Medical Policy Reference Manual
Medical Policy

5.01.017 Human Papillomavirus (HPV) Recombinant Vaccines

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Description

Human Papillomavirus (HPV) is the most common sexually transmitted infection in the United States. There are more than 100 types of HPV, with approximately 30 types of HPV that affect the genital and oropharyngeal areas. There are certain HPV types responsible for oropharyngeal, anal and cervical cancers such as: squamous cell carcinoma; low, moderate, and high cervical dysplasia; and cervical adenocarcinoma. HPV is the cause of genital warts (condyloma acuminata) which are growths that may appear on the cervicovaginal, vulvar, anus and the external genitalia. Regardless of gender, The Advisory Committee on Immunization Practices (ACIP) recommends that HPV vaccination is administered during early adolescence (preferably by age 12) as the vaccine has greater effectiveness before exposure to the virus through sexual activity. The HPV vaccine's preventative abilities diminish for sexually active adults and adolescents with multiple partners, persons with previous HPV (vaccine type) exposure, or those with certain immunocompromised health conditions (Meites, E., et al, 2019).

Three vaccines that prevent infection with disease-causing HPV have been licensed in the United States: Gardasil®, Gardasil® 9, and Cervarix®. The manufacturers of Cervarix® voluntarily pulled the vaccine from the market because of low usage, however the U.S. Food and Drug Administration (FDA) still lists Cervarix® in their licensed vaccine list (FDA, 2023). Since 2016, Gardasil®9 has been the only HPV vaccine available for use in the United States.

Gardasil® 9 (Merck & Co. Inc.) targets HPV types 6, 11, 16 and 18 along with 31, 33, 45, 52, 58—these cause 90% of cervical cancer cases and most cases of genital warts Gardasil® 9 has the following indications for use approved by the FDA:

In people ages 9 through 45 years for the **prevention** of the following diseases:

- Cervical, vulvar, vaginal, anal, oropharyngeal, and other head and neck cancers 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.

Policy

Nonavalent Human Papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) Recombinant Vaccine (Gardasil® 9) is considered a **medically necessary** preventive service for age nine (9) through forty-five (45) years for the *prevention* of HPV-related cancers, precancerous, genital or anal lesions, and genital warts.

Nonavalent Human Papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) Recombinant Vaccine (Gardasil® 9) is considered **experimental / investigational** for ages 8 and under and ages 46 and over as it does not meet TEC criterion #2-5.

Policy Guidelines

Experimental/Investigational

The term "experimental/investigational" describes services or supplies that are in the developmental not stage and are in the process of human or animal testing. Services or supplies that do meet all 5 of the criteria listed below adopted by the BlueCross BlueShield Association (BCBSA) Medical Policy Services (MPS) Assessment Criteria (formerly known as the Technology Evaluation Center (TEC) are deemed to be experimental/investigational:

1. The technology* must have final approval from the appropriate U.S.[1] government regulatory bodies; and
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes; and
3. The technology must improve the net health outcome; and
4. The technology must be as beneficial as any established alternatives; and
5. The improvement must be attainable outside the investigational settings.

* Technology includes drugs, devices, processes, systems, or techniques

Footnote: [1]The BCBSA criteria indicates the technology must have final approval from the appropriate government regulatory bodies; however, CareFirst BlueCross BlueShield ("CareFirst") requires the technology receives final approval from the appropriate U.S. government regulatory body.

1. The technology* must have final approval from the appropriate U.S.[1] government regulatory bodies.

The FDA has only provided clearance for Nonavalent Human Papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) or Recombinant Vaccine (Gardasil® 9) for the *prevention* of HPV-related cancers, precancerous, genital or anal lesions, and genital warts for ages 9 through 45 years.

For ages 8 and younger or 46 and older, Nonavalent Human Papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) or Recombinant Vaccine (Gardasil® 9) for the *prevention* of HPV-related cancers, precancerous, genital or anal lesions, and genital warts **do not have FDA clearance**.

All other uses of Nonavalent Human Papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) or Recombinant Vaccine (Gardasil® 9) including as a *treatment* for genital warts or HPV related cancer **do not have FDA approval.**

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

Guidelines from the National Comprehensive Cancer Network (NCCN) discuss treatments of HPV-related genital warts, precancerous or dysplastic lesions or cancers (Cervical, vulvar, vaginal, anal, oropharyngeal and other head and neck cancers caused by Human Papillomavirus). Carusi, A. (2023) in an UpToDate review notes that the HPV vaccine, as a treatment for anogenital warts or prevention of recurrent disease, remains investigational and is not advised. Cox, J.T. (2023) in an UpToDate review, advises that the HPV vaccine is not considered a treatment for the human papillomavirus and that it has not been proven to remove existing HPV infections or anogenital intraepithelial neoplasia (AIN).

3. The technology must improve the net health outcome.

Pham, C. T. et al (2020) in a systematic review of 63 publications (N=4439), finds that inconsistent methodology, publication bias and lack of prior HPV immunization status render outcomes to be insufficient to support clinical use outside of research. Additional research is needed to validate improvement in net health outcomes. Husein-El Ahmed H (2020) authored a systematic review and meta-analysis exploring the effect of HPV vaccine in preventing the relapse of anogenital warts. Outcomes from the analysis do not support the use of the HPV vaccine for prior medical history of anogenital warts. Husein-El Ahmed noted that no secondary benefit was found for this population and further stated that because of a dearth of RCTs, results cannot be generalized.

4. The technology must be as beneficial as any established alternatives:

There is no available research comparing, Nonavalent Human Papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) Recombinant Vaccine (Gardasil® 9) to established alternatives for any indication. Therefore, it is not possible to determine whether Nonavalent Human Papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) Recombinant Vaccine (Gardasil® 9) is as effective as established alternatives for the treatment of HPV-related conditions including cancer or genital warts.

5. The improvement must be attainable outside the investigational settings:

A net health outcomes improvement has not been demonstrated in the investigational settings for Nonavalent Human Papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) Recombinant Vaccine (Gardasil® 9) except for the medically necessary indications noted in this policy. Therefore, it is not possible to determine whether an improvement outside

of the investigational setting can be expected for Nonavalent Human Papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) Recombinant Vaccine (Gardasil® 9) for any other use.

Rationale:

Update 2023: A search of the peer-reviewed literature and evidence-based criteria was performed for the period of 11/01/2021 through 10/01/2023. Findings in the literature do not change the conclusions regarding the use of Nonavalent Human Papillomavirus (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58) Recombinant Vaccine (Gardasil® 9). Therefore, the policy statements remain unchanged.

Update 2021: On June 12, 2020, the FDA approved the additional indication for Gardasil® 9 for the prevention ®of oropharyngeal and other head and neck cancers caused by HPV types targeted by the vaccine according to the regulations for accelerated approval. Under accelerated approval regulations, the FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. This approval requires the manufacturer to study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.

There has been no update for the HPV vaccine in the ACIP recommendations dated August 16, 2019, published in the CDC's MMWR. The policy statement reflecting the ACIP recommendations is unchanged.

Update 2019: On October 5, 2018, the FDA approved a supplemental application for Gardasil® 9 expanding the current indications and usage of the vaccine to include members aged 27 through 45 years. The FDA's approval was based upon a two-phase clinical trial that evaluated efficacy (i.e., an initial base and long-term extension follow-up). The base study was a 4-year randomized, double-blind, placebo controlled, multi-center study of 3253 women aged 27 through 45 years. Efficacy of Gardasil® against the combined endpoint of HPV 6, 11, 16, 18 related persistent infection, genital warts, vulvar intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VaIN), vulvar cancer, vaginal cancer, cervical dysplasia (any grade of cervical intraepithelial neoplasia (CIN)), adenocarcinoma in situ (AIS), and cervical cancer in the per-protocol efficacy (PPE) population was 87% (95% CI: 75.4%, 94.6%). In the same population, the efficacy of Gardasil® against the combined incidence of HPV 6, 11, 16, 18 related genital warts or cervical dysplasia was 95.0% (95% CI: 68.7%, 99.9%). The long-term extension study was randomized to the Gardasil® group in the base study of n= 600 subjects from Colombia. No cases of HPV 6, 11, 16, 18 related CIN of any grade or genital warts were observed in the PPE population. Effectiveness of Gardasil® 9 in men aged 27 through 45 was inferred from efficacy data in women 27 through 45 years of age and by immunogenicity data from a clinical trial in which 150 men (27 through 45 years of age) received a 3-dose regimen of Gardasil®. Effectiveness in males in this age group for the additional 5 HPV types in Gardasil® 9 was extrapolated similar to those described for women.

In addition, the FDA updated its' recommendation regarding dosing for Gardasil® 9 to include ages 27 through 45 years for members. The FDA label states Gardasil® 9 should be administered intramuscularly as a 0.5-mL dose. The schedule is as follows:

- Age 9 through 14 years: 2-dose regimen at 0, 6 to 12 months*
- Age 9 through 14 years: 3-dose regimen at 0, 2, 6 months
  (*If the second dose is administered earlier than 5 months after the first dose, administer a third dose at least 4 months after the second dose.)
- Age 15 through 45 years: 3 dose regimens at 0, 2, 6 months.

The Advisory Committee on Immunizations Practices (ACIP) published in the CDC's Morbidity and Mortality Weekly Report (MMWR) new recommendations regarding HPV vaccination on August 16, 2019. Recommendations included implications for catch-up vaccination (for all persons through age 26 years) and vaccinations for adults aged 27 through 45 years. ACIP's Work Group evaluated the quality of evidence from eleven clinical trials focusing primarily on safety, efficacy, and effectiveness. The trials' focal point was on 9vHPV (9-valent, Gardasil® 9), 4vHPV (quadrivalent, Gardasil®), and/or 2vHPV (bivalent, Cervarix®) in adults aged 27 through 45 years. Supplemental bridging immunogenicity data was also considered. An efficacy trial that was based upon 9vHPV licensure for adults aged 24 through 45 years, PPE of 4vHPV among women aged 24 through 45 years was 88.7% (95% CI=78.1–94.8%). Its intention-to-treat efficacy was 47.2% (95% CI = 33.5–58.2%) against a combined endpoint of persistent infections, extragenital lesions, and CIN 1+ related to HPV types 6, 11, 16, or 18. In per-protocol analyses from three trials, 4vHPV and 2vHPV demonstrated significant efficacy against a combined endpoint of persistent vaccine-type HPV infections, anogenital warts, and CIN of grade 1 (low-grade lesions) or worse. Seroconversion rates to vaccine-type HPV after 3 doses of any HPV vaccine was 93.6%–100% at 7 months after the first dose (in nine trials). A small number of serious

adverse events were reported in nine clinical trials. In general, the evidence on benefits and harms was rated as moderate-quality evidence (GRADE evidence level 2).

The medically necessary indications within the Policy statements have been updated to reflect ACIP's recommendations.

Update 2017: The FDA gave approval for Gardasil® 9 (Human Papillomavirus 9-valent Vaccine Recombinant: Merck & Co.) to include a 2-dose schedule regimen for adolescents 9 through 14 years of age on October 7, 2016. According to the Advisory Committee on Immunization Practices (ACIP), the 2-dose series is highly effective and safe and a powerful tool for reducing HPV infections and HPV-associated cancers.

Update 2015: The FDA gave approval for marketing to Merck and Co. of its , nonavalent Gardasil® 9 vaccine on December 11, 2014. The vaccine is aimed at 9 strains of HPV; according to the American Cancer Society, the new vaccine is expected to prevent approximately 90% of cervical cancers, while continuing to provide protection against genital warts.

Update 2009: On October 16, 2009, the U.S. FDA approved Cervarix® (Human papillomavirus bivalent (types 16 and 18) vaccine, recombinant) for females ages 10 through 25 and added males ages 9 through 26 to the indications for Gardasil®. On October 21, 2009, the ACIP approved updated provisional recommendations for HPV Vaccine (see Provider Guidelines). These recommendations, when published in the MMWR, will replace recommendations published in the 2007 MMWR on the HPV vaccine. The medical necessity indications in this policy have been updated to reflect these changes.

Immunization with Gardasil® or Cervarix® should not reduce the importance of cervical screening in women which has been effective in reducing cervical cancer rates by 75 percent nationwide. These vaccines are most effective in preventing cancer if given prior to becoming sexually active.

Update 2008: Clinical trials, regarding the benefits of females receiving the vaccine, greater than 26 years of age, are ongoing. Clinical trials are also ongoing regarding the immunization of males. No peer-reviewed literature was identified addressing children younger than 9 years of age receiving the vaccine.

The Advisory Committee for Immunization Practices (ACIP) has recommended (updated, 2009) **October 21, 2009, ACIP provided updated provisional recommendations for use of human papillomavirus (HPV) vaccine, including recommendations for the bivalent HPV (types 16 and 18) vaccine Cervarix® for females and the quadrivalent HPV (types 6, 11, 16, 18) vaccine (Gardasil®) for females and males.

Provisional Recommendations for Females

- Routine vaccination of females aged 11 or 12 years with 3 doses of HPV vaccine. The vaccination series can be started beginning at age 9 years.
- Females aged 13 through 26 years who have not been previously vaccinated or who have not completed the full vaccination series. Ideally, vaccine should be administered before potential exposure to HPV through sexual contact.
- Vaccination with either the bivalent HPV vaccine or the quadrivalent vaccine for prevention of cervical cancers and precancers.
- Vaccination with the quadrivalent HPV vaccine for prevention of cervical cancers and precancers, and genital warts.

Provisional Recommendations for Males

The 3-dose series of quadrivalent HPV vaccine may be given to males aged 9 through 26 years to reduce their likelihood of acquiring genital warts. The nonavalent HPV vaccine is indicated for males from age 9 through age 26 years of age. Ideally, vaccine should be administered before potential exposure to HPV through sexual contact.

Benefit Applications

The purpose of this Medical Policy Reference Manual is to provide clinical criteria and/or local, state, or federal coverage requirements for applicable services, devices, and drugs. Specific contract provisions, restrictions, and exclusions will take precedence over the clinical criteria, as the member contract supersedes clinical criteria adopted by CareFirst. Always check the member's contract for benefits.

Coverage of preventive health care services, including immunizations, is defined by contract. Therefore, the member's contract should be consulted to be certain of limitations of coverage prior to quoting benefits, adjudicating claims, or performing services.

Benefits **are not provided** for preventive services when the member does not have coverage for preventive services under their contract.

Benefits **are provided** for preventive services when:
- the member has coverage for preventive services under their contract; and
- the services rendered meet the criteria for coverage (if any), as specified in the member's contract.

When benefits **are provided** in the member's contract, benefits are provided for Gardasil® 9 administration.

When benefits are provided in the member's contract, benefits are provided for Gardasil® administration when administered by a qualified dental professional and/or oral health care professionals. Benefits are **not provided** in the FEP member's contract for Gardasil® administration when administered by a qualified dental professional and/or oral health care professionals.

Provider Guidelines

Provisional Recommendations for Administration, Precautions and Contraindications

- The nonavalent (Gardasil® 9) is administered in a 2 or 3 dose schedule as per ACIP guidelines. https://www.cdc.gov/vaccines/schedules/hcp/index.html
- If the HPV vaccine schedule is interrupted, the vaccine series does not need to be restarted.
- HPV vaccines are not live vaccines and can be administered either simultaneously or at any time before or after an inactivated or live vaccine.

The vaccine is not intended to be used for the treatment of active genital warts; cervical cancer; CIN, VIN, or VaIN. This vaccine will not protect against diseases that are not caused by HPV.

Note: Cervarix® and quadrivalent Gardasil® (Gardasil 4) are no longer being distributed in the United States. This vaccination does not substitute for routine cervical cancer screening. Women who receive or have received Gardasil®, Gardasil® 9 or Cervarix® should continue to undergo cervical cancer screening per standard of care. Please refer to the Preventive Services Guidelines at www.carefirst.com in regard to cervical cancer screening.

Cross References to Related Policies and Procedures

10.01.003A Preventive Services, Procedure

References

The following were among the resources reviewed and considered in developing this policy. By reviewing and considering the resources, CareFirst does not in any way endorse the contents thereof nor assume any liability or responsibility in connection therewith. The opinions and conclusions of the authors of these resources are their own and may or may not be in agreement with those of CareFirst.

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