REVIEW ARTICLE

Preventing Cancer with Two Injections, A Clinical Review of the HPV Vaccination

Gerald Julian, OMS II[1]; David Go, OMS II[2]; Jay H. Shubrook, DO, FACOFP[2]

[1]Ohio University Heritage College of Osteopathic Medicine
[2]Touro University California College of Osteopathic Medicine

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ABSTRACT: Human Papilloma Virus (HPV) has become a major public health concern in the United States. HPV has high subclinical infection rates and is a major cause of preventable cancers (cervical, vaginal, vulvar, anal, penile, and oropharyngeal).[1,2] Despite availability of an effective vaccine against several common and carcinogenic strains of HPV, it remains the most common STI.[2] Gardasil 9 is a widely available vaccine that protects against nine strains of HPV. Seven of those strains are known to cause a wide range of cancer, and the other two strains are the most common cause of condylomas (genital warts).[3] Yet, patients are not completing this vaccination series. There are a constellation of reasons for this, including failure of the provider to offer it to patients and patient refusal.4 Either way this easy public health intervention is significantly underutilized. This review explores the infection process of HPV; its link to cancer; a comparison of vaccines offered in the past, such as Cervarix and Gardasil 4, compared to the currently offered Gardasil 9; and finally, an exploration of the beliefs and views around vaccination of the STI and cancer by looking at patient/physician stances against the vaccine tied with the ways to help patient compliance.

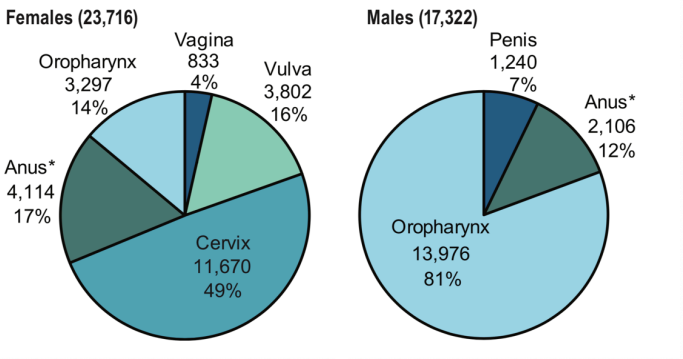
INTRODUCTION

Human Papillomavirus (HPV) is the most common sexually transmitted infection (STI) worldwide, and it is causative of some of the most common cancers, including cervical, oropharyngeal, anal, penile, and others. The cancers linked to HPV and the rate at which they occur are shown in *Figure 1*.[1,2] HPV has become so common it is estimated that every non-vaccinated, sexually-active person will have been infected at some point in their life.[2,3] Nearly half of US adults 18-59 years old during 2013-2014 were actively infected.[2,5]

There are over 150 types of HPV, but not all strains carry the same risk of significant infection. HPV is a nonenveloped, double-stranded circular DNA virus of the papillomavirus family.[6] Forty of the 150+ strains are associated with infections of the genital tract. Specifically, HPV 6 and 11 cause approximately 90% of HPV-associated genital warts and can cause infection in the respiratory tract, conjunctiva, and oral cavity.[6] HPV 6 and 11 can cause malignancy of the respiratory tract. HPV 16 and 18 cause about two thirds of cervical cancers.[2] HPV 16 is strongly associated with penile cancer and oral cavity infection.[6] The lesions are referred to as warts when on the skin and condylomas on mucosal surfaces. Transmission rates are relatively high, with condylomas developing in about two thirds of sexual partners of a person with a condyloma.[6] There are several typical courses for an HPV infection: the infection may resolve spontaneously without symptoms, resolve with symptoms, persist without pre-cancerous dysplasia, or become pre-cancerous.[5]

FIGURE 1:

Number of new HPV-related cancers from 2010-2014.
Source: CDC, Data Brief Cancers associated with HPV[7]



CORRESPONDENCE:
Jay H. Shubrook, DO, FACOFP | Jay.Shubrook@tu.edu

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PATHOGENESIS AND CLINICAL PRESENTATION

Infection with any HPV strain requires skin-to-skin contact. Skin condition/integrity also plays a role in risk of infection. During intercourse the epithelium and mucosal membranes may be damaged by disruption of the cellular tight-junctions, exposing the basal layer of cells. It is believed the micro-trauma of intercourse increases the susceptibility of developing chronic HPV infection (and other STI's).[6] Clinically, exposure can be hard to determine as the incubation period of this virus may be weeks to months. This also makes tracking the source of infection harder in those with multiple sexual partners. After incubation, HPV warts/condylomas may show persistence, latency, and some people may never show symptoms and go directly to latency.[6] Latency is believed to be achieved when there is damage to the epithelial barrier; the virus bypasses the non-dividing, protective cells and gains access to the basal, dividing cells. Infection can persist longer and potentially indefinitely in these stem cells. The infection is capable of remaining subclinical in latency or persistent as a condyloma.[6] Thus, during intercourse there is a higher risk of epithelial damage which in turn leads to a stronger chance of HPV infection. Risk of infection with an anogenital strain of HPV is very much like the risk-profile for other STI's; increased with lifetime number of partners, partner's lifetime number of partners, condom use, alcohol use, illicit drug use, being under 25 and condom use.[3]

All viral STI rates have been on the rise since the 1960's, with HPV showing a steeper increase than others.[8] Incidence of condyloma-related-visits in a study from Minnesota rose from 13 per 100,000 to 106 per 100,000.[9] This is in contrast to bacterial STI rates, which have been on the decline since 1980.[8] This stark increase in HPV prevalence is very concerning. The prevention of this disease must be a high priority because cervical cancer is the most common cancer in women in developing countries.[4] In the US there are about 15,000 newly diagnosed cases of cervical cancer each year, and about one third will die.[6]

Diagnosis of HPV infection is typically made by clinical presentation confirmed with a few subsequent tests, such as pap testing and PCR analysis. When a patient presents with a non-genital wart, diagnosis can be made upon physical exam with visual inspection. Laboratory methods are then used for testing a suspected condyloma. The procedures and recommendations are thoroughly explained for all age groups in the "Updated Consensus Guidelines for Managing Abnormal Cervical Cancer Screening Tests and Cancer Precursors."[10] The guidelines for women 30 and over are summarized in *Table 1* from the CDC.

Cells obtained from the cervix may be stained by Papanicolaou staining (Pap smear/Pap test). Infection is shown by the presence of koilocytosis, a condensed nucleus with a prominent perinuclear clear zone.[6] Cervical and other samples may also be analyzed by PCR and a hybrid capture assay. These additional tests are useful for typing the HPV infection and may dictate best management for the patient but must be considered case-by-case.[6] The hybridization assays are less sensitive than PCR for viral detection but may give additional insight to the potential for malignancy. Squamous cell carcinomas make up about 85% of the malignancy while most other cases are adenocarcinomas, and very few are neuroendocrine small cell tumors.[6]

HPV SCREENING RECOMMENDATIONS

Screening for condylomas and nonvisible/asymptomatic infection by pelvic exam and pap smear should be completed routinely in at-risk groups. Routine pap tests should begin for all women aged 21 years.[11] From age 21-30 women should be screened every 3 years by pap smear alone and at age 30-65 should receive cytology and HPV co-testing every 5 years.[11] After age 65, if the women has had 3 consecutive negative pap tests or 10 years of negative HPV co-tests with the most recent being negative, screening may be discontinued in the absence of high risk behavior.[11] High risk behavior are those outlined as the risk profile for STIs.

TABLE 1 :

Summary of Cervical Cancer Screening Results and Management for Women 30 Years of Age or Older

Test Results	What to Do Next
Normal Pap and Negative HPV	**Rescreen in 5 Years.**
Normal Pap and Positive HPV	**Repeat co-test in one year or do HPV DNA typing now (ASCCP guidelines).**
ASCUS Pap, No HPV Test	**Repeat cytology in one year or do HPV test now (see ASCCP guidelines).**
ASCUS Pap and Negative HPV **LSIL Pap and Negative HPV**	**Repeat Pap and co-test at interval as per ASCCP guidelines.**
ASCUS Pap and Positive HPV **LSIL Pap and Positive or Unknown HPV** **ASC-H Pap** **HSIL Pap**	**Colposcopy and/or referral to gynecologist.**

VACCINATION

HPV is largely preventable via the vaccine, but implementation of the vaccination is currently less than satisfactory. With the rising rates of HPV infection the need for vaccination programs is critical. A multiprong approach is needed to change the course of this disease. Education on effective condom use is becoming more often utilized and may help to reduce spread, but more can be done. Vaccination against an infection that is known to commonly progress to cancer seems like an excellent solution.

The L1 major capsid protein of HPV is capable of reassembly without the minor capsid protein L2 to create an immunogenic structure closely mimicking the natural HPV epitopes.[12] L1 reassembly product is then used to create viable vaccines against HPV capable of generating robust IgG responses. All three FDA approved vaccines are recombinant non-living vaccines.[13]

Originally the quadrivalent vaccine, Gardasil, was approved in 2006. A bivalent vaccine, Cervarix, was released in October of 2009. Cervarix and Gardasil were recommended only for girls and women (9-26 years old) upon the initial release of each.[13] Both vaccines have been taken off the market since introduction of the newer nine-valent vaccine (9vHPV, Gardasil 9) was adopted. The vaccines previously available summarized in *Table 2*.

Currently, vaccination with Gardasil 9 is recommended for boys and girls starting at 11 years old, but is approved for use at nine years old. The increased coverage of 9vHPV have made older versions of the vaccine obsolete leading to sales/production to cease. The new 9vHPV protects against 9 strains of HPV; HPV 16, 18, 31, 33, 45, 52, and 58 that can cause cancer (cervical, vaginal, vulvar, anal, penile, and oropharyngeal) and HPV 6 and 11 that cause about 90% of HPV-condylomas.[3,14] The vaccine may be given to women while breastfeeding, but should be avoided in pregnancy.[3]

The recommended vaccination schedule for Gardasil 9 can be completed in a two or three-dose regimen. The two-dose regimen is recommended for girls and boys nine to 14 years old at an interval of time 0 months for the first dose and 6-12 months for the second dose. The three-dose regimen may be used for anyone nine to 26 years old at an interval of time 0 months for the first dose, two months for the second dose, and six months for the third and final dose. Each dose is a 0.5 mL suspension administered intramuscularly. If the second dose of the two-dose schedule is given before five months, the schedule should be adjusted to the three-dose regimen, with the final dose at least four months after the second.[3]

The vaccine has had a very strong and positive impact countering the continued rise of HPV infection. Vaccinated women, compared to their unvaccinated counterparts, showed a significant decrease in HPV prevalence since introduction of the first vaccine.[15] In the past decade since the 4 valent HPV vaccine introduction there was a nearly 83% decline in HPV infection (34.8% to 6%, OR .12, 95% CI .07–.20), and a 72% decline in HPV prevalence with the 9-valent vaccine (46.4% to 13.1%, OR .17, 95% CI .12–.26). The remaining 5 additional HPV types included in the 9-valent vaccine decreased from 67%. (23.5% to 7.7%, OR .27, 95% CI .16–.44).[15] In comparison, there was no notable change in the prevalence for unvaccinated women.[15]

The continued use of a readily available vaccine with insurance coverage can greatly reduce the prevalence of genital cancer for men and women of all ages. However, just starting on the vaccination schedule does not guarantee full adherence to the regimen and therefore not full protection. This is the second area of concern. In 2016, only 60% of teens aged 13-17 received one or more doses of HPV vaccine, and many in that population are not completing the vaccination series. Only 49% of teens are up to date on all the recommended doses of HPV vaccine.[16] This is in strong contrast to other vaccines series, as shown in *Figure 2*.

FIGURE 2 :

Vaccination completion rates for regularly recommended vaccines in the US.
Source: CDC Fast Stats[17]

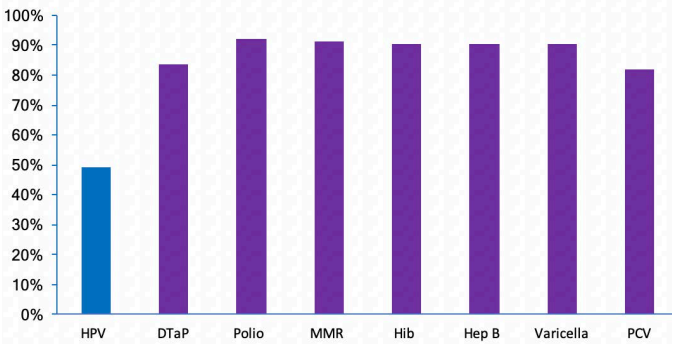

TABLE 2 :

Different versions of the HPV vaccine no longer on the market.

Vaccine	Approval	Coverage	Recommendation	Discontinued
Cervarix	October 2009	HPV 16,18	Females 9-26	October 2016
Gardasil (4, Female)	June 2006	HPV 6, 11, 16, 18	Females 9-26	May 2017
Gardasil (4, Male)	October 2009	HPV 6, 11, 16, 18	Males 9-26	May 2017

REASONS FOR OPPOSITION TO VACCINATION AND COUNTER-ARGUMENTS

Even though there is convincing evidence demonstrating the HPV vaccine's effectiveness at decreasing the risk for certain cancers, firm opposition from some politicians, parents, and healthcare providers remains.

What separates the HPV vaccine from other mandated childhood vaccines is that it prevents an infection that is only sexually transmitted and not spread by casual contact in other settings.[18,19] This difference in transmission has ignited deep-rooted controversies regarding adolescent sexuality.[20] Some politicians have labeled the HPV vaccine as "the promiscuity vaccine" arguing that it confers implicit approval to engage in sex while also giving a false sense of security against STIs.[19,20] These sexual disinhibition arguments are based on the assumption that the vaccine will change current behaviors. However, fear of HPV has not historically deterred teens from engaging in sexual activity.[19] Other evidence that indicates that sexual disinhibition is unlikely includes research on sexual education and condom distribution programs at schools which have not led to increased sexual behavior among high school students.[21]

Parents who oppose HPV vaccination argue that mandating vaccination at the early age of 11 or 12 years will undermine abstinence only messages or force them to discuss sex with their children prematurely.[18] In response, Gardasil 9 manufacturer Merck has recommended providers to center their message on prevention of cancer, rather than an STI in order to deemphasize the sexual ties of the vaccine. Framing the vaccine in a culturally acceptable way is critical for public acceptance and raising vaccination rates.[20] Therefore, providers can counsel conservative parents that there is no need to mention the sexually transmitted nature of the infection if they don't feel comfortable discussing it with their children. Parents can instead focus on the cancer preventing aspects of the vaccine.

In addition to parents, there are also healthcare providers who oppose the HPV vaccination due to their religious views on sexuality. In a survey of 1,144 practicing U.S. physicians, 63% said it would be ethical for morally conflicted doctors to explain their objections to their patients. Only 86% felt obliged to present all medical options and only 71% would refer the patient to another provider who does not object.[22] This raises the question, does a provider's beliefs take priority over a patient's health? The authors believe that all women and men have a right to information about the vaccine whether or not their provider opposes a vaccine. They should not have to miss the chance of taking advantage of this medical milestone due to a provider's beliefs. Therefore those providers who personally do not support the use of this vaccine should still present information about the HPV vaccine, but share that they are not comfortable administering it because of their values and refer their patient to another clinician. This will allow the provider to uphold their personal morals while still fully caring for the patient.

Since the HPV vaccine was introduced in 2006, some clinicians have opposed mandating the vaccine due to its relative newness compared to other childhood vaccines. The long term side effects of the HPV vaccine and length of protection are currently unknown.[19] Yet, according to the CDC with over 100 million doses distributed in the United States, the HPV vaccine has a reassuring safety record that's backed by 10 years of monitoring and research. Current studies suggest vaccine protection is long-lasting and that there is no evidence of weakened protection over time.[23]

With the safety of this vaccine established, it should be asked, at what age should children receive the vaccine? One study found that Gardasil was 99% effective in preventing cervical cancer and pre-cancerous lesions in women who never had vaginal sex but only 44% effective in sexually experienced women who may have potentially already been exposed to HPV.[20] Based on this evidence it is critical to vaccinate children prior to them becoming sexually active which is why the CDC recommends completion of the vaccination series by the age of 11-12. The vaccine series can even be started as early as age 9 based on FDA approval.[23]

HOW TO INCREASE VACCINATION RATES

Osteopathic Family Physicians are the gatekeepers to vaccine usage and are essential to increasing adolescent HPV vaccination rates and potentially reducing preventable cancers. There are many strategies to accomplish this. Providers can create a culture of immunization in their office by training all office staff on how to explain the importance of the HPV vaccine.[24] In addition, offices can also use an EHR-based alert system for when vaccinations are due. One randomized trial focusing on physicians examined the use of EHR-based alerts and showed an increase in timeliness of the HPV vaccination by 27% while another study showed an 8% increase in vaccination initiation.[25,26] Providers can also recommend the HPV vaccine and other vaccines at all visit types or can combine the recommendation with other scheduled adolescent vaccines instead of proposing the vaccine individually.[24] In response to patients who ask if the vaccine is required, providers should strongly endorse the vaccine by emphasizing its protective effects and discussing possible negative outcomes if vaccination is missed including risk of numerous preventable cancers. If the patient is hesitant, the provider can offer educational materials and make a note to ask the patient again at the next visit as timeliness of the HPV vaccination is critical for effectiveness. After the patient receives their first dose, they should be promptly scheduled for their next appointment during the current visit to ensure completion of the series. Office staff can also provide patients with reminder calls or letters for their upcoming appointments. One study showed that using these two types of reminders increased HPV vaccination rates by 27%.[27]

Federal and state governments can also play a role in boosting immunization rates through legislation and funding. Since 2006, 42 states have introduced some type of legislation to either require the HPV vaccine, fund the vaccine, or educate the public about the vaccine.[28] There is a growing push for mandating HPV vaccination, however opposition remains firm as only three states including Rhode Island, Virginia, and District of Columbia currently require the HPV vaccine series for public school attendance.[28] Hawaii has approved the mandate and will begin implementation in 2020.

Virginia and District of Columbia both enacted the mandate in 2007, but only required the vaccine for girls. Rhode Island enacted the requirement in 2015 and made the requirement for both girls and boys.[28] In 2007 the Texas governor mandated all female 6th graders receive the vaccine via executive order. However, legislators later overrode the order.[28] As of May 2018, New York is the only state that currently has pending legislation to mandate the HPV vaccine for school attendance.[28]

CONCLUSION

According to the CDC, without the HPV vaccination 80% of sexually active people will get an HPV infection in their lifetime without the HPV vaccination.[29] It is known that HPV can cause numerous cancers in women and men. Though the current HPV vaccines do not provide protection against every strain of HPV, it has decreased infections with the HPV types that cause most HPV cancers and genital warts by 71%.[29] Despite the availability of an effective HPV vaccine, there are still 32,000 new cases of HPV related cancers (cervical, vaginal, vulvar, anal, penile, and oropharyngeal) every year in the U.S. Because preventing cancer is more effective than treating it, it is critical to start the vaccine at the CDC recommended age.[29] The intense controversy surrounding government mandated HPV vaccination for school entry has unfortunately shifted the focus away from the demonstrated benefits of HPV vaccination.[19] Providers can bring the focus back by continuing to educate patients and parents about the magnitude of what the HPV vaccine can do regardless of its associated controversies.

AUTHOR DISCLOSURES:
The authors have no financial disclosures or conflicts of interest.

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