration

Gardasil is an intramuscular injection; is administered three times in either the deltoid muscle or the upper thigh region. The second dose is given two months after the first, and the third dose is administered four months later. Clinical studies have shown that three doses administered within one year create maximum efficacy for the patient (Gardasil.com, 2013).

Cervarix’s instruction label has similar directives as Gardasil’s. Cervarix is for females ranging from ages 9-25, and it is an

Table 1: Characteristics of the HPV vaccines Gardasil and Cervarix

Characteristic	Gardasil	Cervarix
Manufacturer	Merck Frosst Canada Ltd.	GlaxoSmithKline Inc.
Type	Prophylactic vaccine consisting of virus-like particles containing L1 capsid proteins	Prophylactic vaccine consisting of virus-like particles containing L1 capsid proteins
Antigens	Quadrivalent vaccine: HPV types 6 (20 µg/dose), 11 (40 µg/dose), 16 (40 µg/dose) and 18 (20 µg/dose)	Bivalent vaccine: HPV types 16 (20 µg/dose) and 18 (20 µg/dose)
Antigen expression system	Yeast	Baculovirus
Adjuvant	Alum: 225 µg aluminum hydroxyphosphate sulfate	ASO4: 500 µg aluminum hydroxide and 50 µg 3-deacylated monophosphoryl lipid A
Dose and schedule	0.5 mL intramuscular injection at 0, 2 and 6 months	0.5 mL intramuscular injection at 0, 1 and 6 months
Availability in Canada	Approved for sale	Not yet available

Table 1-

The similarities and differences of the two available vaccines for HPV prevention: Some countries only have one vaccine available, like Canada, and others have both vaccines available, like the United States. (Source: Dawar et al., 2007)

intramuscular injection –preferably in the deltoid – that should be administered three times: the second a month after the first injection and the third six months after the original injection. The common side effects are swelling and redness in the area of where the vaccine was administered, headaches, fatigue, syncope, myalgia, and gastrointestinal symptoms. Because of the dangers of syncope, as with a Gardasil injection, it is necessary for all patients to wait fifteen minutes in the medical office before leaving for observation (Cervarix.com 2013).

One major concern about Cervarix and Gardasil is their limitations in preventing cervical cancer. They do not guarantee a 100% success rate against cervical cancer, as Cervarix only fully protects against two strains of HPV and partially cross-protects against another two. HPV 33, HPV 52 and HPV 58 are other highly potent strains that are not protected and may cause cervical cancer. Therefore, a broader vaccine is still needed to protect fully against around 90 percent of all cancer-causing strains. Some researchers believe that the future plans of cervical cancer vaccines should implement L2 as the antigen to use to cultivate a broad spectrum of antibodies (Basu et al., 2013).

Another major concern which Basu, Banerjee, Singh et al., raise is the unknown knowledge of how long the vaccine is viable and active. Because these vaccines are new, studies regarding their efficacy are not abundant. Perhaps a booster is needed after a few years. Banerjee and his fellow researchers state in their report that studies show that immunity seems to last for about 5.5 years. However, that is not long enough, as pediatricians believe that pre-teens are the ideal age for the vaccines and as aforementioned, the manufacturers' recommended age for receiving these vaccines is between ages 10-25. Therefore, if a child is 11 when she receives the vaccine, she will be 16.5 when the vaccine loses its effect, while she is still a growing and developing teenager. In addition, not enough years have passed to fully observe the long-term effect this vaccine has on people.

Basu says that around the age of thirty people begin to develop their own antibodies against the virus. However, there is a 12.5-year gap between the time when the vaccine diminished and when an individual became naturally immune to it. On the other hand, more research is needed on the exact length of protection against HPV in order to conclude whether a longer length of vaccine protection is needed, a booster should be administered, or the current vaccines Cervarix and Gardasil are sufficient (Basu et al., 2013).

Prevention, not treatment

The vaccine does not mitigate or affect pre-existing HPV in any way. The basal epithelial cells and cervical cancer cells do not seem to exhibit a considerable amount of their capsid antigen, L1 or L2. If a vaccine targets the L1 or L2, these cells would remain

untouched. The true need is to rid all HPV from the world; however, there are too many people who are already infected and are infecting those who are unprotected. (Basu et al., 2013). Therefore, it is crucial to remember that for an individual already infected by HPV, the best course of action is to consider treatment with medications, as the vaccine would be ineffective at this point. New research is being done to perhaps target the E6 and E7 proteins to help those who are already infected and therefore cannot use the vaccine as a solution. In the meantime, infected patients should resort to chemotherapy, radiation, surgery, and antibody therapy as possible treatments (Han & Sin, 2013).

Side effects of Gardasil

According to Gardasil's website, the vaccine has a few minor side effects: redness or swelling around the injection site, headaches, dizziness, nausea, fainting and fever. In 2009, due to an increase of fainting and syncope, the FDA took initiative and ordered the manufacturer of Gardasil, Merck, to add on to the instruction label that it is mandatory for every patient to sit in the office for 15 minutes upon injection. The FDA says that by having the patient lie or sit in one position for fifteen minutes, the medical supervisor can monitor for the initial symptoms that generally develop into syncope, such as paleness, dizziness, sweating, changes in vision and ringing in the ears (Sullivan, 2009). According to Gardasil, the most common side effect is headaches. However, Sullivan states that syncope following injection should not be taken lightly, as about 40 percent of syncope cases as a side effect develop into a tonic-clonic seizure-like activity which necessitates hospitalization. If a syncope or seizure-like activity occurs, the health professional should have the patient lie down to allow blood to continue circulating throughout the body. (Merck points out that fainting is not a side effect only to Gardasil, as it is also common after donating blood, receiving other injections, and is a typical response to pain.) (Sullivan, 2009)

From January 2005 until July 2007, 70 cases of syncope resulting from a Gardasil injection were reported. According to Sullivan in her Pediatricnews.com article, about five percent of the cases were considered serious, 38 cases occurred on the vaccination day, and 37 cases required hospitalization. As of May 2009, out of 24 million vaccinations, 13,758 VAERS reports were filed. 93 percent of those reports were considered not serious, including symptoms such as fainting, swelling, fever, headaches, and nausea. However, seven percent of those events were considered serious (Sullivan, 2009).

Immune response difference

Throughout studies, it has become evident that Cervarix produces a larger antibody response than Gardasil. In one study performed by GSK testing the two vaccines, "geometric mean titers of serum neutralizing antibodies ranged from 2.3- to 4.8-fold higher for HPV-16 and 6.8- to 9.1-fold higher for HPV-18 after vaccination

with Cervarix, compared with Gardasil, across all ages” (Einstein et al., 2009). One major possibility which researchers focus on is the ASO4 adjuvant, as both vaccines use VLPs. Although it is unknown for how long each vaccine is viable, one study claims Cervarix lasts up to 6.4 years. However, both manufacturers believe that they will know when the vaccine becomes irrelevant before the people who were already vaccinated will lose their protection.

How do most healthcare professionals decide which of the two to give? It will usually depend on the cost. However, patients should be notified of the benefits and differences of the two vaccines because they are not interchangeable in their protection (Pichichero, 2009).

HPV infections cannot be treated; only their lesions may undergo treatment. Treatment options for the precursors of genital wart, vaginal and vulvar lesions have different options of removing the lesion and therapy.

Methods

The information in this research paper was obtained from many journals, studies and research papers from the national website of Pubmed and Touro College's Online Library and Database. This paper's purpose is to educate the reader about what HPV is, how it develops into a cancer, why a vaccine is necessary, and how the vaccine is assembled. In addition, this paper will point out the different treatments for HPV, cancer, and genital warts and how a vaccine will make an imprint on the world. Using the manufacturers' (Merck's and GSK's) websites the reader will develop a vast knowledge of every aspect of the vaccines, ranging from what they cover to who should be vaccinated. Also, studies conducted on the vaccines will be examined to find any inaccuracy that exists which might lead those who are not knowledgeable in this area to be misinformed, and to help the reader develop his/her own opinion on the matter. Lastly, the effects of the vaccine on the world will be analyzed to see what the future has in store for its future of HPV and all that it may cause.

Discussion

A study was done in 2003 by the Future II study group of the New England Journal of Medicine on a newly developed quadrivalent vaccine, which eventually became Gardasil, on the recommendations of the World Health Organization (WHO) and the FDA. The goal of the study was to determine the efficiency of the vaccine against HPV 6, 11, 16, and 18 and lesions. The study consisted of 12,167 non-pregnant women from 131 different countries who had normal Papanicolaou smear results and had not had more than four partners in their lifetimes. After the subjects were vaccinated, they were evaluated by gynecologists for the average of the three years for which they were observed. At the conclusion of the study, it appeared that the vaccine is 98% effective in the

population that was never exposed to HPV 16 and 18. However, the vaccine was only 44% effective in the pre-exposed population to HPV and cervical lesions. In other words, 42 subjects of this study were infected within the first three years. Once again, the idea that researchers do not know what to expect past the years of research is alarming. Also, the pharmaceutical company Merck, which is currently the supplier of Gardasil, sponsored this study. There might be a risk of bias because of the financial backer (Future II Study Group, 2007).

Prophylactic vaccines that fight against HPV 16 and 18 have a high success rate against CIN 2 and 3 and some external genital lesions. However, because much is needed to persuade the population of the success of the vaccine to prevent CIN, a study was done to create a baseline before the creation and availability of HPV vaccines to the world.

The subjects of this study were from population-based registries from Denmark, Iceland, Norway and Sweden who were “diagnosed with incident cervical vulvar and vaginal cancer and pre-invasive neoplasia from January 1, 2004 until December 31, 2006, with only the primary tumors allowed to be included yielding to over 100,000 subjects in the number.” According to the data collected in all countries, the age range of 20 through 29 years old experienced an immense increase of cases and a peak in the thirties age range for cervical cancer, yielding about 10 percent of the cases. However, cervical pre-invasive neoplasia was most commonly found in people in their twenties in all four countries. Nevertheless, vulvar and vaginal cancer peak past the age of 40 and peak in women over 70. These researchers were able to mathematically predict the impact of vaccination by including the fact that only 30% of CIN3 would develop into cancer if not treated. Besides the fact that overtreatment of CIN3 is costly, it is dangerous for those in their reproductive years, as it increases the risk of preterm births. Therefore, it is in the best interests of all involved to prevent neoplasia in women. The researchers state that if the vaccine is really close to 100% efficacy, based on literature review, the cases of pre-invasive neoplasia should decrease by 52 to 67 percent, totaling about 2,471 to 2,911 fewer cases of diagnosed and treated cervical cancer in these four countries (Nygard et al., 2014).

Another study was done in England on the effects of Cervarix and its ASO4 adjuvant. The study was a PATRICIA (Papilloma Trial against Cancer in Young Adults) trial which was “phase III, double-blind, randomized and using the Hepatitis A vaccine as a control.” The study did not exclude anyone based on previous or current history of genital warts. The subjects had a cervical sampling done every six months for HPV DNA typing and tested for 14 cancerous HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) and another 11 non-cancerous HPV genotypes. In addition, all women were examined every twelve

months and had a colposcopy if necessary. In total, 18,644 women received at least one dose and were included in this study from May 2004 until November 2009. The average monitoring time was 43.7-47.4 months. The results of this study are quite interesting: although the bivalent vaccine only officially covers HPV 16 and 18, a cross-protection was found that prevents HPV 6, 11, 31 and 45. The reason for cross-protection may be from the similarities in structure and homology within the L1 VLP. However, when comparing the response from the L1-specific T helper cell that are caused by HPV 6 and 11 in the bivalent and the quadrivalent vaccines, the numbers of cells were analogous to each other. The study also proves that there was a greater helper T cells response for HPV 31 and 45 in the bivalent vaccine. The reason for cross protection may be from the similarities in structure and homology within the L1 VLP. The study concluded that the risks of persistent effects decreased with the use of vaccines (Szarewski et al., 2013).

England was the first country to try a national immunization program involving Cervarix. As a result, researchers were able to study the records from the general practices and the genitourinary medicine clinics of the general public to observe the trends of genital warts. Although it has been proven that Gardasil prevents HPV 6 and 11, the main causes for genital warts, Cervarix seems to cross-protect them, which also results in a prevention of genital warts. This was proven when the study conducted in England noticed the large decrease in genital warts in the immunized female teenage population. The teenage male population also had a decreasing rate in reports of genital warts, but it was not as significant as the female's population. However, there are many reasons that may have contributed to the decline; one big factor is that the population became more aware of the dangers of HPV and genital warts and therefore realized the need to protect themselves by abstaining from unsafe intercourse. More studies like this one are needed in order to conclusively state that it is the vaccine lowering the cases of genital warts in England (Howell-Jones et al., 2013).

Beginning in 2006, the National Immunization Survey-Teen in the United States conducted a study by calling random landlines and cellular phones for its sample. In total, 14,133 adolescents (with their guardians' consent) submitted their vaccination history. The results showed that the number of adolescents receiving the vaccine for each dosage increased each year until the number stagnated in 2012. However, in 2012, questionnaires began to ask why people opted not to vaccinate their daughters. The most common answers were that the vaccine is not needed, the vaccine is not recommended, there are questions about the safety of the vaccine, there is a lack of knowledge about the vaccine or disease, and that their daughter is not sexually active (Centers for Disease Control and Prevention [CDC], 2013).

According to the CDC, about 56 million dosages of Gardasil were administered from June 2006 through March 2013, and from October 2009 through May 2013, about 611,000 dosages of Cervarix were administered in the United States. Analysis of vaccine safety by the CDC is limited to Gardasil because it covers 99% of the vaccinated population. Of the 54 million vaccines administered, 21,194 unusual cases were reported in females, and 92.1% of those cases were considered non-serious. The main bulk of these reports were from 2008. Yet, the remaining 7.9% of those cases were considered serious, with the highest total from 2009. However, these symptoms that occurred after patients received the dose are usual symptoms that may occur for most vaccines (CDC, 2013).

The ACIP conducted its own trials and safety studies on Cervarix. Each Cervarix vaccine administration was observed for any symptoms upon injection, like development of a new autoimmune disease or chronic diseases, injection-site reaction, systemic symptoms, and death. Of the 23,713 females studied in the study, 92% complained of injection-site swelling, 48% had redness, and 44% had swelling. Other common side-effects were myalgia, fatigue and headaches. Only about 5.3% complained of serious results; however, 5.9% in the control group also complained of serious results (CDC, 2010).

Gardasil also performed its own studies on a variable population with all different types of ethnicities, ages, gender, and previous history. In total, 28,413 people participated in this study, the majority of whom were women. In the 16-26 age range for females, the efficacy, which was marked by almost one hundred development of CIN, VAIN, AIS, VIN, and genital warts, was close to 100 percent in all categories, with the lowest rate at 96.9%. The rate in older women was not as high as the younger population, where the

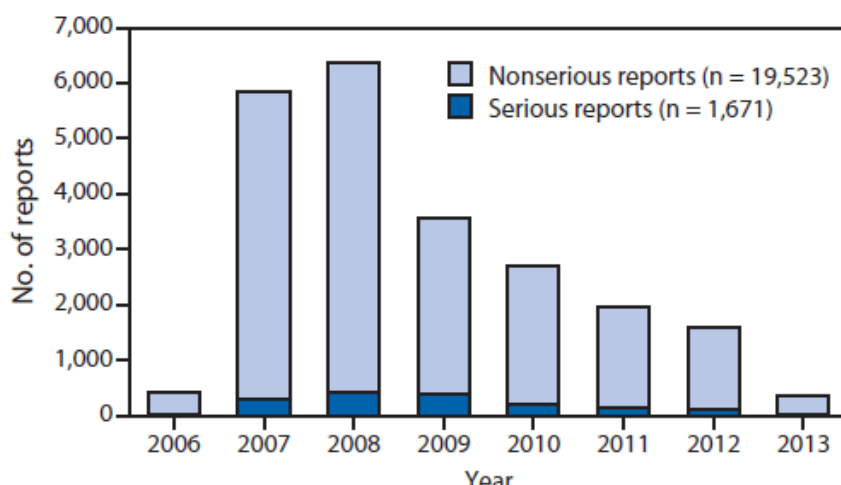


Figure 2: The number of serious and non-serious reports of side effects of Gardasil by year from June 2006-March 2013 (CDC, 2013).

efficacy rate was approximately 85%. Men ranging from 16-26 had about a 90% efficacy rate. However, the numbers dipped, even at some points close to 60% efficacy, in the prior or currently HPV-infected population. The immunological tests showed good results for geometric mean titers and a high percentage of antibodies that are anti-HPV 6, 11, 16 and 18 in all subjects. During clinical trials, safety was a major area of observation; very few abnormal cases and mainly all typical vaccine reactions, like headache, pyrexia, diarrhea, nausea, and vomiting were noted. In addition, 258 out of 29,323 subjects complained of serious reactions like headache, appendicitis, gastroenteritis, urinary tract infection, and pneumonia. Forty people were healthy and died from motor vehicle accidents, overdose, cancer, gunshot wounds and pulmonary embolus. Those people reflect the all deaths notified in their report so no person actually died from the vaccine directly.

Many more studies like the ones mentioned above have been conducted and analyzed. The common thread among all of them is that the vaccine causes an increase titer of antibodies in close to 100% of the subjects, subjects' side effects include the regular side effects common to all vaccines with the additional of chance of syncope, and only less than 10 percent may have had serious implications afterwards, but nobody ever came close to death because of vaccination (Gardasil.com, 2013).

Based on all of these studies, the vaccine seems to enable the production of antibodies against HPV in all those vaccinated to prevent future cancer. The side effects seem reasonable in comparison to all other vaccines. No serious ailments are connected to the vaccine directly and the vaccine is deemed to be safe. The biggest concern that still remains is how long the vaccine's immunity will last. Since Gardasil has only been distributed to the population for eight years and has been studied for a bit over a decade, not much is known as to the long-term effects, both positive and negative. Cervarix is even less studied because its worldwide distribution began only five years ago. Questions do remain on the preference of the two vaccines: Cervarix leads to more than double the number of antibodies, whereas Gardasil prevents more genotypes and genital warts. As mentioned before, it should be the patient's choice as to which vaccine should be administered to him/her. Realistically, the fact that 54 million people had received Gardasil while only 600,000 had received Cervarix through 2013 sheds light on the fact that doctors only have one vaccine in the office. This might be because of costs or health insurance coverage. Nevertheless, patients should be advised about both vaccines and should have the right to ask for whichever one they think is properly suited for them.

Conclusion

In 2006, a new era of science began with the development of a cancer vaccine – the HPV vaccine. If an individual has persistent HPV infections, he/she has a chance of that HPV virus growing into an abnormal growing stage which will eventually become cancerous. The newly discovered vaccine has been proven to prevent any further growth of lesions from the HPV virus and to prevent these lesions from becoming cancerous. The vaccine also gives the vaccinated community anti-HPV antibodies. Gardasil is a quadrivalent vaccine and protects against HPV 6, 11, 16, 18 and genital warts. Cervarix is a bivalent vaccine that only protects against HPV 16 and 18. HPV 16 and 18 are the most significant strains as it causes about 70% of all HPV cases. Furthermore, each vaccine also cross-protects against other HPV genotypes. Both vaccines have an unusual and yet close to 100% efficacy rate and the side-effect for each vaccine are minimal. Very few cases of serious side-effects have been reported, which none of them led near death or death situation. The vaccine is catered for the 10- to 25-year-old age range and best results occur when given to individuals who are not yet active or pre-exposed, because the vaccine does not cure HPV infections whatsoever. Although most people think HPV is not “catchy,” it is in fact highly contagious and is similar to influenza and chicken pox in that it spreads through direct contact. HPV can spread from person to person in people ten years and older, with the help of the fact not everybody knows they have it. Therefore, HPV is a serious matter and the number of cases must lessen. If fewer individuals are infected, there will be fewer cancers in the world. Similarly, just like the polio vaccine fewer to less outbreaks of polio, hopefully one day fewer people will contract anal, vaginal, penile and cervical cancer because of the influence of the HPV vaccine. It is important for the public to be educated about the harms of HPV, the cancers HPV cause, and the benefits and risks of preventive HPV vaccines, Gardasil and Cervarix, in order to make the world a healthier place.

References

- Basu P, Banerjee D, Singh P, Chatterjee C, Biswas J. 2013. Efficacy and safety of human papillomavirus vaccine for primary prevention of cervical cancer—a review of evidences from phase III trials and national programs. *South Asian J Cancer* 2:187–92.
- Centers for Disease Control and Prevention. 2010. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). *MMWR* 59(20):626.
- Centers for Disease Control and Prevention. 2013. Human papillomavirus vaccination coverage among adolescent girls, 2007–2012, and postlicensure vaccine safety monitoring, 2006–2013—United States. *MMWR*. 62(29): 591.
- Cervarix [Package Insert] GlaxoSmithKline. NC. 2013.
- Dawar M, Deeks S, Dobson S. 2007. Human papillomavirus vaccines launch a new era in cervical cancer prevention. *CMAJ*. 177:456–461.
- de Noronha AF, de Figueiredo EM, Franco TM, Cândido EB, Silva-Filho AL. 2013. Treatments for invasive carcinoma of the cervix: what are their impacts on the pelvic floor functions? *Int Braz J Urol*;39:46–54.
- Einstein MH, Baron M, Levin MJ, et al. 2009. Comparison of the immunogenicity and safety of Cervarix™ and Gardasil® human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18–45 years. *Human Vaccines* 5:705 - 719
- Future II Study Group. 2007. Quadrivalent Vaccine against Human Papillomavirus to Prevent High-Grade Cervical Lesions. *NEJM* 356(19):1915–1927.
- Gardasil [Package Insert]. Merck and Co., PA. 2013.
- Howell-Jones R, Soldan K, Wetten S, et al. 2013. Decline in genital warts in young women in England associated with HPV 16/18 vaccination: an ecological study. *J Infect Dis* In press.
- Markowitz, LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger, ER. 2007. Quadrivalent Human Papillomavirus Vaccine Recommendations of the Advisory Committee on Immunization Practices. *ACIP*. 56(RR02);1–24.
- Monie A, Hung CF, Roden R, Wu TC. 2008. Cervarix: a vaccine for the prevention of HPV 16, 18-associated cervical cancer. *Biologics*. 2:97–105.
- Nygård M, Hansen, BT, Dillner J, et al. 2014. Targeting Human Papillomavirus to Reduce the Burden of Cervical, Vulvar and Vaginal Cancer and Pre-Invasive Neoplasia: Establishing the Baseline for Surveillance. *PLoS one*. 9(2): e88323.
- Petrovsky N, & Aguilar JC. 2004. Vaccine adjuvants: current state and future trends. *Immunology and cell biology* 82(5):488–496.
- Pichichero ME. 2009. Gardasil, Cervarix: Not Interchangeable. *Pediatric News* 43(12): 10–10.
- Sullivan MG. 2009. FDA Strengthens Syncope Warning for Gardasil. *Internal Medicine News*. 2009; 42(13): 23–23
- Szarewski A, Skinner SR, Garland et al. 2013. Efficacy of the HPV-16/18 AS04-Adjuvanted Vaccine Against Low-Risk HPV Types (PATRICIA Randomized Trial): An Unexpected Observation. *Journal of Infectious Diseases*. 208(9)1391–1396
- Tachezy R, Smahelova J, Kaspírkova J, Salakova M. 2013. Human papillomavirus type-specific prevalence in the cervical cancer screening population of Czech women. *PLoS One* 8(11):e79156. 10.1371/journal.pone.0079156
- Vici P, Mariani L, Pizzuti L, et al. 2014. Emerging Biological Treatments for Uterine Cervical Carcinoma. *J Cancer*. 5(2):86–97.
- Vidyasagar P, Sridevi VN, Rajan S, et al. 2014. Generation and characterization of neutralizing monoclonal antibodies against baculo-expressed HPV 16 VLPs. *European Journal of Microbiology and Immunology* 4(1), 56–64
- Wang, JW, & Roden, RB. 2013. Virus-like particles for the prevention of human papillomavirus-associated malignancies. *Expert review of vaccines* 12(2):129–141.