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Benefits of HPV Vaccination in Adolescent Males

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by

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Abstract

Human papilloma virus (HPV) is a collection of between 120-150 viral strains that effect epithelial and mucosal tissue. Infections due to HPV are extremely common and some of the more high-risk strains can lead to severe consequences later in life. HPV is the most common sexually transmitted infection in the United States, affecting approximately 75-80% of young adults at some point in their lives, and it is also known to be directly related to several forms of cancer including cervical, vaginal, penile, anal, oral, and oropharyngeal cancer. Vaccination against several high-risk strains of HPV first became available in the U.S. in June of 2006 and has been proven to be effective in creating antibodies against several strains of high-risk HPV, potentially decreasing and preventing more than 30,000 new cases of HPV related cancers each year. Despite this fact, HPV vaccination rates remain low. Although vaccination is recommended for both female and male adolescents, male vaccination rates remain lower than female, likely due to the fact that HPV is most commonly associated with cervical cancer. However; evidence shows that among certain male populations, such as homosexuals, HPV related cancer rates may be as high in males as cervical cancer rates in females, demonstrating the potential impact of HPV vaccination in males. Lack of knowledge, and a perception of a lack of necessity for male vaccination are substantial barriers for achieving targeted vaccination rates. There is evidence demonstrating that proper education, or simply having meaningful conversation with patients, can help to increase patient compliance of receipt of HPV vaccination. Additionally, there is an abundance of unverified information attempting to link HPV vaccination to severe adverse reactions. There is minimal evidence to support such a correlation, but some studies do suggest it. A need for further investigation is warranted.

Introduction

Over the past decade or so, people have become increasingly hesitant to receive many recommended vaccinations. There are several causes related to this hesitation; increasing number of recommended vaccines, public misconception, and just poor understanding of vaccination and/or the diseases these vaccines are preventing. One vaccine with a large amount of public skepticism is the Human Papilloma Virus (HPV) vaccine. Since 2006, when HPV vaccine was first approved, there has been an increasing push by health agencies and medical professionals to vaccinate against HPV. Many people do not have a solid understanding of what HPV really is. Rather than a single virus, Human Papilloma Virus (HPV) is a collection of many different viruses. There are approximately 120-150 different strains of HPV, some more virulent than others. Most strains of HPV cause common skin warts and are eradicated by the human body before causing any serious disease process. Others, however, may be more difficult for the human immune system to eradicate on its own, and in turn may lead to secondary complications. Conditions such as sexually transmitted infections, most commonly (genital warts), are caused by certain strains of HPV. Some strains of HPV are also known to lead to several types of cancer later in life. The most well known of the cancers directly linked to HPV is cervical cancer; however, HPV is also significantly linked to numerous other types of cancer, such as vaginal, oropharyngeal, anal, and penile. These other forms of cancer are not as commonly known to be linked to HPV, especially in the male population. According to the CDC, each year about 42,700 new cases of cancer are found in parts of the body where human papillomavirus (HPV) is often found. It is estimated that HPV causes about 33,700 of these cancers.

Number of HPV-Associated Cancer Cases per Year

Cancer site	Average number of cancers per year in sites where HPV is often found (HPV-associated cancers)	Percentage probably caused by any HPV type[a]	Number probably caused by any HPV type[a]
Cervix	11,866	91%	10,751
Vagina	846	75%	635
Vulva	3,934	69%	2,707
Penis	1,269	63%	803
Anus[b]	6,530	91%	5,957
Female	4,333	93%	4,008
Male	2,197	89%	1,949
Oropharynx	18,226	70%	12,885
Female	3,412	63%	2,160
Male	14,814	72%	10,725
TOTAL	42,671	79%	33,737
Female	24,391	83%	20,260
Male	18,280	74%	13,477

(Centers for Disease Control and Prevention, 2016)

In June of 2006, The United States Food and Drug Administration (FDA) approved the first vaccine to prevent HPV infection in hopes to decrease the prevalence of HPV related cancers, as well as prevention of genital warts among young sexually active adults. Since its inaugural release the HPV vaccine has evolved to cover a greater number of some of the more virulent strains of HPV. Despite recommendations from the CDC (Centers for Disease Control and Prevention) and healthcare providers, there is still a large portion of the population that either refuses HPV vaccination or doesn't know enough about the vaccine to make a responsible decision for themselves or their children, specifically, when choosing for adolescent males to receive the HPV vaccine.

Statement of the Problem

A review of the literature shows that many sexually transmitted infections as well as some types of cancers have been proven to be directly linked to different strains of HPV in both males and females. Despite this evidence, there is significant resistance for adolescent males to receive this vaccine. Proper education should be given to parents and patients regarding the benefits HPV vaccination. There are many misconceptions about the HPV vaccine, as well as the virus itself. Much of the public misconception is due to the thought of HPV vaccination being only relevant to individuals who are sexually active and not necessary at the ages the vaccine is recommended by the CDC. It is well established and accepted that HPV can lead to cervical cancer in females later in life, but the consequences in males who have HPV are not as known or accepted by much of the public. This causes parents of adolescent male patients to be more hesitant in agreeing to vaccinate their male children. What many people may not realize is that the vaccine in not as effective if given after a person has become sexually active and may have already been exposed to HPV. Additionally, there are many non-verified reports across social media and the internet stating that the HPV vaccine may cause different autoimmune diseases such as Gilliam Barre Syndrome or other severe conditions such as postural orthostatic tachycardia syndrome (POTS). This information leads to increased skepticism and hesitancy in receiving recommended HPV vaccination. It is the responsibility of health care providers to properly educate patients and parents of patients whom are recommended to receive vaccination against HPV and prevent potentially severe complications later in life. Unfortunately, this is often not what actually happens.

Research Questions

In adolescent male patients, does vaccination against human papilloma virus (HPV) significantly decrease incidence of several types of cancer later in life, compared to adolescent males who have not received an hpv vaccine?

Does vaccination against Human Papilloma Virus cause potentially severe adverse reactions, such as autoimmune diseases?

Can adequately educating patients, or a patient's caregiver, lead to an increase in compliance in receiving HPV vaccination in male adolescents?

Research Methods

An extensive article search was performed using several electronic research databases including PubMed, Clinical Key, Dynamed Plus, and Cochrane Library. A review of the current literature was performed, using both keyword and mesh terms, to explain the epidemiology of different strains of HPV, different types of HPV vaccines, and to evaluate the impact of HPV vaccination in the adolescent male population. The literature was further searched to clarify and explain the possibility of severe adverse side effects that may be caused or exacerbated by HPV vaccination. Keywords used for database searches include Human Papilloma Virus, HPV genotypes, vaccination, 9vHPV, Gardasil, Cervarix, pathophysiology, adverse effects, males, adolescent males. Articles used include meta-analyses, randomized control trials, double blind random controlled trials, Cochrane review articles, PubMed articles, and other peer-reviewed scholarly articles. Information was also gathered from the U.S. Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC) websites. A textbook published in 2014 was also used to define the pathophysiology of Human Papilloma Virus.

Theme 1: What is HPV?

According to the Centers for Disease Control and Prevention (CDC), human papillomavirus (HPV) is a group of more than 150 related viral strains. These viruses are transmitted through skin to skin contact. Some of the more virulent strains are commonly transmitted though intimate contact during sexual activity, including vaginal, anal, or oral sex. The reason these more virulent strains are passed during intimate contact is because they are passed between mucous membranes rather than outer skin. The CDC (Centers for Disease Control and Prevention, 2016) states that HPV is so common that approximately 80% of all men and women are exposed to one of the many strains of HPV at some point in their lives. Most strains of HPV are asymptomatic and are cleared by the human immune system before they can cause any significant form of disease, other than common skin warts. Other strains however can manifest later with significant consequences, such as genital warts and certain types of cancers.

The Centers for Disease Control and Prevention (CDC) is a United States Government run organization. The content found above was gathered in conjunction with The National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention; National Center for Immunization and Respiratory Diseases; National Center for Chronic Disease Prevention and Health Promotion. This information will aid in this paper to educate the reader about the what HPV actually is. The information is this part of my paper is mostly educational and not much opinion, but with the CDC, the main weakness in this information is that it is restricted to only the United States.

The ClinicalKey database (Elsevier Point of Care, 2018) goes into detail regarding the causes and virulence of different strains of human papillomavirus. Human Papilloma Virus (HPV) is defined as “an infection that is caused by at least one of the more than 120 types of HPV identified; all affect the epidermis, while different types are associated with cutaneous

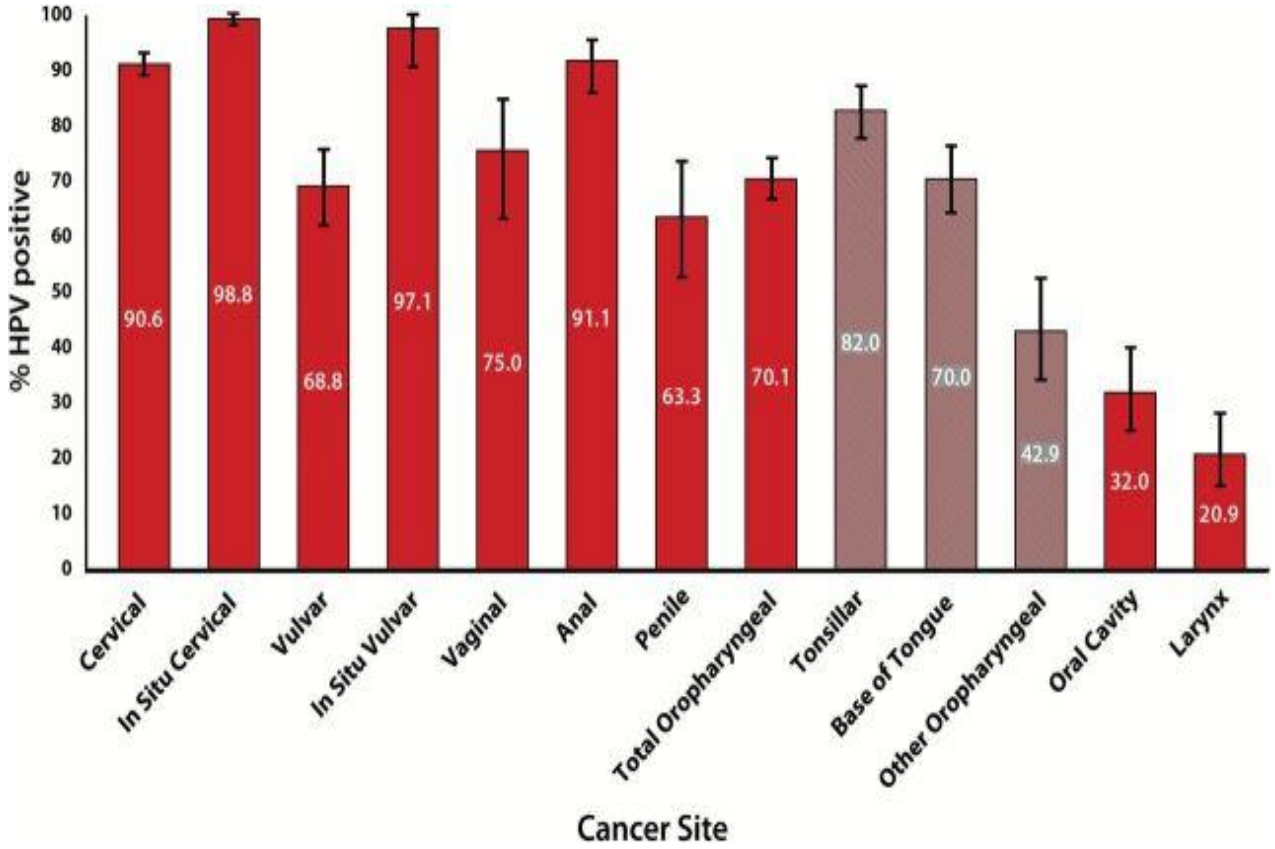
(nonmucosal) and genital (mucosal) infections." (Elsevier Point of Care, 2018) As stated before, most HPV infections do not present clinically and are cleared easily by immunocompetent people, but some strains are associated with conditions such as benign warts on skin, genital warts, or even certain types of cancers. HPV 1, 2, 27, and 57 are non-mucosal and associated with cutaneous warts found on outer surfaces of the body. Mucosal HPV infections are more virulent and can be classified as either low or high risk. HPV 16 and 18 are considered high risk and are linked to several types of cancer such as cervical, vulvar, penile, anal, and oropharyngeal cancers, and HPV 6 and 11 are associated with the development of genital warts.

ClinicalKey is a medical database own by publishing company Elsevier. Elsevier is a large publisher of medical textbooks and journals. It is a for profit company and the website charges to review. The information is not always well established and often time is only expert opinion. The information found on the ClinicalKey database is retrieved from Elsevier's full database of textbooks, journals, and videos. Due to the amount of information this data is found, there are very few limitations with this information.

Saraiya et al. (2015) conducted a study involving the CDC, partnered with seven US cancer registries in an attempt to determine the prevalence of HPV infection in cancers that are related to HPV infection, and to gauge the impact HPV vaccination could have in preventing certain cancers. HPV testing was performed on 2,670 tissue samples archived between the years of 1993 and 2005. The results reinforced the theory that certain cancers were related to or potentially caused by high risk HPV infection. Amongst the 2,670 samples of cancerous tissue analyzed in this study, HPV DNA was detected in 90.6% of cervical tissue, 91.1% of anal, 75.0% of vaginal, 70.1% of oropharyngeal (82% tonsillar, 70% base of tongue, 42.9% of other

oropharyngeal,) 68.8% of vulvar, 63.3% of penile, 32.0% of oral cavity, 20.9% of laryngeal cancers, as well as in 98.8% of cervical cancer in situ (CCIS).

The graph below represents the above-mentioned percentages of HPV positive results found in each of the 2,670 tissue samples in this study according to the site of cancer.



This study is a good representation of how often HPV DNA is found in certain types of cancers. This study states within the text that most of the statistics presented are consistent with HPV statistics worldwide. These results may be consistent with other studies in other countries, but this article is limited by numbers only evaluating 2,670 tissue samples. It is also limited in the fact that it was only samples gathered in the United States. Even with its limitations, this

study gives a good representation of how prevalent HPV infection is in regard to certain types of cancers, as well as which strains of HPV are likely to cause each type of cancer.

Theme 2: Evolution of HPV Vaccines

In 2015 Di Mario, et al. performed a systematic review of literature comparing the efficacy of HPV vaccines available at the time. Bivalent vaccine (Cervarix) and Quadrivalent vaccine (Gardasil) were the two vaccines that were compared. An extensive evaluation of the literature was performed involving the Cochrane Library, MEDLINE, and EMBASE. Three trials involving 20,797 women met the strict criteria for the review. All studies were double blind random controlled trials. This study shows possibly increased efficacy of the bivalent vaccine in preventing high risk HPV 16/18 which are highly related to cervical cancers. The quadrivalent vaccine showed slightly less efficacy for prevention of cervical cancer, but also had coverage against HPV 6/11 which are highly related to genital warts.

This article does a great job of explaining the differences between the two vaccines. The limitations with the material found in this article is similar to limitations in others that I have found. The study only consists of women of child bearing age, and the longest post vaccine serology for HPV antibodies are approximately four years. So, more long-term post vaccination serologies are necessary to test long term efficacy of HPV vaccination. This article further reinforces the importance of HPV vaccination and also illustrates where the data is lacking.

Between 2009 and 2013, Van Damme et al. conducted a study to evaluate the efficacy of the 9vHPV vaccine. A total of 3,074 subjects from 72 clinical sites throughout 17 countries were included in this study. Three separate cohorts were evaluated: girls 9 to 15 years of age, boys 9 to 15 years of age, and young women 16 to 26 years of age. All subjects were administered a 3-

dose regimen of the 9vHPV vaccine at day 1, month 2, and month 6. At month 7, all three cohorts displayed >99% seroconversion to all nine strains of HPV present in the 9vHPV vaccine (HPV 6/11/16/18/31/33/45/52/58).

The evidence found in this study clearly shows the effectiveness of the 9vHPV vaccine in producing antibodies of several high and low risk disease causing HPV infections. One of the strengths of this study is its broad evaluation of HPV in different countries, giving a more global perspective. As with most of the evidence I have found in my research, these vaccines are relatively new and long-term evaluation of seroconversion of HPV antibodies is needed.

Theme 3: Benefits of Vaccine in Males

In an article from (Palefsky, 2010), some of the cancers and other complications involving HPV infection in men are summarized. As stated in this article, it is well established that the most common cause of cancer related to HPV infection is cervical cancer, which is obviously only found in women. As of 2010, when this article was published, Cervical cancer was one of the leading causes of cancer-related mortality, responsible for 250,000 deaths globally each year. However, research has shown that high risk HPV infection can also manifest into several other types of cancers, such as penile in men, vaginal and vulvar in women, and anal or oral cancers in either sex. The incidence of anal and oral cancers related to HPV is increasing in the general population and is growing even faster among individuals who are immunocompromised due to other co-morbidities such as HIV infection. HPV penile infection of some type is very common among heterosexual men and remains high throughout a wide range of ages. Anal HPV infection and anal intraepithelial neoplasia are very common throughout a wide range of ages in both HIV-negative and HIV-positive men who have sex with men. The prevalence of anal intraepithelial neoplasia (AIN) among sexually active HIV-negative MSM

was shown to be high, with a range between 18% to 23% across various age groups. This rate was even higher in HIV-positive MSM, approximately 50%. The article also states that in developing countries incidences of cervical cancers are far more prevalent than other cancers caused by HPV due to lack of routine screening, but in the developed world where routine screenings are performed, rates of cancers in men related to HPV are estimated to be much closer to rates of cervical cancer caused by HPV.

Oral cancers and their relation to HPV are also discussed within this article. Although most oral cancers are associated with alcohol and tobacco use, a smaller percentage of oral cancers are associated with HPV and high-risk sexual behaviors associated with HPV acquisition, specifically oral sex. The incidence of oral and oropharyngeal cancers related to HPV is increasing in the general population in contrast to oral cancers associated with tobacco and alcohol use, which are declining. HPV related oral and oropharyngeal cancers effect both males and females equally.

This article also discusses male to female HPV transmission as an additional risk factor. It states that sexual transmission of HPV is a well-known fact and penile lesions are frequently found in sexual partners of women with cervical cancers related to HPV. According to this article, multiple studies from various countries have shown that sexual partners of women with cervical cancer or cervical carcinoma in situ have a higher prevalence of HPV than sexual partners of control women in the studies. In addition, the risk of cervical cancer was shown to be increased in this population if the male partners were admittedly engaging in high risk sexual behaviors, such as sexual experiences with multiple partners or contact with prostitutes.

Other risk factors related to HPV infection in males are briefly mentioned in this article as well. Genital warts, condylomata acuminate, is one of the complications discussed. These lesions are usually found on the penis or anus and are rarely carcinogenic; however, they are associated with psychosocial stigma, depression, and lower quality of life. The quadrivalent HPV vaccine has been shown to be highly efficacious in preventing HPV 6 and 11, which causes approximately 90% of genital warts. Treatment of genital warts often requires multiple treatments as well as multiple visits to a health care provider. Treatment may be costly, and warts may recur. The incidence of genital warts is high in the general population, with approximately one million new cases annually; the incidence of genital warts is increasing every year and, consequently, the economic burden is high.

Another serious consequence of oral HPV infection is recurrent respiratory papillomatosis (RRP), which is a rare disease with substantial morbidity that occurs in a bimodal pattern. In this condition, HPV infection occurs in the larynx and elsewhere in the upper respiratory tract. The resulting warts lead to morbidity through obstruction of the narrow-diameter respiratory passages. RRP first peaks in young children who acquire HPV 6 or 11 primarily through perinatal transmission. Male and female children are affected with equal frequency. Multiple surgeries are often required to relieve the obstruction. A second peak of RRP occurs in young adulthood, and HPV acquisition in this population is associated with sexual behaviors, particularly oral sex. In rare instances, laryngeal HPV infection may lead to laryngeal cancer.

Even though this article is a little older, it is a great illustration of the risk factors for men associated with HPV infection. Although very informative, this article is somewhat limited by

the fact that it has only one author, an author who receives grant/research support from Merck & Co., Inc., the company who manufactures the HPV vaccine "Gardasil."

Rodríguez-Álvarez, et al. (2018) performed a systematic review and meta-analysis of literature to determine the prevalence of and risk factors associated with HPV infection in male patients. Databases consulted for this meta-analysis include PubMed, Scopus, CINAHL, LILACS, Proquest Health and Medical Collection, Dialnet and SciELO. A sample of 16 studies and 18,106 male patients was evaluated. The meta-analysis revealed a prevalence of 49% of any type of human papillomavirus and 35% of high-risk human papillomavirus in all men within the studies reviewed. Risk factors discussed included sexual promiscuity, early sexual debut, absence of circumcision, and lack of condom use. The analysis revealed multiple studies that suggested later sexual initiation resulted in reduced rates of HPV infection. Studies also revealed that there is a significantly higher risk of HPV infection with increased number of lifetime female sexual partners. Various studies have also shown that circumcision is related to decreased rates of HPV infection. Evaluation of prevalence of HPV infection amongst uncircumcised men compared to circumcised men showed 46% vs. 29% for all HPV infections, 31% vs. 16% for infection due to high-risk HPV strains, and 31% vs. 12% risk for infection with multiple types of HPV infection. All higher percentages stated above represent uncircumcised men. One study showed a decreased prevalence of HPV infection due to consistent condom use. However, another showed a non-reduction of HPV prevalence, but is thought to be attributed to the detection of HPV DNA at sites not covered by condoms. Several studies have also discovered a correlation between increased HPV risk and tobacco use, with a stronger association observed in patients who smoke more than 10 cigarettes a day. This is thought to be due to the chemicals contained within cigarette smoke that can damage the genetic structure of human DNA.

Consequently, the studies included in this analysis show that stable sexual habits, circumcision, smoking cessation, vaccination, and maybe condom use are potentially protective factors against HPV infection for men.

This is a very strong article that is extremely relevant to this topic. It is the most recent article found, and the only meta-analysis regarding HPV specifically related to male patients. It is a good representation of how prevalent HPV is within the male population. It also does a good job of explaining risk factors associated with male infection of HPV, as well as possible methods of prevention. This study was somewhat limited by its small sample size of studies. The authors were independently funded and declare no conflicts of interest.

In 2015, Park, Introcaso, and Dunne published an article in the journal *Clinical Infectious Diseases* reviewing the current evidence at the time evaluating the most recent update the from the CDC regarding the treatment and prevention of sexually transmitted diseases related to HPV, primarily genital warts. A panel of 11 experts in HPV content was assembled to perform a systematic review of the literature. Six topics were discussed and researched: (1) epidemiology and burden of disease; (2) transmission and natural history; (3) diagnosis and management of anal genital warts (AGWs); (4) occupational exposure of healthcare workers; (5) anal cancer screening among men who have sex with men (MSM); and (6) HPV vaccine recommendations.

Global incidence of anal genital warts (AGWs) ranged from 160 to 289 cases per 100,000 but estimating this incidence rate accurately is difficult because AGWs is not a reportable condition. Based on estimates from a US health claims database, AGW incidence were almost identical amongst men and women, and rates were highest among women aged 20–24 and men aged 25–29.

Genital warts are commonly treated by a wide variety of practitioners in both hospital and outpatient settings with electrosurgical and laser procedures. There is minimal data to appropriately evaluate the risk of performing these types of procedures on patients diagnosed with HPV. Multiple studies mentioned in this article have documented the presence of intact HPV DNA in laser smoke plumes after treatment of genital and common warts with electrosurgical modalities. Two studies examining healthcare workers for HPV DNA contamination did not find evidence of facial/oral contamination after electrosurgical treatment of genital warts with use of proper personal protective equipment. Another small study found that 4 of 19 surgeons tested positive for HPV in their nasal passage after performing electrosurgical ablation of warts. There have also been two case reports of laryngeal papillomas in healthcare workers after treatment of patients with anogenital warts. Both cases revealed that the rooms the procedures were performed in did not have proper ventilation to evacuate the smoke from the laser, presumably resulting in HPV infection of healthcare workers due to occupational exposures.

This is a strong article explaining some of the other risks associated with HPV infection other than the most common cancers. Many studies were reviewed and analyzed to provide the most accurate, up to date information in order to reinforce new treatment and prevention guidelines for HPV infection. The authors reported no conflicts of interest.

Although HPV is known to be very common amongst the male population, certain male populations may have an increased risk for complication. Men who have sex with men (MSM) is one of these populations shown to be at increased risk. Several articles were evaluated to demonstrate this increased risk.

Cranston, et al. (2018) performed a study investigating anal HPV detection in MSM and transgender women. HIV negative, sexually active men with a mean age of 30.9 were enrolled in eight sites, four from the United States, two from Thailand, and one each from South Africa and Peru. Of 182 participants with results available, anal HPV infection was found in 169 samples (93%). Of these 169 positive samples, 132 (76%) were types potentially preventable by the none-valent HPV vaccine, with HPV 16 and HPV 6 being the most common found in the United States. This study is a small sample size, but it does demonstrate an apparent relationship between this population and an increased risk of high-risk HPV infection.

According to an article published by Giuliani et al. (2018) HIV-infected MSM show the highest prevalence of anal HPV infection. The study discussed in this article attempted to evaluate the potential efficacy of quadrivalent and nonvalent HPV vaccines in this population. The study enrolled 313 MSM, of the subjects 49.5 and 71.2% of the 313 enrolled MSM harbored at least one of the 4vHPV and 9vHPV types. What was more significant in this study was the fact that a significantly decreasing percentage of HPV infections was observed with patient's increasing age. Once again this is a very small sample size regarding this topic, but a good indicator of prevalence of HPV inoculation amongst MSM.

Theme 4: Adverse Effects

In September of 2015 Vichnin et al. (2015) published an article discussing the safety of the quadrivalent HPV vaccine observed in available studies between 2006 and 2015. More than 15 studies involving more than one million preadolescents, adolescents, and adults from various countries were evaluated. Only syncope and skin reactions/infections were caused by vaccine at increased rates. Syncopal episodes were observed at an increased rate for the first two years of

vaccine. As a result, a in the United States, a 15-minute observation period post-vaccination was implemented. This decreased the incidence of syncopal episodes post-vaccination. Skin reactions and infections are the most common adverse effect amongst all vaccines, and not a major concern. Serious adverse events, such as adverse pregnancy outcomes, autoimmune diseases (including Guillain-Barre Syndrome and multiple sclerosis), anaphylaxis, venous thromboembolism and stroke, were extensively studied, and no increase in the incidence of these events was found compared with background rates.

This is a very strong article involving a huge and diverse population throughout many countries. Though this article implies that there are very few severe adverse reactions associated with HPV vaccination, the need for long-term follow up studies is acknowledged.

More recently Genovese, La Fauci, A. Squeri, Trimarchi, and R. Squeri (2018) performed a meta-analysis involving six studies on bivalent and quadrivalent HPV vaccine. The total number of subjects included in the meta-analysis comprised 243,289 in the vaccine group and 248,820 in control groups. According to this meta-analysis there is no correlation identified between autoimmune disorders and HPV vaccination.

Contrarily, this article published by D. Geier and M. Geier (2017) determined that there was an apparent link between HPV vaccination and severe autoimmune adverse events (SAAE). An assessment of the vaccine adverse event reporting system database (VAERS) was undertaken for adverse event reports associated with vaccines administered from 2006 to 2014 to 6–39-year-old female recipients. This assessment examined 48,852 adverse event reports located in the VAERS database and determined that there was indeed a slightly increased risk of severe autoimmune adverse events associated with HPV vaccination. SAAEs observed included

gastroenteritis, rheumatoid arthritis, Guillain-barre syndrome, thrombocytopenia, systemic lupus erythematosus, vasculitis, alopecia, CNS demyelinating conditions, ovarian damage and irritable bowel syndrome. Of these, only Guillain-Barre syndrome was not with increased incidence after receiving HPV vaccination.

This article flawed because it only evaluates reports of SAAEs that are actually reported to the VAERS database, therefore, a true control group is not available. The VAERS database reporting is flawed because the reports of these conditions are not always confirmed. Also, only females were included in the evaluation and females are more likely to be diagnosed with autoimmune diseases.

In April 2018, Frisch et al. published an article evaluating a cohort study attempting to link HPV vaccination to different types of conditions including 39 different autoimmune diseases, neurological diseases and venous thromboembolism. The study was conducted in Denmark and evaluated 7,384 boys who received the quadrivalent HPV vaccine between the ages of 10 and 17. The study determined that rates of the diseases evaluated were similar to rates of diseases in the general population, and that HPV vaccination is unlikely to be associated with an elevated risk of autoimmune diseases, neurological diseases and venous thromboembolism.

This is a relatively strong study indicating that HPV is unlikely to be associated with risk of autoimmune diseases, neurological diseases and venous thromboembolism. The study is limited by the inclusion of only males of a certain age, and by only being conducted in a single country. Though this study is suggestive of this conclusion, the authors do acknowledge that further large-scale investigation is warranted.

Theme 5: Can improving patient education regarding HPV vaccination lead to improved acceptance of HPV vaccines?

Despite recent evidence of the benefits of HPV vaccination in children, national vaccination rates remain low. Parental hesitancy is believed to one of the contributing factors. In 2017, Van Wormer et al. conducted a survey study to determine completion rates of 3 shot HPV vaccine series. Out of 1,998 surveys mailed, only 221 parents completed a baseline survey, and of that only 164 were available for one-year follow-up data. Of those 164 children, only 60% received the second dose of the vaccine, and only 38% received the full three shot series. Of the patients who received the full series, a reduction in the parent's uncertainties regarding adverse effects of the HPV vaccine seemed to lead to a greater likelihood of children receiving the full vaccine series.

The article and study described above are a good illustration of patient hesitancy in receiving the fully recommended regimen for HPV vaccination. Due to its very small sample size, its subjective nature, as well as simply the fact that it is a survey-based study, it is a rather low powered example of the problem at hand. With that being said, I believe it is a good representation of one of the bigger problems facing compliance of parents for their children to receive recommended vaccination of HPV.

In 2018 Beavis, Krakow, Levinson, and Rositch conducted a study to determine the what factors most heavily influence parent's decisions to vaccinate their children against HPV. This study used the 2010–2016 National Immunization Survey – Teen (NIS-Teen), annual vaccine monitoring surveys conducted by the Centers for Disease Control and Prevention to evaluate these reasons. Among parents of males, the most common reasons for lack of vaccination in

2010 all decreased marginally over time. These reasons include, perceived lack of necessity (24% in 2010 vs. 22% in 2016), lack of recommendation (22% vs. 17%), lack of knowledge (16 vs. 14%), child's lack of sexual activity (16% vs. 9%), and male gender (13% vs. 2%). Concerns about vaccine safety and side effects increased from 5% to 14% in 2016. Notably, in 2016, parents of females were more likely to report concerns about safety compared to males (22% vs. 14%); parents of males more often reported lack of recommendation (17% vs. 10% for females). Among both genders, the reason “not a school requirement” increased a small but in a significant amount, 1% in 2010 to 4% in 2016. Antivaccination attitudes, lack of medical provider, and concern that vaccination would promote sexual activity were consistently reported by fewer than 2% of parents every year.

In 2017 Cipriano, Scoloveno, and Kelly conducted a small study in a single pediatric office in New Jersey. A simple pre/postintervention study was conducted where an electronic tablet was given to parents with an educational tutorial regarding the risk factors of HPV. An easy to understand PowerPoint presentation was presented to the parents in a fashion to decrease the amount of medical terminology and present it in a more easily understandable fashion. The study indicated that increases in education about HPV and safety of HPV vaccine significantly increased parent cooperation regards to receiving HPV vaccination.

Once again this is a very low powered study because of the sample size, but I believe it is relevant due to the fact of its principle. Evidence based parent education can be pivotal in the effort to increase HPV vaccination rates in the United States, especially in young males.

Discussion

Infection due to Human Papilloma Virus remains an extremely common infection found in the United States and around the world. It is the most common sexually transmitted infection

in the United States. HPV is a group of more than 120-150 different strains of virus that affect epithelial tissue. Most strains affect outer epithelial tissue, result in no disease process, and is eliminated by immunocompetent people rather easily. However; strains of HPV that affect mucosal tissue can be more virulent and are classified as low or high risk. Low risk HPV such as HPV 6 or 11 can result in genital warts, while high risk HPV strains such as HPV 16 or 18 can be directly linked to different types of cancer involving mucosal tissue. According to one article, it is estimated that in the United States alone, 14 million persons are infected with HPV annually, and 79 million persons have prevalent infection. This article also states that data retrieved from the Surveillance Epidemiology and End Results and National Program of Cancer Registries estimates that 34,788 new HPV-associated cancers occurred in the United States in 2009. The overall annual direct medical costs for HPV-associated diseases in the United States are an estimated $8 billion US dollars, including $6.6 billion (82.3%) for routine cervical cancer screening and follow-up, $1.0 billion (12.0%) for cancer treatment, $300 million (3.6%) for anal-genital warts (AGW) treatment, and $200 million (2.1%) for recurrent respiratory papillomatosis treatment. (Park, Introcaso, and Dunne, 2015) The impact of a vaccine that could potentially prevent numerous types of these cancers seems as if it would be an easy decision for a parent to make. Instead this vaccine is met by a public stigma of being directly for sexually transmitted infections. There are also countless reports of unverified information across the internet and social media regarding severe adverse effects has led to less than expected vaccination rates. Additionally studies show another substantial barrier for HPV vaccination is the lack of knowledge regarding the vaccines. Since the initial release of the first HPV vaccine in 2006, the vaccine (Gardasil) has been updated to prevent 9 of the more virulent strains of HPV rather than 4 which is what the initial vaccine prevented. Another vaccination option is the bivalent HPV

vaccine (Cervarix) which only prevents the high-risk HPV strains 16 and 18, however it may be more effective in preventing cancers related to these specific HPV strains. Though the bivalent vaccine may be slightly more efficacious, studies have shown to have greater than 90% success rates in seroconversion of antibodies that prevent HPV in both available vaccines. Despite this evidence, the CDC reports that vaccination rates for HPV are significantly lower when compared to other vaccines recommended for adolescent children. According to the CDC, only 49% of adolescents between the ages of 13 and 17 were up to date with their HPV vaccination schedule. This is well short of the goal of 80% vaccination amongst this age group. (Centers for Disease Control and Prevention, 2016)

Increasingly alarming to the information above is the fact that male vaccination rates are even lower than the already low rates in female patients. Cervical cancer being directly related to HPV infection seems to be universally more accepted by the general population when compared to other cancers being directly related to HPV. Penile, anal, oral, and oropharyngeal cancers can all be related to HPV and vaccination can potentially prevent a significant percentage of these cancers in males if received. Despite this proven fact, many parents are still hesitant to allow their adolescent male children to receive vaccination for HPV. Some parents assume that since HPV is a sexually transmitted disease it is not helpful for their child if he/she is not sexually active, and this is simply not the case. In reality, the vaccine becomes much less effective if a person has already been exposed to HPV, which is highly likely in sexually active persons, especially if sexual activity is initiated at a young age. Studies have shown the best seroconversion rates are among adolescents between 11 and 16 years of age and before first sexual encounter. Another aspect to take into consideration is the increased infection rates amongst the homosexual male community. Men who have sex with other men are much more

likely to be infected by high risk HPV strains, and therefore at an increased risk for cancers associated with HPV. Vaccination for male patients at the recommended age is important to support seroconversion before his first sexual encounter, whether it be with a female or another male.

Another obstacle preventing many people from receiving vaccination against HPV is the fear of severe adverse side effects. With the sensationalistic tendencies of our society today, specifically with the internet and social media, information can be hard to differentiate as fact or rumor. Reports of autoimmune diseases, neurological diseases, and other severe conditions have been spread across the internet over the past few years, yet despite the amount of fear shown by many patients and parents, there is minimal evidence to support any of these reports. The majority of the studies and articles I have found during my research suggests that there is no obvious correlation between HPV vaccination and these adverse side effects. However, I have found a small number of articles that did suggest there were increased occurrences of autoimmune diseases reported after receiving HPV vaccination. The article with the most evidence to support this was somewhat flawed because it was an evaluation of the VAERS reporting system. The most recent safety update regarding HPV vaccines reported by the World Health Organization (WHO) addresses the accusations of the HPV vaccination and its many reported adverse reactions. Anaphylaxis and syncope were initially the first two reactions to be investigated. Anaphylaxis was determined to occur at 1.7 cases per million doses. Syncope was established as a common anxiety or stress-related reaction to the injection. Amongst the new most recent studies looking at Guillain-Barré syndrome (GBS) specifically, a population of millions of doses of the vaccine administered both in the UK and US was observed. Based on their respective data, a risk of >1 case of GBS per million doses of vaccine could now be

excluded. Therefore, this most recent study found no significant increased risk for GBS after any dose of vaccine. These studies also included examination of specific outcomes that included complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), premature ovarian insufficiency, primary ovarian failure, and a further look at the risk of venous thromboembolism. As with GBS, no apparent association was discovered between HPV vaccination and the above-mentioned conditions within these most recent large-scale studies. (World Health Organization, 2017) The one common consensus among all articles I have found is the extreme importance of continued research. Even though these vaccines are well researched, they are still rather new vaccines, and the need for evaluation of long-term follow up and side effects is of the utmost importance.

With the amount of fear and unverified information regarding vaccines in today's society, it is becoming more and more important for people to be given science-based evidence regarding vaccines. Feelings of a lack of necessity in adolescent males and a lack of knowledge regarding HPV vaccination and infection are the two common barriers preventing target vaccination rates in adolescent male patients. It is the responsibility of a healthcare provider to provide his/her patients with the most up to date, significant evidence regarding all vaccinations. It is imperative for patients, or parents of patients, to be given all the facts regarding HPV vaccination. Only then can they be capable of making an informed, responsible decision. The smaller studies I've demonstrated have shown that it may not be as difficult as one would think to properly educate parents about HPV and HPV vaccination.

Although much of the research reported in this project shows great evidence towards prevention of HPV related cancers and sexually transmitted infections, there is one major flaw amongst most of the research. With the HPV vaccine only being FDA approved for the past 12

years, there is an imperative need for long term follow up. Long term side effects as well as prolonged seroconversion must be evaluated to truly gauge the efficacy, safety, and impact HPV vaccination will truly have.

Application to Clinical Practice

This scholarly project was intended to inform and educate parents and clinicians of the importance of HPV vaccination in adolescent male patients, distinguish fact from fiction regarding adverse reactions caused by HPV vaccination, and to identify barriers causing skepticism and hesitancy in receiving HPV vaccination. With society's growing concerns regarding vaccinations, it is increasingly important to inform patients with the most accurate and up to date information about vaccines. HPV is proven to be related to several types of cancer, therefore in essence, vaccination for HPV is indirectly a vaccination against cancer. Despite this fact, vaccination rates remain low. With increasing education about HPV and HPV vaccination, we can potentially improve these vaccination rates and in doing so, decrease rates of HPV related cancers. Hopefully the information provided in scholarly project will aid clinicians to provide patients and parents with the necessary information to make informed decisions on whether to vaccinate their children against Human Papilloma Virus.

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