Vaccines in Current Culture: The HPV Vaccine Controversy

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A Senior Thesis submitted in partial fulfillment
of the requirements for graduation
in the Honors Program
Liberty University
Spring 2020

Acceptance of Senior Honors Thesis

This Senior Honors Thesis is accepted in partial
fulfillment of the requirements for graduation from the
Honors Program of Liberty University.

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Abstract

The use of vaccinations has drastically decreased mortality and morbidity rates related to infectious disease and has become an intrinsic part of modern health care. However, the fear of risks related to vaccines has been partially responsible for the decisions of many parents to delay or avoid vaccinating their children. The human papilloma virus (HPV) vaccine specifically is one of the most controversial vaccines in current culture due to reports of new onset or exacerbation of autoimmune diseases, infertility, and even death following its administration. This review synthesizes information regarding the relevance and safety of the HPV vaccine, as well as its efficacy in preventing cervical cancer and precancerous lesions. There appears to be a need for thorough education regarding concepts of immunity, infection, and vaccine function for those hesitant about receiving vaccines. Particularly regarding the HPV vaccine, practitioners should be familiar with common reasons for vaccine refusal and be prepared to respond with accurate information.

Keywords: HPV vaccine, safety, controversial

Introduction

Vaccines have been an intrinsic part of the public health system since the 1800s, and their routine use has saved countless lives, nearly eradicating many deadly endemic diseases (Davidson, 2019). However, vaccination rates have seen recent decline and this noncompliance has led to multiple outbreaks of vaccine-preventable diseases. The movement against vaccination promoted by media prominent influencers and the media has fostered a general mistrust of the medical community as a whole (Attwell et al., 2019). Perhaps one of the most controversial vaccines currently is Gardasil-9, the HPV vaccine. The aim of this review is to synthesize current research regarding whether the risks of the HPV vaccine outweigh its efficacy in the health promotion of adolescents and young adults.

Vaccines

Introduction to Vaccines

Vaccines are prepared biological substances that are introduced into the body in order to protect individuals from certain diseases (Davidson, 2019). The goal of vaccine administration is to prompt an immune response in the body that creates antibodies for a specific pathogen (Feemster, 2018). According to the World Health Organization (WHO), vaccines are second only to clean water in the effect they have had on the reduction of illness and death and on the growth of the general population. Just by vaccinating against diphtheria, tetanus, whooping cough and measles, two to three million deaths are prevented annually, worldwide. Smallpox, the disease that killed approximately half a billion people, has been completely eradicated because of the use of the smallpox vaccine (Davidson, 2019).

Immunity and Infection

In order to understand how vaccines work, it is important to have an understanding of the immune system and the process of fighting infection. Immunity is the mechanism by which the body defends itself against infection by a virus, bacteria or other pathogen. There are two main aspects to immunity: innate and adaptive.

Innate immunity. Innate immunity is the body's first line of defense and responds to foreign substances immediately, distinguishing invading pathogens through the recognition of foreign cellular patterns (Moriber, 2014). The innate immune system is present from birth and does not require any external stimulation to aid in its development. Innate immunity is nonspecific, meaning the innate immune response is the same no matter what type of pathogen is invading the body. This is also true when infection with a pathogen happens multiple times, the innate immune response has no memory cells and so the response does not change or grow stronger. While innate immunity does respond to foreign pathogens immediately, the maximal response is usually reached within minutes to hours of when the pathogen is detected (Davidson, 2019).

Adaptive immunity. Adaptive immunity develops over time and is dependent upon exposure to a specific pathogen. The first time the body is exposed to a specific pathogen, the adaptive response is delayed for a few weeks while antibodies are produced, and the infected person will display signs of illness. The second time the body is exposed to a pathogen, the adaptive response is immediate, and the pathogen is destroyed fast enough that the person does not experience signs of illness (Moriber, 2014). Every pathogen has cell-specific protein molecules on its surface known as antigens. When the body is exposed to a new antigen, specialized immune cells known as B lymphocytes produce Y-shaped proteins called antibodies.

The antibodies seek out and bind to the antigen, deactivating the invading pathogen and stopping the effects of the disease (Davidson, 2019). Once the body produces antibodies for an antigen, the memory of the antigen is stored by the T lymphocytes, creating immunity to the pathogen. T lymphocytes can be further broken up into helper and killer T cells. When a pathogen enters the body for a second time, helper T cells notify the killer T cells and the pathogen is eradicated. Innate and adaptive immunity cells communicate via cell-to-cell contact, and also by chemical mediators. These chemical mediators are called cytokines, chemokines and CSFs. Cytokines are the primary means of interaction and allow innate immune cells to communicate important information about an invading pathogen to adaptive immune cells. The coordination of innate and adaptive immunity is essential in order to produce a successful immune response (Moriber, 2014).

Herd immunity. Herd immunity occurs when many people in a specific area have been vaccinated against a disease, or have immunity to a disease from exposure, and unvaccinated people in the same area are also protected from that disease (Davidson, 2019). Vaccinated individuals cannot be infected by diseases they have been vaccinated against, and they cannot spread infection to others. Therefore, unvaccinated individuals who are part of a larger, vaccinated community are protected from certain diseases as there is no one to spread it to them (Feemster, 2018). This concept of herd immunity requires a higher ratio of vaccinated individuals to unvaccinated individuals depending on the contagiousness of the disease. For example, one person infected with either measles or whooping cough can infect 12-18 other unvaccinated individuals. This means that 94% of the population would need to be vaccinated to stop either of these diseases from spreading (Davidson, 2019). When immunization rates are low, there is a greater risk of infection. If infection occurs, it develops into an outbreak, spreading to

all of the susceptible individuals in the community. The fewer people immunized, the more the outbreak spreads as there is less protection from herd immunity. An outbreak ends when enough people become immune to the disease, either through immunization or exposure (Feemster, 2018).

Infection. During the immune system's primary response to a new pathogen, the affected individual will experience signs of infection. Infectious disease can be marked by five stages: incubation, prodrome, acute, convalescence, and resolution. Incubation occurs when the invading pathogen begins active replication in the body, but no symptoms of illness have been displayed. The prodromal stage involves the appearance of symptoms, which may include fever, fatigue, headache, and myalgia. In the acute stage the body begins fighting the pathogen, and the host experiences the full impact of the process of infection (Grossman, 2014). The innate immune response to an infection involves inflammation, which leads to tissue damage and eventually the destruction of the pathogen. When a pathogen first enters the body, chemokines alert leukocytes to the pathogen's presence. The leukocytes begin carrying out a process called margination, adhesion and transmigration, which involves accumulating and binding to adhesion molecules within the vessel walls. When the leukocytes adhere to these molecules, the endothelial cells become separated and the leukocytes are able to migrate from the vessels into the body tissue. The chemokines lead the leukocytes to the site of infection, followed by macrophages, monocytes and neutrophils. These cells complete a process called phagocytosis, where the invading pathogen is engulfed, destroyed and excreted by enzymes. Histamine, cytokines and plasma proteins are chemical mediators that produce signs of inflammation in the body such as heat, swelling, and redness (Grossman, 2014).

How Vaccines Work

The purpose of a vaccine is to prompt an immune response by the host against a specific pathogen, thereby protecting the host from future infection by that pathogen. When an individual comes into contact with a pathogen they have been vaccinated against, adaptive immunity will take over and the disease will be wiped out before the individual becomes symptomatic (Feemster, 2018). Vaccines must achieve a balance between being weak enough not to cause the disease symptoms they are protecting against, and being strong enough to stimulate the development of antibodies by B cells and memory by T cells. The immunity an individual acquires through vaccination is called artificially acquired immunity. This is slightly different than naturally acquired immunity, which would occur by having the disease and recovering, but it eliminates the symptoms and risks that come with the disease (Davidson, 2019). In order for a vaccine to be effective, antibody production must be stimulated, and antibodies need to be attracted to a specific pathogen. Antibodies themselves cannot simply be injected into an individual to protect against a disease, as they do not work unless they bind to the antigen of a specific pathogen. In order to achieve an adequate balance between disease and immunity, vaccines do not contain the same number of antigens that an invading pathogen does. The part of the pathogen that causes disease and the part that induces antibody response are separated during the development of the vaccine, allowing stimulation of the immune system, without endangering the health of the individual being vaccinated (Feemster, 2018).

History of Vaccines

The knowledge that survivors of infection from a certain disease become less prone to recurring infection with the same disease goes back to ancient Greece, and inoculation against smallpox has been reported in China and India from the 1500s to as early as 200 BC (The

College of Physicians of Philadelphia, 2019). Inoculation is the process of infecting an individual with a pathogen for the purpose of building immunity, while vaccination involves injecting a weakened or attenuated pathogen for the purpose of building immunity against the stronger pathogen. The first vaccination was not introduced in the United States until the 18th century. In 1796 an English doctor named Edward Jenner discovered milkmaids he was treating for cowpox were not becoming infected with smallpox, the more prevalent disease at that time. Cowpox is a similar viral disease to smallpox, but less common and less severe. Jenner then conducted several experiments, including inoculating farmers exposed to cowpox with smallpox. The farmers did not develop smallpox, so Jenner then inoculated a young boy with cowpox, followed by smallpox a few weeks later. The boy did not develop symptoms of smallpox, and Jenner had proven cowpox provides immunity against smallpox. Five years later, over 100,000 people across Europe had received the first smallpox vaccine.

Vaccine acceptance was slower in America, as cows in the United States were not affected by cowpox and the virus was more difficult to access. This led to the development of fraudulent vaccines on the black market, causing harm to those injected and nearly bringing an end to the vaccination movement in America. However, Thomas Jefferson established the widespread importation of cowpox fluid from Europe and collaborated with doctors in several studies to prove smallpox vaccinations were effective. By the early to mid 20th century vaccines were being developed to prevent tuberculosis, yellow fever, typhus, pertussis, influenza, measles, mumps and polio (Feemster, 2018).

Vaccine Development

During the 20th century when many of the aforementioned diseases were prevalent, vaccines were developed based on how quickly they could reduce the incidence of a disease.

Current vaccine development is now largely based on benefit versus risk (Feemster, 2018). The other factors considered when developing a vaccine include the type of pathogen, the potential adverse effects caused by the vaccination, the number of doses needed, the speed of pathogen mutation, and the population needing vaccination. It is also important to consider the ease of large-scale production, shelf life, storing and transportation conditions, and route of administration. A vaccine can be live attenuated, inactivated/killed, subunit, conjugate, polyvalent, or combination (Davidson, 2019).

Live attenuated vaccines contain live pathogens that have been weakened so they do not cause the disease but do cause the production of antibodies. Inactivated vaccines render a virus unable to reproduce, but still cause an immune response. Killed vaccines are the equivalent of inactivated vaccines for bacterial diseases. The immune response is weaker with inactivated/killed vaccines and so requires multiple doses to achieve immunity (Davidson, 2019). Subunit vaccines use inactivated proteins from bacteria to induce an immune response. Similarly, recombinant vaccines use inactivated viral proteins. In recombinant vaccines, the gene that makes the protein is inserted into the DNA of a yeast cell. The yeast reproduces, as does the DNA, creating a protein which is purified and made into a vaccine. Human papilloma virus vaccines are created using this technique (Feemster, 2018). Polyvalent vaccines protect against multiple strains of a disease, HPV vaccines are also polyvalent (Davidson, 2019). Conjugate and polysaccharide vaccines are similar to subunit vaccines in that they use a sugar or polysaccharide found on the capsule of specific bacteria to illicit an immune response, rather than a form of the pathogen itself (Feemster, 2018).

Objections to vaccination.

Trends of the anti-vaccine movement tend to rise or fall in relation to outbreaks of vaccine-preventable diseases becoming less or more common. Most of the concerns related to vaccines today include skepticism about their efficacy and safety, religious objections and concern that mandatory vaccinations violate personal liberty. There has been resistance and skepticism related to inoculation and vaccination since their inception. Real vaccine resistance began to occur when the Vaccine Act of 1853 came into effect in England and Wales, making vaccination mandatory for infants in these countries. The act was not received well and sparked the formation of the first anti-vaccination movement, the British Anti-Vaccination League. In response to the pressure and large following of the Anti-Vaccination League, British Parliament issued the Vaccine Act of 1898. This act authorized conscientious objection to vaccination. At the start of the Boer War in 1899, vaccination of soldiers against typhoid was made voluntary for similar reasons. Because of this only 5% got the vaccine and 58,000 soldiers developed typhoid. Mandatory military vaccination was reinstated in Britain after World War I (Davidson, 2019). In 1852, certain American states began requiring free public education and compulsory attendance. Because of the level of contagious disease children would be required to be exposed to, proof of smallpox vaccination was required for school attendance. Today, all public schools and most private schools and daycares require proof of certain vaccinations or proof of exemption. Opposition to vaccines grew more slowly in America because there were no national laws, but eventually the Anti-Vaccination Society of America was established in 1879. This was followed by two more leagues in New England and New York. Claims began to spread about vaccines, for example, that an increase in leprosy at the time was caused by the smallpox vaccine (Davidson, 2019).

The start of the modern anti-vaccination movement in America began in the 1980s with the formation of the National Vaccine Information Center (NVIC). This organization was formed after a documentary called *DPT: Vaccine Roulette* was broadcast by WRC-TV. This documentary voiced claims of parents who stated their children had been harmed by receiving the diphtheria, pertussis, and tetanus (DPT) vaccine. Their claims mentioned developmental regression and mental and physical disabilities following DPT vaccination. The station reportedly received over 2,000 calls following the broadcast of parents who believed their children's symptoms were also caused by the DPT vaccine (Davidson, 2019). Vaccine scientists reported the rate of injury from the DPT vaccine could only feasibly be one in 100,000. Perhaps the most well-known claim promoting vaccine resistance was that of Andrew Wakefield in 1998. Wakefield claimed research he and 12 colleagues completed proved the measles, mumps, and rubella (MMR) vaccine was connected to the development of autism. Wakefield's article was published by *The Lancet*, a reputable and peer-reviewed scientific journal. The article spread across Europe, to America, Australia, and Japan and parents began refusing the MMR vaccine for their children. Wakefield's research was later determined to be fraudulent and inaccurate. Ten of his colleagues rejected the article, it was redacted, and Wakefield had his medical license revoked. However, the study and rejection of Wakefield's research could not take back the fact that his theory was circulated worldwide (Davidson, 2019).

Human Papilloma Virus (HPV)

HPV – The Infection

Human papilloma virus is the most common sexually transmitted disease in America, affecting over 79 million individuals in their teens and early 20s. Symptoms of this disease are not always present, and 90% of the time HPV infections go away on their own and become

undetectable after two years. However, when HPV stays in the body it can lead to genital warts and certain cancers. The virus does not spread through blood or body fluids, but through skin-to-skin sexual contact. Human papilloma virus is spread by vaginal, anal, and oral sex and affects the vulva, vagina, cervix, penis, scrotum, mouth, and throat. A person may also be infected with multiple strains of HPV at once, and it has been determined that most sexually active individuals contract HPV at some point in their lives (NYULH, 2019). Since it is spread from skin-to-skin contact, the HPV virus affects the mucosal and cutaneous epithelium and causes benign or cancerous lesions. It is an oncogenic virus that has developed mechanisms allowing it to escape from the host immune defenses, and therefore prolong the length of infection. An individual infected with HPV could be infected for several months before the immune system initiates a response. Because of this characteristic of the disease, immunosuppressed individuals are at increased risk of developing lesions and cancer. However, this delay of the immune response is observed in individuals who are immunocompromised as well as those who are not (Ashrafi & Salman, 2016).

One of the ways HPV avoids detection by the host immune system is its nonlytic property. When HPV infects a cell, it does not break it down. This causes less exposure of the viral antigen to the T cells, and results in a lack of inflammation. Certain strains of the virus contain HPV oncoproteins E5, E6, and E7. These oncoproteins assist in the disruption of the functions of major histocompatibility complex class I (MHC I) and the interferon (IFN) pathway. E6 and E7 disrupt the IFN pathway by inhibiting IFN production in natural killer (NK) cells. This inhibits the NK cells from doing their job in destroying the virus, as the role of IFN is to “flag” certain cells for destruction. E5 is located in the endoplasmic reticulum and Golgi body of HPV infected cells. E5 retains surface MHC I within the Golgi body, disabling it. This allows the

infected cells to evade destruction via cytotoxic T cells and establishes the prolonged length of the HPV infection. The persistence of HPV is what leads to the development of malignant lesions and cancer (Ashrafi & Salman, 2016).

HPV and cancer

There are over 150 types of HPV that infect humans. Forty of those types are linked to cancer and nine of those types are known to cause the majority of HPV-related cancers and genital warts (NYULH, 2019). These are HPV types six, 11, 16, 18, 31, 33, 45, 52 and 58 (MSD, 2019). HPV types six and 11 are identified as low risk and cause 90% of genital warts and mild cervical dysplasia (NYULH, 2019). About 70% of cervical cancers and 50% of high-grade cervical lesions are associated with HPV types 16 and 18 (Niccolai et al., 2017). Along with types 16 and 18, types 31, 33, 45, 52 and 58 are also identified as high risk and are responsible for most HPV-related cancers (MSD, 2019).

Cervical cancer. Cervical cancer is the third most common cancer among women across the world. Approximately 13,000 new cases and 4,100 deaths from cervical cancer occur each year in the US. Cervical cancer occurs at a much higher rate in less developed countries, with 569,000 cases and 300,000 deaths yearly worldwide. The risk of cervical cancer doubles with the first sexual intercourse occurring before age 18 compared with after age 21. Giving birth before age 18, and multiple vaginal births (>4) are also risk factors. Smoking can negatively affect cervical cells, as well as compromise the immune system. This increases the risk of an HPV infection developing into cancer. Human immunodeficiency virus (HIV) infection and prolonged use of oral contraceptives (>5 years) also increase the risk of cervical cancer (Johnson, James, Marzan & Armaos, 2019).

The early clinical presentation of cervical cancer is usually asymptomatic, but commonly includes irregular vaginal bleeding and discharge. Later signs include radiating pelvic and lower back pain, and bowel or bladder changes such as hematuria. If cervical cancer is suspected, a pelvic examination is performed, and any abnormal lesions are biopsied. The definitive diagnostic test for cervical cancer is a colonoscopy, followed by histological examination of cervical biopsy. The two most common types of cervical cancer are squamous cell carcinoma (85%) and adenocarcinoma (25%). Prognosis is generally worse in non-squamous cell presentation, as well as in metastasis to the pelvic or para-aortic nodes. Treatment of cervical cancer includes surgery, radiation, chemotherapy and immunotherapy. Many of these treatments can lead to problems of their own, such as bladder dysfunction, bowel dysfunction, premature ovarian failure, sexual dysfunction, lymphedema, fatigue and psychosocial issues (Johnson et al., 2019).

Oropharyngeal cancer. While cervical cancer occurs more frequently in less developed countries, oropharyngeal cancer is more common in developed countries. Ninety percent of oropharyngeal cancers are squamous cell carcinomas. In the United States oropharyngeal cancers have increased by 3.9% in men and 2.1% in women. The risk for oropharyngeal cancer increases with tobacco and alcohol use, however with HPV positive oropharyngeal cancers, the demographic tends to have less tobacco and alcohol exposure. Patients with HPV also tend to be in their mid 50s and have a higher socioeconomic class and education. Oropharyngeal cancer caused by HPV is also more common in Caucasians and is three times more likely to occur in men. Ninety to ninety-five percent of oropharyngeal cancer is caused by HPV type 16, the survival of which may be facilitated in the tissue of the tonsils, which are histologically similar to cervical tissue. This type of cancer usually presents with a tumor and lymph node involvement

in the early stages; however, metastasis is usually delayed (Elrefaey, Massaro, Chiocca, Chiesa & Ansarin, 2014). Oropharyngeal cancer caused by HPV usually has a better outcome than other oropharyngeal cancers, with a 28% lower risk of death and a 49% lower risk of recurrence. This improved prognosis can be due to contracting HPV at a young age, fewer genetic alterations in the tumors, higher radiosensitivity, and absence of field cancerization. Because of better prognosis, nonsurgical treatments such as chemotherapy and radiation are preferred for this type of cancer. Side effects of this treatment are xerostomia, chronic aspiration, dysphagia, and chronic fatigue. In order to decrease these side effects, minimally invasive procedures such as transoral robotic surgery (TORS), which uses lower adjunct doses of chemotherapy and radiation (Elrefaey et al., 2014).

HPV vaccine

Gardasil was the first HPV vaccine developed and was approved by the FDA in 2006. Gardasil is also known as the quadrivalent vaccine, and protects against HPV types six, 11, 16 and 18 (Johnson et al., 2019). In 2009 a bivalent vaccine known as Cervarix was approved to cover just HPV types 16 and 18 (Elrefaey et al., 2014). The only HPV vaccine currently available in the United States is the 9-valent vaccine or Gardasil-9, approved in 2014. Gardasil-9 covers HPV types six, 11, 16, 18, 31, 33, 45, 52 and 58, the nine types known to cause the majority of HPV-related cancers (Johnson et al., 2019). The HPV vaccine is recommended for 11 to 12-year-old girls and boys, but it can be started as early as age nine, especially if the patient has a history of sexual abuse. It is ideal to receive the vaccine before sexual contact and consequential exposure to HPV. However, the HPV vaccine can still be beneficial to individuals who are sexually active. While the vaccine cannot treat an existing HPV infection, it can protect an individual from certain HPV types they may not yet have been exposed to. The CDC

recommends two doses at least six months apart for nine to 14-year-olds, and three doses over 6 months for those beginning the vaccine series at ages 15 through 26. Response to the vaccine is better at younger ages which is why three doses are recommended after the age of 14. The HPV vaccine has also recently been approved for men and women ages 27 to 45, as it has been proven to still be effective later in life (Mayo Clinic, 2019). Gardasil-9 is composed of virus like proteins (VLPs) that closely resemble HPV and stimulate antibodies that also react against the HPV virus. The vaccine does not contain live or killed HPV virus or DNA from the virus and is therefore not infectious. The VLPs have been proven to be highly effective, as they stimulate a strong immune response (NIH, 2019). The vaccine contains aluminum as an adjuvant to assist in stimulating the immune system, and polysorbate 80 to stabilize the vaccine. The vaccine also contains sodium chloride, water, L-histidine (an amino-acid, which makes up a protein), and sodium borate (Nicol et al., 2015).

Controversy

There are many topics of controversy surrounding the HPV vaccine. The main points of dispute include the vaccine's relevance, efficacy, and safety.

Relevance

The relevance of the HPV vaccine is often disputed by those who believe it promotes promiscuity in young adults. Some also state that because the vaccine does not cover all strains of the virus, there is no point in getting it. Others mention that because of screenings such as pap smears and HPV testing, a vaccine is not needed (Holland et al., 2018).

Promoting promiscuity. One of the most common presumptions about the HPV vaccine is that it promotes the promiscuity of young adults by protecting them from the most common sexually transmitted disease. There have been multiple peer-reviewed studies completed that

disprove this theory. A study done in Canada compared a cohort of eighth-grade girls two years before and two years after implementation of the country's HPV vaccination program. The cohort consisted of 260,493 girls, 128,712 of which were eligible for the vaccination program. The study measured incidence of pregnancy and sexually transmitted diseases that were non-HPV related. The study identified 15,441 incidences of pregnancy and sexually transmitted diseases out of the entire cohort but found that there was no increased risk in those who received the vaccine (Smith, Kaufman, Strumpf & Lévesque, 2015). A recent study in the United States compared youth high risk behavior in states that had passed legislation promoting the HPV vaccine with states that had not. The study utilized the results of 886,981 Youth Risk Behavior Surveillance System (YRBSS) surveys of high school students from 2001-2015. The results of this study found no significant difference in sexual behaviors in states that had passed legislation compared with those that had not. In states with HPV vaccination legislation there was actually a reported decrease in adolescent sexual intercourse by 0.9% and increase in condom use by 0.96%. Therefore, implementation of the HPV vaccine does not appear to increase the risk of sexual behavior in adolescents (Cook, Venkataramani, Kim, Tamimi, & Holmes 2018).

Real risk of cancer. Because there are many strains of HPV that appear and resolve on their own, some may not feel the need to vaccinate against it. While it is true the vaccine does not cover all strains of HPV, it does cover the most common strains to cause cancer (ACS, 2017). Globally each year, HPV causes 570,000 and 60,000 cancer cases in women and men, respectively (de Martel, Plummer, Vignat, & Franceschi, 2017). In the United States, HPV causes >90% of all cervical and anal cancers, 70% of vaginal, vulvar and oropharyngeal cancers, and >60% of penile cancers (CDC, 2019a). Some who oppose the vaccine argue it is not worth giving, as cervical cancer only accounts for 0.8% of cancers in the United States (Holland,

Rosenberg, Iorio, & Montagnier, 2018). While this is true, cervical cancer kills >4,000 women (ASCO, 2019), and oropharyngeal cancer kills >9,000 people (OCF, 2019) every year in the United States. There is a way to greatly reduce these numbers, as research has shown 70-90% of all HPV-related cancers can be prevented by HPV vaccination (de Martel et al., 2017). Based on this evidence, it would seem that vaccination is both justifiable and necessary.

Alternative prevention methods. Some sources question the relevance of the HPV vaccine in terms of cancer prevention when more desirable alternatives exist such as pap smears and HPV tests (Holland et al., 2018). Pap smears and HPV tests are methods of screening that may prevent the development of cancer if abnormal cells are caught early enough. Conversely, the HPV vaccine prevents most cancer-causing HPV types from ever infecting an individual, stopping cancer before it starts. Because the vaccine does not cover every strain of HPV, it is important to utilize screening methods in combination with the vaccine. However, pap smears cannot be relied on as the primary method of prevention, as they can only diagnose the need for further testing by identifying abnormal cervical cells. The majority of HPV-related cancers are not cervical cancers, and the pap test cannot prevent these (Simpson, 2018). Human papilloma virus tests are done when a pap smear result is abnormal in order to detect the presence of the HPV virus, however it does not test for all HPV types. The test does not diagnose cancer but determines the presence of an HPV type that may cause cancer. It is usually followed up with further testing (Mayo Clinic, 2018). There are currently no FDA approved screening methods for men, or for other types of HPV-caused cancers besides cervical cancer (ACS, 2017). This includes oropharyngeal cancer, which is the most common type of HPV-caused cancer in the United States (Van Dyne et al., 2018). Therefore, the HPV vaccine remains the best overall prevention method for HPV and HPV-caused cancers.

Efficacy

The ability of the HPV vaccine to prevent infection with the virus, the formation of cancerous lesions, and the development of cancer is often disputed.

Prevention of HPV infection. The initial goal of the HPV vaccine is to prevent the development of HPV infection. There have been multiple studies done to prove the efficacy of the HPV vaccine. One study determined the vaccine has reduced the prevalence of HPV by 86% in the United States over the course of 10 years. This reduction was observed across racial and ethnic groups (McClung et al., 2019). A study done in Norway compared a vaccinated cohort to a nonvaccinated cohort. Five years post-vaccination, an 81% reduction of HPV infections was found in the vaccinated group compared to the unvaccinated group (Feiring et al., 2018). Another study done in England from 2010-2016 showed vaccine effectiveness of 82% (Mesher et al., 2018). There was a long-term follow-up study done over 12 years in Finland. This study analyzed 2,500 serum samples from recipients of Gardasil and Cervarix and found anti-HPV-16 and anti-HPV-18 antibodies remained stable and higher than they would be from a natural infection for up to 12 years following vaccination. These results confirm previous reports of long-term protection against HPV (Artemchuk et al., 2019).

Prevention of precancerous lesions. It is also important to monitor the development of HPV-caused cervical lesions, as these can lead to the development of cervical cancer (Niccolai et al., 2017). The vaccine has also shown efficacy in preventing precancerous lesions. A study using data from the CDC of over 10,000 women displays how the vaccine is effectively reducing the incidence of precancerous lesions. The results of the study indicated that incidence of lesions declined in HPV vaccinated women from 55.2% to 33.3% over 6 years. There were also declines seen in unvaccinated women (from 51% to 47.3%) suggesting herd immunity (Simon, 2019). A

study done in Connecticut showed declines of high-grade cervical lesions from the years 2008-2015. The rates declined by up to 74%, with greater declines observed in younger women (Niccolai et al., 2017). Another study was done in Northern California to demonstrate the effectiveness of the vaccine in preventing precancerous lesions in those who began HPV vaccination later (>17 years old). Protection against precancerous lesions was observed in women with the first dose of three between the ages of 14-20 compared with women who had no previous vaccination, or those who began their HPV vaccinations over 21 years old. According to this study, those who received ≥1 HPV vaccine dose were at a significantly decreased risk of developing precancerous lesions than those who were unvaccinated (Silverberg et al., 2018). Finally, a study from Australia found the rate of cervical lesions decreased by nearly 75% in women < 20 years old and by 50% in woman aged 20-24 since the implementation of their National HPV Vaccine Program in 2007 (VCCS, 2017).

Prevention of cervical cancer. Some sources advocating against the HPV vaccine state the vaccine has never been proven to prevent cancer (Holland et al., 2018). However, according to evidence-based research, this is simply not true. The primary goal of the HPV vaccine is to prevent the development of HPV-related cancers, the most recognized type being cervical cancer. One study utilized a mathematical model to determine the natural occurrence of cervical cancer and length of protection from HPV the vaccine provides. The model projected that over half of cervical cancer-causing HPV infections occur by the age of 20. This means if the vaccine protects for 20 years, vaccinating by age 12 would reduce the lifetime risk of developing HPV-caused cancer by over half (Burger, Kim, Sy & Castle, 2017). Another study aimed to determine how protected individuals would be after only receiving part of the recommended three-dose vaccine. The study found significant reductions of cervical intraepithelial neoplasia (CIN) in

partially vaccinated individuals ages 15-19. CIN1 (mild cervical dysplasia) had an annual percentage change (APC) of -9.0%, CIN2 (moderate dysplasia) had an APC of -10.5%, and for CIN3 (severe dysplasia) the APC was -41.3%. This study demonstrates even those who are only partially vaccinated against HPV will experience decreased incidence of CIN (Benard et al., 2017). A systematic review compiling data from Medline and Embase determined that CIN2 incidence decreased by over half in girls aged 15-19 years and by 31% in women aged 20-24 years up to nine years post-vaccination (Drolet et al., 2019).

Prevention of other cancer types. There are about 44,000 new cases of HPV-associated cancers per year in the United States, including cervical, vaginal, oropharyngeal, anal, penile and vulvar. Oropharyngeal squamous cell carcinoma (SCC) is now the number one cancer caused by HPV in the United States, outnumbering cervical cancer cases 18,915 to 11,788 in 2015. The rate of oropharyngeal SCC is 2.7% in men and 0.8% in women (Van Dyne et al., 2018). One study found a reduction of 88% in oral HPV infections among vaccinated individuals compared with unvaccinated individuals. The study also found no evident HPV infection in vaccinated males, which seems to indicate a 100% reduction rate. As oropharyngeal SCC is three to five times more prevalent in men, this information is vital to increase vaccine coverage in men (Chaturvedi et al., 2018). A study done in Norway analyzed the increasing trends in all types of HPV-caused cancers that are not monitored by screening methods over the course of 60 years. The study determined that the 9-valent HPV vaccine may prevent 478 cancers per year in Norway alone (Hansen, Campbell & Nygård, 2018).

Safety

Perhaps the most disputed topic of controversy regarding the HPV vaccine is its safety. There is concern around the safety of the vaccine ingredients, the reported side effects, and the reports of infertility, autoimmune disease, and death following HPV vaccination.

Ingredients. Two of the most controversial ingredients in the HPV vaccine include aluminum and polysorbate 80. Aluminum is the world's most common metal. It can be found in the air, water, dirt, plants, and in food such as flour, dairy products, fruit, and vegetables. The average person consumes 7-9 milligrams (mg) of aluminum per day. Aluminum is used in vaccines as an adjuvant, meaning it enhances the body's immune response. Aluminum is used as an adjuvant in nearly all infant vaccinations and the amount of aluminum they receive in the first six months of life (4.4 mg) is less than the amount found in breast milk (7 mg) or formula (38 mg) (CHOP, 2018). The amount of aluminum in the HPV vaccine is minute for an adult, 225 micrograms (mcg) or 0.225 mg (Nicol et al., 2015). There have been studies that attest the aluminum in vaccines is harmful, and that it can build up in the body causing neurotoxicity and contribute to diseases such as Alzheimer's (Holland et al., 2018). However, the amount of aluminum in the vaccine is so small, one would absorb much more by drinking a glass of tap water. Furthermore, according to the Children's Hospital of Philadelphia (CHOP), all studies have not seen consistently high levels of aluminum in Alzheimer's patients, and causation cannot be proven (CHOP, 2018).

The HPV vaccine also contains 50 mcg of polysorbate 80 (Nicol et al., 2015), used in many other vaccines, as well as for an emulsifier in ice cream, cosmetics and medications. In the HPV vaccine, polysorbate 80 is used as a stabilizer and emulsifier, to keep the other vaccine ingredients evenly distributed (Schwartzberg & Navari, 2018). Some sources say polysorbate 80

content in vaccines opens the blood brain barrier (BBB), allowing adjuvants such as aluminum to permeate into the brain (Holland et al., 2018). A study done in 1985 is the main source of the dangerous claims about polysorbate 80 breaking down the BBB. In this study, large amounts of polysorbate 80 were injected into rats and mice and depression of the central nervous system resulting in paralysis and ataxia was observed. Based on this study, a safe dosage of polysorbate 80 was determined to be 1 milliliter (ml) per kilogram (kg) (Varma et al., 1985). One ml equates to 1 gram (g), so for an average 45kg adolescent receiving this vaccine, a safe dosage would be 45g or 45,000,000mcg. This "safe dosage" is 900,000 times larger than the 50mcg found in the HPV vaccine. Therefore, in order to have effects like those of the mice in this study, 45g would need to be injected intravenously.

Side effects. According to the CDC, the most common side effects following HPV vaccination are redness and swelling around the injection site, headache, fever, nausea, and fatigue (CDC, 2019b). However, the safety of the HPV vaccine has been questioned frequently due to reports of more serious adverse effects, and compliance with HPV vaccinations has been lower than recommended because of this. The CDC reported that in 2018, 53.7% of girls and 48.7% of boys were up to date with the HPV vaccine, which was a slight improvement from the year before (Jenco, 2019). There have been multiple large-scale studies done to establish the overall safety of the HPV vaccine. One study including almost one million girls from two different countries compared vaccinated and unvaccinated cohorts. Of the 696,420 girls that were vaccinated, exposure to the vaccine was not related to serious adverse effects (Arnheim-Dahlström, 2013). A long-term follow-up study taking place over the course of eight years compared the HPV vaccine with a saline control group. The saline group received the vaccination at the 30-month mark, and the groups showed no difference in adverse effects, and

no new adverse effects for 8 years following vaccination (Ferris et al., 2014). A more recent study also confirmed these findings. The study involved two years of surveillance of 838,991 recipients of the HPV vaccine for adverse effects; nothing of concern was identified (Donahue et al., 2019).

Side effects that patients believe to be associated with vaccines can be reported to the Vaccine Adverse Event Reporting System (VAERS). One study searched the VAERS database for reports of adverse events following HPV vaccination. 97.4% of the 7,244 reports gathered from 2014-2017 were determined to be nonserious, including dizziness, injection site reactions, syncope, and headache (Shimabukuro et al., 2019). These findings are consistent with the CDC's most commonly listed side effects (CDC, 2019b). The study found that there were 259 reports to VAERS out of every one million HPV vaccines given. 2.6% of total reports to VAERS reported serious adverse events including anaphylaxis, primary ovarian insufficiency (POI), autoimmune disease onset, and death. However, many of these reports did not meet the diagnostic criteria for the reported disease, and the two confirmed deaths had no information to suggest that they were caused by the HPV vaccine (Shimabukuro et al., 2019). Despite this evidence, the safety of the HPV vaccine is still questioned.

Primary ovarian insufficiency (POI). There have been some connections between the HPV vaccine and POI. Primary ovarian insufficiency occurs in women less than 40 years old and causes fluctuation of ovary function leading to ovarian failure. 74%-90% of the time, the cause of POI is unknown, and the incidence of POI in early to mid-adolescence is so rare that there are no age-specific background rates (Little & Ward, 2014). A case report study was done in 2014, focusing on three cases. Case one was a 16-year-old who received the HPV vaccine at age 14. Her cycles became irregular and scant in the following year and she was diagnosed with ovarian

failure at 16. Case two was an 18-year-old who began taking oral contraceptive pills (OCP) at 12 years old and received the first HPV vaccine a few months later. The OCP was stopped at age 18 and the patient experienced amenorrhea for several months before she was diagnosed with ovarian failure. Case three was a 17-year-old who received the HPV vaccine at age 14, and experienced amenorrhea after the third vaccination dose and experienced symptoms of premature menopause a few months later. She was diagnosed with ovarian failure at age 17. However, because there is no evidence to suggest that the vaccine initiated POI onset, these case reports cannot establish causation. This was stated by the authors of the case reports (Little & Ward, 2014). A recent cohort study of nearly 200,000 young women was done to evaluate POI in relation to the HPV vaccine. From a group of 58,871 women who received the vaccination during the study, only one idiopathic case of POI in an adolescent with onset following HPV vaccination was identified. Others who developed POI in this study were over the age of 26, which is consistent with other population-based studies. If POI were to be triggered by HPV vaccination, it would be expected that a higher incidence of POI would occur in younger women who were receiving the vaccine. The study found no evidence of increased diagnosis of POI following HPV vaccination (Naleway et al., 2018).

Guillain-Barré syndrome (GBS). Guillain-Barré syndrome is a rare and serious autoimmune disease that causes demyelination of the peripheral nervous system, resulting in muscle weakness. The onset of GBS is generally not understood, however it is thought to be related to molecular mimicry, generally preceded by some type of infection. Onset of GBS has been connected to vaccines previously, as there was an increase in the number of cases after the swine influenza vaccination in 1976. However, following this incident, GBS has not been connected with the influenza vaccine or other vaccines. There have been several large population

studies done relating the risk of GBS following HPV vaccination in the United States, England, France and Scandinavia. All of these studies found no increase in the incidence of GBS following HPV vaccination, except France (Gee, Sukumaran & Weintraub, 2017). In 2017 a retrospective cohort study was done following 2.2 million girls, 37% of which received the vaccine. The incidence of GBS increased from 0.4 cases per 100,000 in the unvaccinated to 1.4 cases per 100,000 in the vaccinated (Miranda et al., 2017). However, a separate study was done in England in response to the French study. The UK study gave 10.4 million doses of the HPV vaccine and observed no increased risk of GBS throughout the next year following vaccination (Andrews, Stowe & Miller, 2017). A separate study by the US identified seven cases of GBS following administration of >2 million doses of the vaccine. Of those seven cases, only one was determined to be a new diagnosis of GBS. Both the UK and the US study support the risk of less than one case of GBS per one million doses of HPV vaccine (Gee et al., 2017). This is lower than the average rate, as GBS is typically contracted in one to two people out of every 100,000 (NORD, 2017).

Complex regional pain syndrome (CRPS) and Postural orthostatic tachycardia syndrome (POTS). Complex regional pain syndrome and POTS are both disorders that were not originally associated with autoimmunity, but some sources list them as potential autoimmune syndromes associated with the HPV vaccine. Complex regional pain syndrome is a chronic pain syndrome affecting one limb, and POTS is a form of orthostatic intolerance where the heart rate increases abnormally following sitting or standing, and is accompanied by fainting, headaches, nausea, dizziness and fatigue. Case reports of CRPS following HPV vaccination in Japan resulted in the withdrawal of government recommendation for the vaccine. However, these cases were later determined to be unrelated to vaccination by the Global Advisory Committee on

Vaccine Safety (GAVCS) (Philips, Patel, Pillsbury, Brotherton & Macartney, 2018). Denmark reported two case series of POTS following HPV vaccination, however these reports were criticized as they lacked specificity of symptoms. In 2015 the European Medicines Agency (EMA) completed a review including data from clinical trials as well as post-marketing literature and surveillance to assess the evidence of a causal link between the HPV vaccine and onset of POTS or CRPS. The review The EMA review found no increased occurrence of POTS or CRPS in HPV vaccinated groups, as the rate of POTS and CRPS in unvaccinated and vaccinated groups did not differ. Therefore, there was no causal link between HPV vaccination and disease onset (Philips et al., 2018). A study of POTS was done in Finland over the course of 10 years before the HPV vaccine was implemented in the country. In 2002 at the start of the study, there were two annual cases of POTS out of every 100,000 people. In 2012 at the end of the study, that number had increased to 13 annual cases out of every 100,000 people. This increase was attributed in part to increased awareness of the condition by physicians (Barboi et al., 2019). This study was followed by another Finnish study to assess the incidence of POTS following vaccination from 2013-2016. The year the vaccine was introduced, the incidence of CRPS stayed the same, and the incidence of POTS actually decreased (Skufca et al., 2018). According to the findings from these studies, there is no causal link between the HPV vaccine and the onset of POTS or CRPS.

Autoimmune vasculitis and death. In 2012, six years after the approval of the HPV vaccine, a study was published linking the vaccine to fatal autoimmune vasculopathies. The study was based on the cases of two young women who died after receiving the HPV vaccine. Case one was a 19-year-old who died in her sleep six months after receiving the third dose of Gardasil. Case two was a 14-year-old who developed confusion, speech problems, migraines and

inability to walk two weeks after receiving her first dose of the vaccine. These symptoms resolved, but she was found unconscious 15 days after her second dose and later pronounced dead at the hospital. Autopsies were completed for both patients and showed no abnormalities in either of their brains that could account for a potential cause of death. The autopsy for case 2 demonstrated cardiac arrest which lead to ischemic encephalopathy. The study involved analyzing samples of brain tissue from the two cases utilizing standard hematoxylin and eosin (H&E) staining and immunohistochemical (IHC) methods, which involves incubation, counterstaining and observation using a light microscope. The findings showed evidence of cross-reactive HPV-16L1 antibodies within the cerebral vasculature, which is believed to have caused autoimmune vasculitis in both cases (Tomljenovic & Shaw, 2012).

The Centers for Disease Control and Prevention (CDC) issued a response that same year to the Tomljenovic article, utilizing a working group made up of professionals with expertise on the subject to address the study. These professionals convened from universities including Vanderbilt, John's Hopkins, Columbia and Duke, as well as the FDA. This working group identified several scientific concerns with the Tomljenovic article. In order for vasculitis to be histologically diagnosed correctly, there would have to be evidence of an infiltrate associated with inflammation and destructive changes within the cerebral vessels. This evidence would have been clearly observable with normal H&E staining. Of the IHC and H&E images in the Tomljenovic article, none of them displays damage to the vessels, or an inflammatory infiltrate. The only thing displayed in the images is hemorrhage, which is a common occurrence in autopsy specimens (CDC, 2012). Furthermore, an immune-based vasculitis would have been visible as obvious inflammation on H&E slides to the pathologist completing the autopsy. However, both autopsies of the cases in question determined that there were no brain abnormalities that could

have been the cause of death. In fact, the cause of death in case two was determined to be cardiac arrest which lead to ischemic encephalopathy. Ischemic encephalopathy is swelling in the brain due to a lack of oxygen, caused by the failure of the heart to pump blood (Gorski, 2012). The study also lacks the use of negative antibody and tissue control samples. Without these control samples, it is not possible to measure immunoreactivity quantitatively, which is something the study lists as a limitation (Tomljenovic & Shaw, 2012). The study reports finding HPV-161 particles in the cerebral vasculature, as well as the walls of some blood vessels. However, the CDC working group clarified that antibodies such as HPV cannot be seen with the use of a standard light microscope, such as the one reportedly used in the Tomljenovic article. In order to view these viral particles, the use of an electron microscope would have been necessary, and its use is not reported in the article. Finally, there was no method of measurement reported by the authors related to the specificity of the IHC staining methods used. There are many instances of false positives related to immunostaining methods. Due to these concerns, the CDC working group determined the authors' conclusions negated (CDC, 2012).

Molecular mimicry. Most autoimmune diseases reportedly caused by the HPV vaccine are proposed to have occurred via molecular mimicry. Molecular mimicry is the theory that when viral human-like proteins and peptides in the form of antigens are introduced to the body, the immune system becomes confused between self and non-self. Because the invading antigen has similar proteins and peptides to those found in the body, the immune system initiates a continuous inflammatory response against the protein sequence naturally found in the body, causing an autoimmune disease (Holland et al., 2018). There are several instances where molecular mimicry is known to occur, albeit as a result of pathogenic infection, not vaccination. For example, when an individual is infected with group A streptococcus, the body forms an

immune response against it. However, a protein found in the group A streptococcus sequence mimics a protein found within the myocardium. This similarity causes the body to fight its own tissues, resulting in the autoimmune disease known as rheumatic fever, which can lead to rheumatic heart disease (CHOP, 2017).

One study identified similar heptapeptide motifs between several human proteins and the HPV16 polyprotein found in the vaccine (Kanduc, 2009). However, the probability of these exact proteins occurring in the correct sequence is small. Even if this did occur, it is known that molecular mimicry alone is not sufficient to initiate an autoimmune response. Other factors such as pathogenic infection, tissue damage and chronic inflammation would be necessary as well. There was a study done on a vaccination for Lyme disease, which contains a very similar epitope to the human lymphocyte function-associated antigen 1 (LFA-1). Lyme disease itself is known to cause arthritis due to this similarity. However, there was no increased incidence of arthritis in those who received this vaccine (Vadalà, Poddighe, Laurino & Palmieri, 2017). Furthermore, natural infection with HPV does not cause autoimmune disease. The HPV virus, when caught naturally, replicates itself thousands of times creating a much stronger immune response than the vaccine, which does not replicate at all and consists of just one protein from nine strains of the virus (CHOP, 2017). This combined evidence indicates that autoimmune disease resulting from the HPV vaccine is highly unlikely, if not impossible.

Conclusion

History and evidence-based practice have proven vaccines to be efficacious, safe, and necessary. However, vaccine resistance has as long a history as vaccines themselves. The HPV vaccine is one of the more recent vaccines to fall under scrutiny. The relevance, efficacy and particularly, safety of the HPV vaccine are frequently disputed. There have been claims of

autoimmune disease onset, infertility and even death occurring after receiving the HPV vaccine. These claims have been largely refuted by multiple peer-reviewed, large-scale studies. However, despite the evidence, the use of the HPV vaccine is still questioned. According to the research, it is clear the efficacy of the HPV vaccine in reducing infection, cervical lesions and multiple types of cancer outweigh the risks, since such risks have yet to be proven. Implications for practice may include more thorough education on reasons for vaccine refusal for practitioners, so that patients are able to receive accurate information about the issues they perceive with vaccines. Nurses can support HPV vaccination by promoting patient and family health literacy on the risks associated with not receiving the vaccine, as well as the proven safety of the vaccine. It is important moving forward that doctors and nurses understand the reasons for HPV vaccine refusal, so they may be better prepared to combat them. This increased awareness and education may assist in increasing HPV vaccine compliance, thereby decreasing infection rates, cervical lesions, and the occurrence of cancer.

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