Human Papillomavirus (HPV) Vaccine

- Clinical Policy Bulletins
- Medical Clinical Policy Bulletins

Number: 0726

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Policy

Scope of Policy

This Clinical Policy Bulletin addresses human papillomavirus (HPV) vaccine.

1. **Medical Necessity**

    1. Aetna considers human papillomavirus (HPV) 9-valent vaccine (Gardasil 9) a medically necessary preventive service for persons age 9 to 45 years.
    2. Aetna considers Gardasil 9 vaccination not medically necessary for persons who have completed a three-dose series with Gardasil or Cervarix. If vaccination providers do not know or do not have available the HPV vaccine product previously administered, or are in settings transitioning to Gardasil 9, then Gardasil 9 HPV vaccine product is considered medically necessary to continue or complete the three-dose series.

2. **Experimental, Investigational, or Unproven**

    Aetna considers Gardasil 9 experimental, investigational, or unproven for the following indications (not an all-inclusive list) because their effectiveness for indications other than ones listed in Section I (above) have not been established:

    1. Anal squamous cell carcinoma
    2. Benign squamous papilloma
    3. High-grade anal dysplasia
    4. Post-treatment HPV vaccination as adjunctive treatment of women undergoing excision of cervical intraepithelial neoplasia
    5. Prevention of recurrence of anogenital warts
    6. Treatment of active genital warts; cervical, vulvar, and vaginal cancers
    7. Use of human papillomavirus vaccine as adjuvant therapy for juvenile-onset recurrent respiratory papillomatosis.

3. **Policy Limitations and Exclusions**

    1. Not all plans provide coverage of preventive services. Please check benefit plan descriptions for details.
    2. Bivalent Cervarix and quadrivalent Gardasil are no longer being distributed in the United States.

4. **Related Policies**

    - CPB 0443 - Cervical Cancer Screening and Diagnosis

CPT Codes / HCPCS Codes / ICD-10 Codes

CPT codes covered if selection criteria are met:

Code	Code Description
90651	Human Papillomavirus vaccine types 6, 11, 16, 18, 31, 33, 45, 52, 58, nonavalent (9vHPV), 3 dose schedule, for intramuscular use

CPT codes not covered for indications listed in the CPB:

90649	Human Papillomavirus vaccine, types 6, 11, 16, 18, quadrivalent (4vHPV), 3 dose schedule, for intramuscular use
90650	Human papillomavirus vaccine, types 16, 18, bivalent (2vHPV), 3 dose schedule, for intramuscular use

Other CPT codes related to the CPB:

90471	Immunization administration (includes percutaneous, intradermal, subcutaneous, or intramuscular injections); one vaccine (single or combination vaccine/toxoid)
90472	each additional vaccine (single or combination vaccine/toxoid) (List separately in addition to code for primary procedure)

Other HCPCS codes related to the CPB:

D1781	Vaccine administration – human papillomavirus – Dose 1
D1782	Vaccine administration – human papillomavirus – Dose 2
D1783	Vaccine administration – human papillomavirus – Dose 3

ICD-10 codes not covered for indications listed in the CPB:

A63.0	Anogenital (venereal) warts
C44.520	Squamous cell carcinoma of anal skin
C51.0 - C53.9	Malignant neoplasm of vulva, vagina and cervix uteri
D06.0 - D07.2	Carcinoma in situ of cervix uteri, vulva and vagina
D10.0 - D10.9	Benign neoplasm of mouth and pharynx [benign squamous papilloma]
D14.1	Benign neoplasm of larynx [benign squamous papilloma][Juvenile-onset recurrent respiratory papillomatosis]
K62.82	Dysplasia of anus
N87.0 - N87.9	Dysplasia of cervix uteri

Background

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the United States which, in some individuals, can lead to certain types of cancer. According to the Centers for Disease Control and Prevention (CDC), every year about 14 million Americans become infected with HPV, which is spread through genital contact (vaginal, anal, or oral sex) with someone who has the virus and may not be aware of it. Sexually active adolescents are at particularly high-risk for HPV infection. Although most HPV infections will resolve on its own, for some the infection can last longer than 2 years and over time, may develop into cancer, such as cancer of the cervix, vagina and vulva in women, penile cancer in men, and cancer of the anus and oropharynx for both women and men. Per the CDC, HPV causes 33,700 cases of cancer each year in the United States, with cervical cancer being the most common cancer among women, and oropharyngeal cancer the most common among men (CDC, 2018; CDC, 2019). Studies show that HPV vaccinations are safe and highly effective in preventing a lasting infection, reducing precancerous lesions and leading to fewer cancers caused by the HPV infection (ASCO, 2019).

There are over a 100 different types of HPV, with most men and women having no symptoms or health problems to indicate when they have HPV. Although not all HPV infections will cause cancer, some low-risk HPV types (e.g., HPV-6 or HPV-11) can cause papillomas, or genital warts, a common benign condition that causes significant morbidity. The high-risk types, such as HPV 16 and 18, can develop into cancer over time. Cervical cancer, a major health problem for women, is causally associated with 14 high-risk types of HPV (Williamson et al, 2005). The American Cancer Society estimates the annual incidence of cervical cancer in the U.S. to be approximately 13,170 new cases and predicts 4,250 will die from the disease in 2019. The 5-year survival rate for all women with cervical cancer is 66%; however, when detected at an early stage, the overall 5 year survival rate for invasive cervical cancer is about 92 % (Cancer.net, 2019). Per the CDC, HPV is thought to be responsible for more than 90% of anal and cervical cancers, about 70% of vaginal and vulvar cancers, and more than 60% of penile cancers. Oropharyngeal cancers traditionally have been caused by tobacco and alcohol; however, studies now show that about 70% of cancers of the oropharynx may be linked to HPV. Many cancers of the oropharynx may be caused by a combination of tobacco, alcohol, and HPV (CDC, 2018).

There is no treatment for the virus itself. HPV management consists of screening, monitoring, and if medically feasible, the removal of warts, lesions, or cancerous tissue via chemical or surgical procedures. Currently, there is no cure for HPV; however, protection with vaccination is now readily available in the United States. Gardasil 9 (9vHPV, Merck) is the only HPV vaccine being distributed in the U.S. to prevent certain types of HPV infection. Bivalent Cervarix (2vHPV, GlaxoSmithKline) and quadrivalent Gardasil (4vHPV, Merck) are no longer being distributed in the United States. Gardasil 9 offers protection against 7 oncogenic (cancer-causing) HPV types (16, 18, 31, 33, 45, 52 and 58) and two HPV types that cause most genital warts (6 and 11) (Immunication Action Coalition, 2019).

Most cervical cancers are squamous cell carcinomas (Castellsague et al, 2006). Although the incidence of cervical squamous cell carcinomas has decreased, that of cervical adenocarcinoma has increased in recent years. The extent to which HPV infection and co-factors may explain this differential trend is unclear. Castellsague et al (2006) found that HPV16 and HPV18 were the 2 most commonly detected HPV types in patients with invasive cervical adenocarcinoma and control subjects. These 2 HPV types were present in 82 % of the patients. Co-factors that showed clear statistically significant positive associations with cervical adenocarcinoma overall and among HPV-positive women included never schooling, poor hygiene, sexual behavior-related variables, long-term use of hormonal contraception, high parity, as well as herpes simplex virus-2 sero-positivity. Human papillomavirus appears to be the principal risk factor for cervical adenocarcinoma. Although cervical cancer screening has lowered the incidence of and mortality from invasive cervical cancer, it is not completely protective. Vaccination against main HPV types should reduce the incidence of cervical cancer.

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination of females aged 11 or 12 with 3 doses of either HPV2 or HPV4. The vaccination series can be started beginning at age 9 years. Both vaccines might provide protection against some other HPV-related cancers in addition to cervical cancer, although there are currently only data sufficient to recommend HPV4 for protection against vulvar and vaginal cancers and precancers. HPV4 is recommended for prevention of genital warts.

Mathematical modeling suggests that adding male HPV vaccination to a female-only HPV vaccination program is not the most cost-effective vaccination strategy for reducing the overall burden of HPV-associated conditions in males and females when vaccination coverage of females is high (>80%).

According to NCCN, both the bivalent and quadrivalent vaccines are recommended in women for the prevention of cervical cancer. Although HPV 16 and 18 are responsible for an estimated 70% of cervical cancer, vaccinated women are still at risk for cervical cancer related to less common types of oncogenic HPV. Both HPV vaccines offer cross-protection against non-HPV vaccine types that also cause cervical cancer. However, HPV vaccination does not alter screening recommendations. Vaccinated women should continue cervical cancer screening according to the guidelines.

In a randomized, double-blind, placebo-controlled, phase II clinical trial, Villa and associates (2005) evaluated the effectiveness of a prophylactic quadrivalent vaccine targeting the HPV types associated with 70 % of cervical cancers (types 16 and 18) and with 90 % of genital warts (types 6 and 11). A total of 277 young women (mean age of 20.2 years) were randomly assigned to quadrivalent HPV (20 ug type 6, 40 ug type 11, 40 ug type 16, and 20 ug type 18) L1 virus-like-particle (VLP) vaccine; and 275 young women (mean age of 20.0 years) to one of two placebo preparations at day 1, month 2, and month 6. For 36 months, subjects underwent regular gynecological examinations, cervico-vaginal sampling for HPV DNA, testing for serum antibodies to HPV, and Pap testing. The primary endpoint was the combined incidence of infection with HPV type 6, 11, 16, or 18, or cervical or external genital disease (namely, persistent HPV infection, HPV detection at the last recorded visit, cervical intraepithelial neoplasia [CIN], cervical cancer, or external genital lesions caused by the HPV types in the vaccine). Main analyses were done per protocol. Combined incidence of persistent infection or disease with HPV type 6, 11, 16, or 18 fell by 90 % (95 % confidence interval [CI]: 71 to 97 %, $p < 0.0001$) in those assigned vaccine compared with those assigned placebo. These investigators concluded that a vaccine targeting HPV types 6, 11, 16, 18 could substantially reduce the acquisition of infection and clinical disease caused by common HPV types. This is in agreement with the finding of Harper and colleagues (2004) who reported that the bi-valent HPV16/HPV18 L1 VLP vaccine was effective in preventing incident and persistent cervical infections with HPV16 and HPV18, and associated cytological abnormalities and lesions (n = 1,113), as well as that of Koutsky and co-workers (2002) who reported that administration of HPV16 vaccine reduced the incidence of both HPV16 infection and HPV16-related CIN (n = 2392).

Mao and colleagues (2006) noted that HPV VLP vaccines have demonstrated effectiveness in preventing persistent HPV infections. Whether protection lasts longer than 18 months and, thus, impacts rates of CIN 2-3, has not yet been established. In a randomized, double-blind, placebo-controlled study, these investigators presented results from an HPV16 L1 VLP vaccine trial through 48 months. A total of 2,391 women, aged 16 to 23 years, participated in this trial. Either 40 ug HPV16 L1 VLP vaccine or placebo was administered intra-muscularly at day 1, month 2, and month 6. Genital samples for HPV16 DNA and Pap tests were obtained at day 1, month 7, and then 6-monthly through month 48. Colposcopy and cervical biopsies were performed if clinically indicated and at study exit. Serum HPV16 antibody titer was measured by radioimmunoassay. Among 750 placebo recipients in the per protocol population, 12 women developed HPV16-related CIN 2-3 (6 CIN2 and 6 CIN3). Among 755 vaccinated subjects, there were no cases (vaccine efficacy 100 %, 95 % CI: 65 to 100 %). There were 111 cases of persistent HPV16 infection in placebo recipients and 7 cases in vaccinated subjects (vaccine efficacy 94 %, 95 % CI: 88 to 98 %). After immunization, HPV16 serum antibody geometric mean titers peaked at month 7 (1,519 milli-Merck units [mMU]/ml), declined through month 18 (202 mMU/ml), and remained relatively stable between month 30 and month 48 (128 to 150 mMU/ml). These researchers concluded that the vaccine HPV16 L1 VLP provides high-level protection against persistent HPV16 infection and

HPV16-related CIN 2-3 for at least 3.5 years after immunization. Administration of L1 VLP vaccines targeting HPV16 is likely to reduce risk for cervical cancer.

Gardasil

Gardasil (human papillomavirus vaccine) is a recombinant vaccine indicated for the prevention of human papillomavirus (HPV) infections and the diseases associated with these infections.

Gardasil quadrivalent is effective against HPV types 6, 11, 16, and 18. Gardasil nine-valent is effective against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Gardasil quadrivalent is indicated in girls and women nine through 26 years of age for the prevention of anal cancer, cervical cancer, vulvar cancer, vaginal cancer, genital warts (condyloma acuminata), cervical intraepithelial neoplasia, cervical adenocarcinoma in situ, vulvar intraepithelial neoplasia, and vaginal intraepithelial neoplasia caused by Human Papillomavirus (HPV) types included in the vaccine. Gardasil quadrivalent is Food and Drug Administration (FDA)-approved in boys and men nine through 26 years of age for the prevention of anal cancer and genital warts caused by HPV types 6 and 11.

Gardasil nine-valent is indicated in girls and women 9 through 26 years of age for the prevention of the following diseases:

- Cervical, vulvar, vaginal, and anal cancer caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58.
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11.

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma in situ (AIS).
- Cervical intraepithelial neoplasia (CIN) grade 1.
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3.
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3.
- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

Gardasil nine-valent is indicated in boys 9 through 15 years of age for the prevention of the following diseases:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58.
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11.

And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:

- Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

A U.S. Food and Drug Administration (FDA) advisory panel recommended approval of Gardasil (Merck & Co., Inc., Whitehouse Station, NJ) the first vaccine developed to prevent cervical cancer. Gardasil, a quadrivalent HPV types 6, 11, 16, 18, recombinant vaccine, protects against the 2 strains of the HPV that are thought to cause about 70 % of all cervical cancer cases. The vaccine also protects against 2 other HPV strains that cause roughly 90 % of all genital warts. According to Merck, Gardasil could be administered to all females aged 9 to 26; but would be most effective if administered before females become sexually active. However, the advisory panel noted that vaccination should not reduce the importance of routine screening for cervical cancer, which has been attributed to reducing cervical cancer rates nationwide by 75 %, and that the vaccine would not protect against the many other HPV strains not included in the vaccine or be effective in individuals who are already infected with the four HPV strains in the vaccine. Regular cytology screening may still be necessary after vaccination since it is possible that reduction in the prevalence of the currently most common HPV types (16 and 18) may result in a rise in the incidence of infections with other cancer-associated types.

Gardasil was approved by the FDA for use in girls and young women aged 9 to 26 years. The FDA approved Gardasil for the prevention of cervical cancer, cervical precancers (cervical intraepithelial neoplasia (CIN) 2/3 and adenocarcinoma in situ (AIS)), vulvar precancers (vulvar intraepithelial neoplasia (VIN) 2/3), and vaginal precancers (vaginal intraepithelial neoplasia (VaIN) 2/3)) caused by HPV types 16 and 18. Gardasil is also approved for the prevention of genital warts and low-grade cervical lesions (CIN 1) caused by HPV types 6, 11, 16 and 18.

Gardasil (human papillomavirus vaccine) is available as 0.5-mL suspension for injection as a single-dose vial and prefilled syringe. Gardasil is administered in 3 separate intramuscular injections in the upper arm or in the higher anterolateral area of the thigh over a 6-month period. It is recommended that the 2nd dose be administered 2 months after the 1st dose, and the 3rd dose 6 months after the 1st dose. The ACIP (2016) states that women through age 26 and men through age 21 who began HPV vaccination before age 15 and received two doses at least 5 months apart do not need another dose.

The FDA's approval of Gardasil was based on the results of 4 phase II and phase III randomized controlled clinical trials involving a total of 20,541 women aged 16 to 26 years. Study participants were followed up to 5 years after enrollment. In these studies, Gardasil prevented all of the HPV 16- and 18- related cervical precancers and non-invasive cervical cancers (CIN 2/3

and AIS). Gardasil prevented 95 % of low-grade cervical dysplasia and precancers (CIN 2/3 or AIS) caused by HPV 6, 11, 16 or 18. Gardasil was also found to prevent 99 % of genital warts caused by HPV 6 or 11. Gardasil also prevented 100 % of HPV 16- and 18-related vulvar and vaginal precancers (VIN2/3 or AaIN2/3) in women not previously exposed to the relevant HPV subtypes. These studies also showed that administration of Gardasil to women who are already infected with one or more vaccine related HPV types prior to vaccination protects them from clinical disease caused by the remaining vaccine types but may not alter the course of an infection that is already present.

The FDA approved Gardasil for use in adolescent girls aged 9 to 15 years based on a comparison of immune responses to Gardasil in adolescent girls to that for older women. Studies were performed to evaluate the immune responses for Gardasil in 10 to 15-year old girls compared to those in 16- to 23-year old adolescents and young adult women. The immune responses to Gardasil in 10- to 15-year-old girls were similar to those in 16- to 23-year-old women. Similar outcomes were observed in a comparison of immune responses among 9- to 15-year old girls to immune responses in 16- to 26-year old adolescents and women.

Gardasil is contraindicated in individuals who are hypersensitive to the active substances or to any of the excipients of the vaccine.

The efficacy and safety of the vaccine in members less than nine years of age and over 26 years of age has not been established.

Vaccines may cause syncope, sometimes resulting in falling with injury. Observation for 15 minutes following administration is recommended.

The Advisory Committee on Immunization Practices (ACIP) is intended to guide national policy on use of the vaccine; its recommendations are typically adopted by professional medical associations and set the standards of practice for physicians. ACIP recommends routine vaccination of 11 and 12 year old males and females against HPV. The vaccination series may be initiated as early as 9 years of age.

ACIP recommended an upper age limit of 26 for females and 21 for males. A permissive recommendation for men 21 through 26 years of age was also provided. The committee felt that the burden of disease in males justified routine vaccination. They thought that there was likely to be an additional benefit to girls and women by reducing the spread of the virus and that the burden of disease in males alone was sufficient to recommend the vaccine.

The committee reviewed a variety of models that looked at the cost effectiveness of different vaccination strategies. This is an important component of what the committee reviews for every vaccine recommendation, but there is not threshold that they use. Male vaccination is most cost effective when coverage of females is low and unfortunately here in the U.S. coverage of females is currently low. The committee also undertook extensive review of data on vaccine safety. Tens of millions of doses of HPV vaccine have been distributed in the United States. The clinical trials that have been carried out smaller numbers have shown the quadrivalent vaccine to be safe and effective males as well as females.

Gardasil (human papillomavirus vaccine) should not be utilized in the following:

- A history of anaphylactic reaction to any component of the vaccine including the excipients.
- Gardasil (human papillomavirus vaccine) has not been demonstrated to protect against diseases due to HPV types not contained in the vaccine.
- Impaired immune responsiveness; and/or members that are or may be pregnant.

Hildesheim et al (2007) examined if vaccination against HPV types 16 and 18 increases the rate of viral clearance in women already infected with HPV. A total of 2,189 women aged 18 to 25 years were included in this study. Subjects were positive for HPV DNA at enrollment, had at least 6 months of follow-up, and had follow-up HPV DNA results. Participants were randomly assigned to receive 3 doses of a bivalent HPV-16/18 L1 protein virus-like particle AS04 candidate vaccine (n = 1,088) or a control hepatitis A vaccine (n = 1,101) over 6 months. Presence of HPV DNA was determined in cervical specimens by a molecular hybridization assay using chemiluminescence with HPV RNA probes and by polymerase chain reaction using SPF10 primers and a line probe assay detection system before vaccination and by polymerase chain reaction after vaccination. These researchers compared rates of type-specific viral clearance using generalized estimating equations methods at the 6-month visit (after 2 doses) and 12-month visit (after 3 doses) in the 2 study groups. There was no evidence of increased viral clearance at 6 or 12 months in the group who received HPV vaccine compared with the control group. Clearance rates for HPV-16/18 infections at 6 months were 33.4 % (82/248) in the HPV vaccine group and 31.6 % (95/298) in the control group (vaccine effectiveness for viral clearance, 2.5 %; 95 % CI: -9.8 % to 13.5 %). Human papillomavirus 16/18 clearance rates at 12 months were 48.8 % (86/177) in the HPV vaccine group and 49.8 % (110/220) in the control group (vaccine effectiveness for viral clearance, -2.0 %; 95 % CI: -24.3 % to 16.3 %). There was no evidence of a therapeutic effect for other oncogenic or non-oncogenic HPV categories, among women receiving all vaccine doses, among women with single infections, or among women stratified by the following entry variables: HPV-16/18 serology, cytologic results, HPV DNA viral load, time since sexual debut, Chlamydia trachomatis or Neisseria gonorrhoeae infection, hormonal contraceptive use, or smoking. The authors concluded that in women positive for HPV DNA, HPV-16/18 vaccination does not accelerate clearance of the virus and should not be used to treat prevalent infections. The findings of this study confirm that HPV vaccine has no therapeutic value for women with pre-existing

infection, thereby reinforcing the importance of immunizing women before they initiate sexual activity and are possibly exposed to infection.

The Centers for Disease Control and Prevention/Advisory Committee on Immunization Practices (ACIP, 2007) stated that no evidence exists of protection against disease caused by HPV types with which females are infected at the time of vaccination. However, females infected with 1 or more vaccine HPV types before vaccination would be protected against disease caused by the other vaccine HPV types. The recommended vaccination schedule is a 3-dose series with the 2nd and 3rd doses administered 2 and 6 months after the first dose. The recommended age for vaccination of females is 11 to 12 years. Vaccine can be administered as young as age 9 years. Catch-up vaccination is recommended for females aged 13 to 26 years who have not been previously vaccinated. Vaccination is not a substitute for routine cervical cancer screening, and vaccinated females should have cervical cancer screening as recommended.

Vaginal and vulvar cancers among younger women are often related to infection with HPV. These cancers are preceded by high-grade vulval intra-epithelial neoplasia (VIN2-3) and vaginal intra-epithelial neoplasia (VaIN2-3). Joura et al (2007) performed a combined analysis of 3 randomized clinical trials to assess the effect of Gardasil on the incidence of these diseases. A total of 18,174 women (16 to 26 years) were enrolled and randomized to receive either Gardasil or placebo at day 1, and months 2 and 6. Individuals underwent detailed anogenital examination at day 1, 1 month after the 3rd dose, and at 6-12-month intervals for up to 48 months. Suspect genital lesions were biopsied and read by a panel of pathologists and vaccine HPV type-specific DNA testing was done. The primary end point was the combined incidence of VIN2-3 or VaIN2-3 associated with HPV16 or HPV18. Primary efficacy analyses were done in a per-protocol population. The mean follow-up time was 3 years. Among women naive to HPV16 or HPV18 through 1 month after the 3rd dose (per-protocol population; vaccine n = 7,811; placebo n = 7,785), the vaccine was 100 % effective (95 % CI: 72 to 100) against VIN2-3 or VaIN2-3 associated with HPV16 or HPV18. In the intention-to-treat population (which included 18,174 women who, at day 1, could have been infected with HPV16 or HPV18), vaccine efficacy against VIN2-3 or VaIN2-3 associated with HPV16 or HPV18 was 71 % (37 to 88). The vaccine was 49 % (18 to 69) effective against all VIN2-3 or VaIN2-3, irrespective of whether or not HPV DNA was detected in the lesion. The most common treatment-related adverse event was injection-site pain. Prophylactic administration of Gardasil was effective in preventing high-grade vaginal and vulval lesions associated with HPV16 or HPV18 infection in women who were naive to these types before vaccination.

In a phase III clinical trial, Garland and colleagues (2007) evaluated the effectiveness of Gardasil in preventing anogenital diseases associated with HPV types 6, 11, 16, and 18. This randomized, placebo-controlled, double-blind trial involved 5,455 women between the ages of 16 and 24 years; 2,723 received vaccine and 2,732 received placebo at day 1, month 2, and month 6. The co-primary composite end points were the incidence of genital warts, vulvar or vaginal intra-epithelial neoplasia, or cancer and the incidence of cervical intra-epithelial neoplasia, adenocarcinoma in situ, or cancer associated with HPV type 6, 11, 16, or 18. Data for the primary analysis were collected for a per-protocol susceptible population of women who had no virologic evidence of HPV type 6, 11, 16, or 18 through 1 month after administration of the 3rd dose. Subjects were followed for an average of 3 years after administration of the 1st dose. In the per-protocol population, those followed for vulvar, vaginal, or peri-anal disease included 2,261 women (83 %) in the vaccine group and 2,279 (83 %) in the placebo group. Those followed for cervical disease included 2,241 women (82 %) in the vaccine group and 2,258 (83 %) in the placebo group. Vaccine effectiveness was 100 % for each of the co-primary end points. In an intention-to-treat analysis, including those with prevalent infection or disease caused by vaccine-type and non-vaccine-type HPV, vaccination reduced the rate of any vulvar or vaginal peri-anal lesions regardless of the causal HPV type by 34 % (95 % CI: 15 to 49), and the rate of cervical lesions regardless of the causal HPV type by 20 % (95 % CI: 8 to 31). The authors concluded that Gardasil significantly reduced the incidence of HPV-associated anogenital diseases in young women.

On September 12, 2008, the FDA approved expanded indications for Gardasil for the prevention of vaginal and vulvar cancer caused by HPV types 16 and 18 in girls and women aged 9 to 26 years. These 2 HPV types cause 70 % of cervical cancers, and are known to also cause some vaginal and vulvar cancers, but the percentages are not well-defined.

On October 16, 2009, the FDA approved the use of Gardasil for the prevention of genital warts due to HPV types 6 and 11 in boys and men aged 9 through 26 years. Gardasil's effectiveness was based on the results of a randomized trial of 4,055 males aged 16 through 26 years old. The results showed that in men who were not infected by HPV types 6 and 11 at the start of the study, Gardasil was nearly 90 % effective in preventing genital warts caused by infection with HPV types 6 and 11. Studies were conducted to measure the immune response to the vaccine in boys ages 9 through 15. The results showed that the immune response was as good as that found in the 16 through 26 years age group, indicating that the vaccine should have similar effectiveness.

On December 22, 2010, the FDA approved Gardasil for the prevention of anal cancer and associated pre-cancerous lesions due to HPV types 6, 11, 16, and 18 in people aged 9 through 26 years. The FDA approval was based on the results of a randomized, controlled trial of men who self-identified as having sex with men. This population was studied because it has the highest incidence of anal cancer. At the end of the study period, Gardasil was shown to be 78 % effective in the prevention of HPV 16 and 18 related anal intra-epithelial neoplasia. Because anal cancer is the same disease in both males and females, the effectiveness data was used to support the indication in females as well.

Gardasil will not prevent the development of anal pre-cancerous lesions associated with HPV infections already present at the time of vaccination. Gardasil's full potential for benefit is obtained by those who are vaccinated prior to becoming infected with

the HPV strains contained in the vaccine.

Pawlita and Gissmann (2009) noted that recurrent respiratory papillomatosis (RRP) is a rare disease. It is characterized by proliferation of benign squamous cell papillomas within the respiratory-digestive tract, predominantly the larynx. This rare disease is caused by oral infection with HPV types 6 or 11. In aggressive disease, which within few months or even weeks requires multiple surgical interventions to remove papillomas, residual impairment of voice and breathing is almost inevitable. Nowadays immune stimulation with interferon alpha or topic application of cidofovir are recommended to lower the recurrence rate in aggressive disease but vaccination against mumps virus and photodynamic therapies has also been administered. The recently developed tetra-valent HPV vaccine Gardasil induces neutralizing antibodies against capsid antigens of the HPV types 16 and 18, which are associated with cervical cancer, as well as against types 6 and 11, which are associated with condylomata acuminata und respiratory papillomatosis. The vaccine has been shown to be safe and highly immunogenic. It can effectively prevent new genital infections by one of the 4 vaccine types as well as the epithelial lesions induced by them. However, the vaccine had no effect against pre-existing genital infections or lesions. These researchers proposed the hypothesis that HPV vaccination could have a therapeutic effect in RRP by preventing new papilloma formation at additional sites. First case reports on Gardasil vaccination in juvenile as well as adult onset RRP have become available. In view of the low risk of this adjuvant immunotherapy, a larger controlled multi-center trial was proposed to verify this hypothesis.

Chaudhary et al (2009) stated that head and neck malignancies are characterized by a multi-phasic and multi-factorial etiopathogenesis. Tobacco and alcohol consumption are the most common risk factors for head and neck malignancy. Other factors, including DNA viruses, especially HPV, may also play a role in the initiation or development of these lesions. The pathways of HPV transmission in the head and neck mucosal lesions include oral-genital contact, more than 1 sexual partner and peri-natal transmission of HPV to the neonatal child. The increase in prevalence of HPV infection in these lesions may be due to wider acceptance of oral sex among teenagers and adults as this is perceived to be a form of safe sex. The prevalence of HPV in benign lesions as well as malignancies has been assessed by many methods. Among these, the polymerase chain reaction is the most sensitive method. Review of literature reveals that HPV may be a risk factor for malignancies, but not in all cases. For confirmation of the role of HPV in head and neck squamous cell carcinoma, large population studies are needed in various clinical settings. Prophylactic vaccination against high-risk HPV types eventually may prevent a significant number of cervical carcinomas. Of the 2 vaccines currently available, Gardasil protects against HPV types 6, 11, 16 and 18, while the other vaccine, Cervarix protects against HPV types 16 and 18 only. However, to the best of the authors' knowledge, the HPV vaccine has not been tried in head and neck carcinoma.

On October 25, 2011, the ACIP recommended routine use of quadrivalent HPV vaccine (HPV4; Gardasil) in males aged 11 or 12 years. The ACIP also recommended vaccination with HPV4 for males aged 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose series; males aged 22 through 26 years may be vaccinated. These recommendations replaced the October 2009 ACIP guidance that HPV4 may be given to males aged 9 through 26 years. For these recommendations, the ACIP considered information on vaccine efficacy (including data available since October 2009, on prevention of grade 2 or 3 anal intra-epithelial neoplasia, a precursor of anal cancer), vaccine safety, estimates of disease and cancer resulting from HPV, cost-effectiveness, and programmatic considerations.

Gardasil-4 (quadrivalent) vaccine is no longer availabe for use in the United States. The last doses expired on May 1, 2017. This vaccine has been replaced with Gardasil-9 (see below) (Immunization Action Coalition, 2019; Markowitz, 2018).

Gardasil 9 for Anal Squamous Cell Carcinoma and High-Grade Anal Dysplasia

Nichols et al (2018) noted that squamous cell carcinoma (SCC) is the 2nd most common form of skin cancer, and its incidence is rising. When surgery is not an option, finding a safe and effective treatment is a challenge. Mounting evidence suggests that the HPV is involved in the pathogenesis of some SCCs. These researchers examined if the 9-valent HPV vaccine could be an effective treatment strategy for cutaneous SCC. A woman in her 90s with multiple, inoperable cutaneous basaloid SCCs was successfully treated at a university-based outpatient dermatology clinic with a combination of systemic and intra-tumoral delivery of the 9-valent HPV vaccine from March 17, 2016, through February 27, 2017, and then followed-up through May 21, 2018. Main outcomes and measures included reduction in tumor size and number after a combination of systemic and intra-tumoral administration of the HPV vaccine. All tumors resolved 11 months after the first intra-tumoral injection of the vaccine; and subject remained tumor-free at the end of follow-up. The authors concluded that, to their knowledge, this was the 1st report of complete regression of a cutaneous malignant tumor following combined systemic and direct intra-tumoral injection of the 9-valent HPV vaccine. They stated that the findings of this study suggested that the HPV vaccine may have therapeutic utility for SCCs in patients who are poor surgical candidates, have multiple lesions, or defer surgery.

Pham et al (2020) stated that HPV infections are associated with common dermatologic and non-dermatologic diseases. Although HPV vaccines are well established as preventive measures for genital warts and cervical neoplasia, their use as therapeutic agents deserves greater attention. These researchers examined the use of HPV vaccine(s) as a treatment modality for cutaneous and/or mucosal disease. They carried out a primary literature search using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in January 2019 by using the PubMed and Cochrane databases. A total of 63 articles with 4,439 patients were included. The majority of patients with cutaneous warts, recurrent respiratory papillomatosis, and squamous and basal cell carcinomas were successfully treated with HPV vaccination. Preliminary data on patients with pre-existing anogenital warts, cervical intraepithelial neoplasia, anal intraepithelial neoplasia, and vulvar

intraepithelial neoplasia is promising. The authors concluded that commercially available 3-dose, quadrivalent HPV vaccine is a potential therapeutic option for the treatment of cutaneous warts, recurrent respiratory papillomatosis, and squamous and basal cell carcinomas. Non-commercially available HPV vaccines demonstrate therapeutic response for treating anogenital warts, cervical intraepithelial neoplasia, anal intraepithelial neoplasia, and vulvar intraepithelial neoplasia. Moreover, these investigators stated that the vaccine's effectiveness as an adjunct therapy for HPV-associated cutaneous and/or mucosal disease warrants further investigation. The authors stated that this review was limited by the lack of controls, patients' previous HPV vaccination status, as well as publication bias.

An UpToDate review on “Human papillomavirus vaccination” (Cox and Palefsky, 2022) states that “Data informing the impact of HPV vaccine on anal squamous intraepithelial lesions (SIL) and anal cancers are more limited than that for cervical disease but suggest efficacy in males and expected efficacy in females”. It does not mention anal squamous cell carcinoma and high-grade anal dysplasia as indications for Gardasil/9-Valent HPV vaccination.

Furthermore, National Comprehensive Cancer Network’s clinical practice guideline on “Anal carcinoma” (Version 1.2022) does not mention HPV vaccination for anal squamous cell cancer and high-grade anal dysplasia.

Cervarix

Cervarix [Human Papillomavirus Bivalent (Types 16 and 18) Vaccine, Recombinant] is a non-infectious recombinant, AS04-adjuvanted vaccine that contains recombinant L1 protein, the major antigenic protein of the capsid, of oncogenic HPV types 16 and 18. Animal studies suggest that the efficacy of L1 VLP vaccines may be mediated by the development of IgG neutralizing antibodies directed against HPV-L1 capsid proteins generated as a result of vaccination.

Cervarix, a bi-valent HPV types 16 and 18, recombinant vaccine, was approved by the FDA on October 16, 2009 for use in girls and young women aged 9 through 25 years for the prevention of cervical cancer, CIN grade 2 or worse and adenocarcinoma in situ, and CIN grade 1, caused by oncogenic HPV types 16 and 18. The FDA’s approval of Cervarix was based on data from clinical trials of nearly 30,000 girls and young women receiving Cervarix. Cervarix was shown to be 93 % effective in the prevention of cervical pre-cancers associated with HPV 16 or 18 in women without evidence of current infection with, or prior exposure to, the same HPV type at the time of vaccination. The majority (approximately 75 %) of cervical cancers in North America are caused by HPV types 16 and 18.

Cervarix bivalent HPV vaccine has been removed from the ACIP immunization schedule. This vaccine has been removed from the U.S. market, and all available vaccine doses have expired.

Gardasil 9

The FDA approved Gardasil 9 (Human Papillomavirus 9-valent Vaccine, Recombinant) vaccine for the prevention of certain diseases caused by nine types of Human Papillomavirus (HPV) (FDA, 2014). Covering nine HPV types, five more HPV types than Gardasil (previously approved by the FDA), Gardasil 9 has the potential to prevent approximately 90 percent of cervical, vulvar, vaginal and anal cancers.

In 2014, Gardasil 9 was FDA-approved for use in females ages 9 through 26 and males ages 9 through 15. It is approved for the prevention of cervical, vulvar, vaginal and anal cancers caused by HPV types 16, 18, 31, 33, 45, 52 and 58, and for the prevention of genital warts caused by HPV types 6 or 11. Gardasil 9 adds protection against five additional HPV types—31, 33, 45, 52 and 58— which cause approximately 20 percent of cervical cancers and are not covered by previously FDA-approved HPV vaccines.

A randomized, controlled clinical study was conducted in the U.S. and internationally in approximately 14,000 females ages 16 through 26 who tested negative for vaccine HPV types at the start of the study (FDA, 2014). Study participants received either Gardasil or Gardasil 9. Gardasil 9 was determined to be 97 percent effective in preventing cervical, vulvar and vaginal cancers caused by the five additional HPV types (31, 33, 45, 52, and 58). In addition, Gardasil 9 is as effective as Gardasil for the prevention of diseases caused by the four shared HPV types (6, 11, 16, and 18) based on similar antibody responses in participants in clinical studies.

Due to the low incidence of anal cancer caused by the five additional HPV types, the prevention of anal cancer is based on Gardasil’s demonstrated effectiveness of 78 percent and additional data on antibodies in males and females who received Gardasil 9 (FDA, 2014).

The effectiveness of Gardasil 9 in females and males ages 9 through 15 was determined in studies that measured antibody responses to the vaccine in approximately 1,200 males and 2,800 females in this age group (FDA, 2014). Their antibody responses were similar to those in females 16 through 26 years of age. Based on these results, the vaccine is expected to have similar effectiveness when used in this younger age group.

Gardasil 9 is administered as three separate injections, with the initial dose followed by additional injections given two and six months later (FDA, 2014). For all of the indications for use approved by the FDA, Gardasil 9’s full potential for benefit is obtained

by those who are vaccinated prior to becoming infected with the HPV strains covered by the vaccine. For youth starting HPV vaccination between ages 9 and 14 years, the ACIP recommends two doses of the HPV vaccine given 6 to 12 months apart. Patients aged 15 to 26 still need three doses. The ACIP (2016) states that women through age 26 and men through age 21 who began HPV vaccination before age 15 and received two doses at least 5 months apart do not need another dose.

The safety of Gardasil 9 was evaluated in approximately 13,000 males and females (FDA, 2014). The most commonly reported adverse reactions were injection site pain, swelling, redness, and headaches.

The ACIP (2015) has recommended Gardasil 9, in addition to Gardasil, for routine vaccination of females aged 11 or 12 years and females through age 26 years who have not been vaccinated previously or who have not completed the 3-dose series. Gardasil 9 or Gardasil can be used for routine vaccination of males aged 11 or 12 years and males through age 21 years who have not been vaccinated previously or who have not completed the 3-dose series. The ACIP recommends either Gardasil 9 or Gardasil vaccination for men who have sex with men and immunocompromised persons (including those with HIV infection) through age 26 years if not vaccinated previously.

The ACIP (2015) states that “9-valent HPV vaccine may be used to continue or complete a series started with a different HPV vaccine product”. There is no ACIP recommendation for additional 9-valent HPV vaccine doses for persons who started the series with quadrivalent or bivalent HPV vaccine and completed the series with 9-valent HPV vaccine.

In October 2018, the FDA approved an age expansion for Gardasil 9 (Human Papillomavirus (HPV) 9-valent vaccine, recombinant) vaccine to include women and men 27 through 45 years of age. FDA approval for the expanded age range was based on data from the clinical trial evaluating Gardasil (quadrivalent) in 3253 women ages 27 through 45 years who were randomized 1:1 to receive either Gardasil or placebo with median follow-up of 3.5 years post-dose 3. Gardasil was found to be 87.7% (95% CI: 75.4%, 94.6%) effective in the prevention of a combined endpoint of persistent infection, genital warts, vulvar and vaginal precancerous lesions, cervical precancerous lesions, and cervical cancer related to HPV types covered by the vaccine. In the long-term extension of that study, subjects from Colombia (n=600) randomized to the Gardasil group were monitored for HPV 6-, 11-, 16-, and 18-related genital warts or cervical dysplasia. The median follow-up post-dose 3 was 8.9 years. During the long-term extension phase, no cases of HPV 6-, 11-, 16-, or 18- related CIN (any grade) or genital warts were observed in the per-protocol efficacy (PPE) population (FDA, 2018; Luna, 2013; Merck, 2018).

Effectiveness of Gardasil 9 in men 27 through 45 years of age is inferred from the data described in the Gardasil trial with women 27 through 45 years of age, as well as efficacy data from Gardasil in younger men (16 through 26 years of age) and immunogenicity data from a clinical trial in which 150 men, 27 through 45 years of age, received a 3-dose regimen of Gardasil over 6 months (FDA, 2018). Per the FDA, since Gardasil-4 and Gardasil-9 are manufactured similarly, the effectiveness of Gardasil in these patient populations is relevant to Gardasil-9, which covers the same 4 HPV types (6, 11, 16, 18) plus an additional 5 HPV types (31, 33, 45, 52, and 58).

At a June 2019 CDC’s Advisory Committee for Immunization Practices (ACIP) meeting, ACIP members reviewed the available data and voted to recommend that persons 27 through 45 years of age to engage in shared decision-making when considering the 9-valent HPV vaccine. Although the public health benefit of HPV vaccination in this age range is minimal, shared clinical decision-making is recommended because some persons who are not adequately vaccinated might benefit. In addition, the committee voted to recommend "catch-up" vaccination for males through age 26 years who are not adequately vaccinated. Previous recommendation was through age 21 years (Meites et al., 2019).

Prevention of Recurrence / Treatment of Anogenital Warts

Husein-ElAhmed (2020) noted that HPV is the most prevalent sexually transmitted infection worldwide and anogenital warts (AGWs) are highly infectious. This virus is transmitted through sexual, anal, or oral contact as well as skin-to-skin contacts. Treatment for this condition has significant morbidity and it can be frustrating in certain cases. The HPV vaccination has been demonstrated as a promising strategy of secondary prevention in HPV-related diseases such as head and neck cancers, cervical diseases, and recurrent respiratory papillomatosis. Regarding AGWs, it is unclear whether vaccination can provide analogous clinical benefit. These investigators reviewed the literature regarding HPV vaccination for secondary disease prevention after treatment of AGWs. From October to December 2018, a systematic search for clinical trials was carried out in 5 data-bases: PubMed, Medline, Embase, Cochrane, and clinicaltrials.gov using a combination of the following descriptors: “gardasil” OR “cervarix” OR “nine-valent” OR “9-valent” OR “vaccine” AND “recurrence” OR “relapse” AND “hpv” OR “papillomavirus” AND “warts” OR “condyloma”. Data were synthetized and entered in the Review Manager software (RevMan 5.3.5) to perform the meta-analysis. The search yielded 824 potentially relevant studies; 2 studies fulfilled the eligibility criteria involving 656 subjects. The meta-analysis estimated the rate of recurrence of AGWs was similar between the vaccine group and the control group. The overall effect estimate was 1.02 (0.75 to 1.38). This was the 1st meta-analysis examining the effect of HPV vaccine in preventing the relapse of AGWs. The authors concluded that these findings suggested that HPV vaccination did not provide secondary benefit in patients with previous AGWs. However, these results cannot be generalized due to the scarce number of RCTs currently available in the literature. The outcomes from future RCTs are needed to further clarify the precise effect of the vaccine.

Villemure and Wilby (2024) noted that AGWs caused by the HPV are a common manifestation of HPV infection. Treatment strategies usually entail topical therapies to promote wart regression or removal through surgical or other means. These strategies are effective but are associated with high rates of recurrence. HPV vaccines are known to be effective for prevention of AGWs; however, preliminary data suggested they may offer therapeutic benefit for regression of active AGWs. In a systematic review , these researchers examined the effectiveness of HPV vaccines for treatment of active AGWs. They carried out a systematic search of PubMed, Embase, and Cochrane Database of Systematic Reviews in July 2023 with no limits on date of publication. The search was supplemented with a manual review of references from identified articles and pertinent review articles. Articles were included if they reported at least 1 patient with active AGWs who received at least 1 dose of any HPV vaccine. The primary outcome of interest was complete or partial regression of AGWs over any time period. Risk of bias was assessed for each study meeting inclusion criteria. A total of 7 articles -- 1 RCT, 1 non-RCT, 3 case series, and 2 case reports – were included. All 7 studies were deemed to have a high risk of bias. Study results showed evidence that HPV vaccines may offer therapeutic benefits to those with active AGWs. Studies reported outcomes for both intralesional and systemically administered vaccines. Outcomes reported improvement according to both partial and complete regression of AGWs. The authors concluded that this systematic review found that there is evidence that HPV vaccines may have a role in the treatment of active AGWs. Findings supported the notion that the vaccine should be offered to previously unvaccinated patients but the role of intralesional administration of the vaccine to vaccinated patients is still unclear.

Human Papillomavirus Vaccine Effectiveness by Number of Doses

Markowitz and colleagues (2018) conducted a systematic literature review of HPV vaccine effectiveness by number of doses, including assessment of biases and impact of varying buffer periods (time between vaccination and outcome counting). Of 3,787 articles identified, 26 full articles were assessed and 14 included in this review. All studies were conducted within the context of recommended 3-dose schedules of bivalent (3 studies) or quadrivalent HPV vaccine (11 studies); 2 studies evaluated effectiveness for prevention of HPV prevalence, 6 anogenital warts, and 6 abnormal cervical cytology or histology. Many studies found differences between 3-, 2- and 1-dose vaccine recipients, indicating possible differences in HPV exposure prior to vaccination or in risk behavior. Adjusted or stratified analyses were conducted to control for potential confounding. All studies found significant vaccine effectiveness with 3 doses, 11 studies with 2 doses at various intervals, and 6 studies with 1 dose. Most studies showed a relationship (not always statistically significant) between effectiveness and number of doses, with greater decreases in HPV-related outcomes with t3, followed by 2 and 1 dose(s). Few studies conducted formal comparisons of 3 versus fewer doses; 3 of 4 studies that examined buffer periods found higher effectiveness and a smaller difference by number of doses with longer periods. The authors concluded that most post-licensure studies reported highest effectiveness with 3 doses; some found no statistically significant difference between 2 and 3 doses. Additionally, almost 50 % found some effectiveness with 1 dose. These researchers noted that several biases impacted estimates, with most biasing 2- and 1-dose results away from showing effectiveness. They stated that future effectiveness studies, examining persons vaccinated prior to sexual activity and using methods to reduce potential sources of bias, can help inform vaccination policy.

HPV Vaccine for the Treatment of Head and Neck Cancer

In a systematic review, Schneider and colleagues (2018) provided an overview of the current clinical trials examining therapeutic vaccines for HPV+ head and neck cancer (HNC) and discussed the future directions of therapeutic vaccine therapy. A systematic search was conducted in PubMed, Embase, Cochrane and clinicaltrials.gov for clinical trials involving therapeutic vaccines. These investigators included studies initiated between 2000 and 2018 with patients diagnosed with HPV+ HNC and extracted data concerning type of vaccine therapy, adverse events (AEs), immunogenicity and clinical outcome measures (e.g., tumor response, progression-free survival [PFS] and overall survival [OS]). These investigators identified 11 studies (n = 376 patients) initiated between year 2005 and 2017; 4 studies (n = 34) presented preliminary results in patients with incurable, recurrent loco-regional or distant metastatic disease indicating a positive immune response with 74 % (n = 25/34 patients) having elevated antibody levels, IFN-γ and/or T-cell response; 5 studies presented data on the vaccines' safety profile, demonstrating predominantly grade 1 and 2 toxicity; 3 studies evaluated the clinical outcome - 1 study showed no complete response (CR) or partial response (PR), 1 study demonstrated stable disease (SD) as the best tumor response in 64 % (n = 9/14 patients) and 1 study showed a 33 % overall response rate (ORR): 1 patient with a CR and 7 patients with a PR. The authors concluded that treatment with therapeutic vaccines is a promising and seemingly safe strategy for patients with HPV+ HNC. However, there are inadequate data to draw any further conclusions and clinical outcome measures and tumor responses to the vaccines are still missing.

On June 12, 2020, the FDA approved an expanded indication for Gardasil 9 for the prevention of oropharyngeal and other head and neck cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58. The oropharyngeal and head and neck cancer indication is approved under accelerated approval based on effectiveness in preventing HPV-related anogenital disease. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial, which is currently underway.

HPV Vaccine for the Treatment of Vulval and Vaginal Intraepithelial Neoplasia

Bryan and colleagues (2019) stated that HPV DNA is found in almost 80 % of vulval and vaginal intraepithelial neoplasia (VIN/VaIN.) Current management is inadequate, with high recurrence rates. In a systematic review, these researchers

evaluated the literature regarding the role of HPV vaccine in secondary prevention and treatment of VIN/VaIN. Database searches included Ovid Medline, Embase, Web of Science, the Cochrane Library and Clinicaltrials.gov . Search terms included HPV vaccine AND therapeutic vaccine* and VIN or VAIN, published in English with no defined date limit. Searches were performed with a UCL librarian in March 2018. These investigators included any type of study design using any form of HPV vaccine in the treatment of women with a histologically confirmed diagnosis of VIN/VaIN. They excluded studies of other lower genital tract disease, vulval/vaginal carcinoma and prophylactic use of vaccines. The outcome measures were lesion response to vaccination, symptom improvement, immune response and HPV clearance. These researchers identified 93 articles, 7 studies met the inclusion criteria; these were uncontrolled case series. There were no randomized controlled trials (RCTs) or systematic reviews identified. Reduction in lesion size was reported by all 7 studies, symptom relief by 5, HPV clearance by 6, histological regression by 5, and immune response by 6. The authors concluded that this review found the evidence relating to the use of HPV vaccine in the treatment of women with VIN/VaIN was of very low quality and insufficient to guide practice. These researchers stated that more studies are needed to examine clinically important patient outcomes (symptoms, non-progression and recurrence rates) with the use of HPV vaccine in a therapeutic setting. Furthermore, it would be prudent to examine its use in secondary prevention of cancer, which would need to be assessed through further longitudinal studies. These investigators stated that the limitations of this study included the following: none of the studies directly compared a control group with HPV vaccination, all studies found were uncontrolled case series, with short-term follow-up for what is a chronic, long-term disease.

Human Papillomavirus Vaccination Guideline Updates

Saslow and colleagues (2020) noted that the American Cancer Society (ACS) presents an adaptation of the current ACIP recommendations for HPV vaccination. The ACS recommends routine HPV vaccination between ages 9 and 12 years to achieve higher on-time vaccination rates, which will lead to increased numbers of cancers prevented. Health care providers are encouraged to start offering the HPV vaccine series at age 9 or 10 years. Catch-up HPV vaccination is recommended for all persons through age 26 years who are not adequately vaccinated. Providers should inform individuals aged 22 to 26 years who have not been previously vaccinated or who have not completed the series that vaccination at older ages is less effective in lowering cancer risk. Catch-up HPV vaccination is not recommended for adults aged older than 26 years. The ACS does not endorse the 2019 ACIP recommendation for shared clinical decision-making for some adults aged 27 through 45 years who are not adequately vaccinated because of the low effectiveness and low cancer prevention potential of vaccination in this age group, the burden of decision-making on patients and clinicians, and the lack of sufficient guidance on the selection of individuals who might benefit.

The ACOG Committee Opinion on “Human papillomavirus vaccination” (2020) stated that HPV causes significant morbidity and mortality in women and men. The HPV vaccine significantly reduces the incidence of anogenital cancer and genital warts in women and in men. Human papillomavirus vaccines are among the most effective vaccines available worldwide, with unequivocal data demonstrating greater than 99 % efficacy when administered to women who have not been exposed to that particular type of HPV. Obstetrician-gynecologists and other health care professionals should strongly recommend HPV vaccination to eligible patients and stress the benefits and safety of the HPV vaccine. Furthermore, obstetrician-gynecologists are encouraged to stock and administer HPV vaccines in their offices when feasible. Ideally, the HPV vaccine should be given in early adolescence because vaccination is most effective before exposure to HPV through sexual activity. Unvaccinated women aged 26 years and younger should receive the HPV vaccine series regardless of sexual activity, prior exposure to HPV, or sexual orientation. The HPV vaccine is now licensed in the U.S. for women and men through age of 45 years. For some women aged 27 to 45 years who are previously unvaccinated, obstetrician-gynecologists and other health care professionals may use shared clinical decision-making regarding HPV vaccination, considering the patient's risk for acquisition of a new HPV infection and whether the HPV vaccine may provide benefit.

Post-Treatment HPV Vaccination for Women Undergoing Excisional Treatment for Cervical Intraepithelial Neoplasia (CIN)

In a systematic review and meta-analysis, Eriksen et al (2022) examined if HPV vaccination administered after excisional treatment of CIN is associated with a reduced risk of recurrence of CIN grade-2 or worse (CIN2+). These investigators carried out a systematic literature search in 3 online databases through June 2021. Observational studies and RCTs were eligible for inclusion if the prophylactic HPV vaccine was administered after excisional treatment for histologically verified CIN. Only English language literature was included. The primary outcome measure was recurrence of CIN2+ after treatment. A meta-analysis was carried out using fixed and random-effects models, and results were reported as pooled odds ratios (OR) with 95 % CI. Quality assessment was performed using ROB2-tool for RCTs and ROBINS-I for observational studies. A total of 1,561 studies were identified, of which 9, including 19,971 women, were included; 2 studies were RCTs and 7 were observational studies. Using the fixed-effect model on the 2 RCTs, the OR for recurrence of CIN2+ was 0.29 (95 % CI: 0.16 to 0.53). Due to considerable heterogeneity in observational studies, the random-effects model was used to estimate pooled OR for CIN2+ recurrence in these studies. Therefore, using unadjusted data from observational studies, the OR for CIN2+ recurrence was 0.35 (95 % CI: 0.18 to 0.67), whereas when using adjusted data, the OR for CIN2+ recurrence was 0.54 (95 % CI: 0.21 to 1.35). However, quality assessment revealed a serious risk of bias for the majority of the studies included. The authors concluded that HPV vaccination post-treatment was associated with a significantly reduced risk of CIN2+ recurrence when using unadjusted estimates from observational studies and RCTs. These researchers found no significant effect of HPV vaccination on risk of CIN2+ recurrence

when using the outcome measure from observational studies with the least risk of bias. They stated that large, well-designed randomized, placebo-controlled trials with sufficient power and follow-up time are needed to examine if post-treatment HPV vaccination should be recommended to all women undergoing excisional treatment for CIN.

The authors stated that review had several drawbacks. First, these researchers observed a substantial heterogeneity between studies with regard to outcome, inclusion and exclusion criteria, as well as confounders. They were unable to perform a meta-analysis by margin status, vaccine type, number of vaccine doses administered or HPV genotype due to limited or missing information on these variables. Second, a considerable indirectness of evidence has to be emphasized due to the lack of adjusting for confounders in the studies included. Third, a small number of studies were included and only 2 were RCTs; these 2 trials had different inclusion criteria; thus, questioning the pooling of the ORs. Therefore, these findings may be subject to an over-estimation of the effect of HPV vaccination post-treatment.

Human Papillomavirus Vaccine as Adjuvant Therapy for Juvenile-Onset Recurrent Respiratory Papillomatosis

Park et al (20220 stated that juvenile-onset recurrent respiratory papillomatosis (JoRRP) is considered a rare disease with high morbidity and healthcare costs. The management of RRP has received much scientific attention in recent years and several treatment methodologies have been investigated, including therapeutic use of HPV vaccine. There has been increasing interest in the off-label use of the vaccine in virus-induced disease processes such as RRP, due to its immunomodulatory effect and activating role on the innate and adaptive immune system. In a systematic review, these investigators examined the effectiveness of the HPV vaccination as a therapeutic tool in the pediatric population. The review of the English literature included 3 electronic databases, PubMed, SCOPUS, and Cochrane, without publication date restrictions. Studies and reports identified by the database search were reviewed and assessed by 2 independent reviewers. The literature searches identified 768 unique citations, from which 204 duplicates were removed (n = 564). A total of 547 studies were excluded as they did not meet our inclusion criteria. A total of 12 studies (3 experimental studies, 3 case series, 6 case reports) that met the inclusion criteria and reported 1 or more of the outcomes of interest were included for this review. The assessment of the outcome measures evaluated (number of surgeries during the follow-up period, inter-surgical interval (ISI), surgeries per month (SPM), Derkay or severity scores, and remission status) revealed that 8 out of 12 studies included in the review showed varying degrees of potential benefits from the administration of the vaccine as a treatment modality compared to surgical interventions and/or concurrent adjuvant therapies alone. The authors concluded that while the therapeutic use of HPV vaccination has shown promise for some JoRRP patients; however, it overall remains uncertain with the currently available data. These researchers stated that there is a need for a prospective, multi-center study with a larger sample size to fully characterize the potential use of the vaccine in the management of JoRRP.

Vaccination in individuals Over 26 Years of Age

An UpToDate review on “Human papillomavirus vaccination” (Cox and Palefsky, 2023) provides the following information:

Vaccination in individuals over 26 years of age -- For most patients >26 years of age, we suggest against catch-up vaccination (Grade 2C), as most individuals in this age range have already been exposed to HPV and vaccination is unlikely to assist in immunity. However, there are some exceptions for whom we do offer vaccination even after age 26 years:

- Previously unvaccinated adults aged 27 to 45 years who have a low likelihood of prior HPV exposure (e.g., no prior sexual experience or a limited number of prior sexual partners) but have a future risk of HPV exposure (e.g., new sexual partners).
- Health care workers who have repeated exposure to HPV in vapors generated during surgical excision or ablation of HPV-associated lesions (e.g., health care providers and operating room and office staff in the fields of gynecology, dermatology, and family practice).

However, clinicians and patients should be aware that HPV vaccination after age 26 may not be covered by insurance providers or other payers, and this may also affect the decision to vaccinate.

Efficacy and Immunogenicity of a Single-Dose of HPV Vaccine Compared to Multi-Dose Vaccination Regimens or No Vaccination

In a systematic review, Whitworth et al (2024) examined the available evidence on the effectiveness and immunogenicity of single-dose HPV vaccination compared to multi-dose schedules or no HPV vaccination. These investigators searched 4 databases for relevant studies published from January 1999 to February 2023. Articles were examined for eligibility for inclusion using pre-defined criteria. Relevant data were extracted from eligible studies and a descriptive quality assessment was carried out for each study. A narrative data synthesis was performed, examining HPV infection, other clinical outcomes and immunogenicity responses by dose schedule. A total of 15 articles reporting data from 6 studies (all in healthy young females) were included. One article was included from each of 3 studies that prospectively randomized subjects to receive a single HPV vaccine dose versus 1 or more comparator schedule(s). The other 12 articles reported data from 3 studies that randomized subjects to receive multi-dose HPV vaccine (or control vaccine) schedules; in those studies, some subjects failed to complete their allocated schedule, and evaluations were carried out to compare subjects who actually received 1, 2, or 3 doses. Across all

effectiveness studies, the incidence or prevalence of HPV16/18 infection was very low among HPV-vaccinated subjects, regardless of the number of doses received; with no evidence for a difference between dose groups. In immunogenicity studies, HPV16/18 antibody sero-positivity rates were high among all HPV-vaccinated subjects. Antibody levels were significantly lower with 1 dose compared to 2 or 3 doses; however, levels with 1 dose were stable and sustained to 11 years post-vaccination. The authors concluded that findings from this review supported recent World Health Organization (WHO) recommendations allowing either 1- or 2-dose HPV vaccination in healthy young females. Moreover, these investigators stated that longer-term effectiveness and immunogenicity data from ongoing studies are awaited. Randomized trials of single-dose HPV-vaccination are needed in other populations, e.g., boys, older, as well as individuals with HIV.

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Policy History

- Last Review 10/24/2024

  Effective: 06/30/2006

  Next Review: 08/14/2025

- Review History
- Definitions

Additional Information

- Clinical Policy Bulletin Notes