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ASCCP Committee Opinion: Adjuvant Human Papillomavirus Vaccine for Patients Undergoing Treatment for Cervical Intraepithelial Neoplasia

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Objectives: Individuals treated for cervical intraepithelial neoplasia grade 2 or worse (CIN2+) are at long-term risk of persistent or recurrent disease despite treatment. This committee opinion aims to summarize and provide evidence-based recommendations for adjuvant human papillomavirus (HPV) vaccination based on available, published literature.

Methods: A task force from the ASCCP Practice Committee reviewed current Centers for Disease Control and Prevention (CDC) guidelines and previously published literature about the role of adjuvant HPV vaccination in previously unvaccinated individuals undergoing treatment for CIN2+ and other HPV-related diseases.

Results: Current CDC guidelines recommend routine or catch-up HPV vaccination for individuals aged 9 to 26 years, and shared decision making regarding vaccination for individuals aged 27 to 45 years. Multiple published studies suggest a possible benefit for adjuvant HPV vaccination in previously unvaccinated individuals undergoing treatment for CIN2+.

Conclusions: The American Society for Colposcopy and Cervical Pathology recommends adherence to current CDC recommendations for vaccination of individuals aged 9 to 26 years and consideration of the possible benefit of adjuvant HPV vaccination during shared decision making for previously unvaccinated individuals aged 27 to 45 years who are undergoing treatment for CIN2+.

Key Words: American Society for Colposcopy and Cervical Pathology, human papillomavirus vaccine, cervical intraepithelial neoplasia, dysplasia, treatment, loop electrocautery excision procedure

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Cervical cancer and other human papillomavirus (HPV)-related cancers and precancers are a major health problem worldwide. Human papillomavirus vaccination, in conjunction with appropriate cervical screening and management, has the potential to reduce cervical cancer incidence.[1,2] Individuals treated for cervical intraepithelial neoplasia grade 2 or worse (CIN2+) are at increased risk of persistent or recurrent disease. This committee opinion reviews the use of adjuvant HPV vaccination at the time of treatment for CIN2+ and provides evidence-based recommendations.

CURRENT GUIDELINES FOR HPV VACCINATION

The American Society for Colposcopy and Cervical Pathology (ASCCP) recommends following current Centers for Disease Control and Prevention (CDC) guidelines for HPV vaccination (https://www.cdc.gov/vaccines/vpd/hpv/hcp/index.html).[3] These guidelines state that routine HPV vaccination is recommended for all individuals aged 11 to 12 years but may start at age 9. Catch-up HPV vaccination is recommended for individuals through age 26 who were not previously vaccinated. Individuals aged between 27 and 45 years can be offered the vaccine using shared clinical decision making between providers and previously unvaccinated patients who are most likely to benefit. There are no current age-based recommendations for HPV vaccination for individuals aged older than 45 years; the vaccine is not Food and Drug Administration-approved in this age range. The HPV vaccination is not recommended during pregnancy, but is safe for use during lactation. In addition to these CDC guidelines, ASCCP issued a statement in February 2020 recommending HPV vaccination for medical professionals who are routinely exposed to the virus through their occupation (https://www.asccp.org/hpv-vaccination).

DOSING OF THE HPV VACCINE

Dosing of the HPV vaccine depends on age (https://www.cdc.gov/hpv/hcp/schedules-recommendations.html). Currently, 2 doses of the HPV vaccine (initial dose plus a 2nd dose at 6–12 mo from the initial dose) are recommended for individuals aged younger than 15 years. For those who are aged 15 years or older, a 3-dose series of the HPV vaccine is recommended (initial dose followed by an additional dose at 1–2 mo and another 6 mo from the initial dose). A 3-dose series of the HPV vaccine is also recommended for individuals aged 9 to 26 years who are immunocompromised, including those with HIV.

SHARED CLINICAL DECISION MAKING FOR INDIVIDUALS AGED 27 TO 45 YEARS

The Advisory Committee on Immunization Practices provides a list of considerations to help inform shared clinical decision making for previously unvaccinated individuals considering HPV vaccination.[3] These considerations include that vaccinating individuals aged 27 to 45 years is a much less cost-effective public health intervention than immunizing younger individuals who have not been exposed to HPV. The HPV vaccination of adults aged 27 to 45 years would likely confer relatively minimal additional health benefits because most individuals in that age range have previously been exposed to HPV, and the risk of exposure to HPV decreases with age. Although certain individuals may be at risk for exposure to HPV if they subsequently have a new sex partner, those who are in a long-term mutually monogamous sexual partnership may not benefit from HPV vaccination because

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their risk of exposure to a new HPV infection is low. Vaccine effectiveness is also likely to be low among individuals who have had multiple lifetime sex partners because of previous exposures. In addition, the vaccine is not likely to be beneficial in those with certain immunocompromising conditions. These considerations may be useful to clinicians and patients weighing the pros and cons of vaccination in the 27 to 45 age group. A description of the Advisory Committee on Immunization Practices' shared decision-making recommendation is located on the CDC web site (https://www.cdc.gov/vaccines/acip/acip-scdm-faqs.html).

HPV VACCINATION IN PREVIOUSLY UNVACCINATED INDIVIDUALS UNDERGOING TREATMENT FOR CIN2+

ASCCP recommends HPV vaccination for previously unvaccinated individuals who fall within the recommended vaccination age group (9–26 y) regardless of whether they are undergoing surgical treatment for CIN2+. HPV vaccination can also be offered to those who are previously unvaccinated in the 27 to 45 age group regardless of whether they are undergoing surgical treatment for CIN2+ based on shared clinical decision making between the provider and patient.

LONG-TERM RISK OF RECURRENCE OF CIN2+ IN INDIVIDUALS TREATED FOR CIN2+

Pooled, long-term follow-up data have found that individuals with a history of treatment for CIN2+ are at an increased risk for cervical cancer for at least 25 years after treatment.[4] The rate of persistent or recurrent disease ranges from 4% to 18%, depending on factors including postsurgical margin status, HPV status, and surgical technique.[5–8]

PROPOSED MECHANISMS OF ACTION OF THE PROPHYLACTIC HPV VACCINE IN PREVENTING CIN2+ RECURRENCE

Prophylactic HPV vaccination may prevent HPV-related disease by inducing neutralizing antibodies directed at virus-like particles of the major capsid protein L1, thereby preventing the HPV virus from entering host cells.[9] Although the prophylactic HPV vaccine does not work as a therapeutic vaccine, vaccinating individuals treated for CIN2+ may be beneficial if the vaccine provides protection from new future infections with HPV types that the individual has not been previously exposed. In addition, HPV vaccination may provide cross-protection to other HPV types not covered by the vaccine[10] and may also boost the immune response to HPV infection from the same type, thereby providing additional protection from reinfection with the same HPV type.[11,12]

POSSIBLE BENEFIT OF ADJUVANT HPV VACCINE IN PREVIOUSLY UNVACCINATED INDIVIDUALS TREATED FOR CIN2+

Multiple recent studies have examined if adjuvant prophylactic HPV vaccination pretreatment or posttreatment of CIN2+ in individuals who are previously unvaccinated reduces the risk of recurrence. These studies have focused on either the bivalent or quadrivalent vaccine and vary widely in timing of vaccine administration in relation to CIN2+ treatment. They also have heterogeneous study designs, including retrospective, prospective nonrandomized, randomized controlled trials, and post hoc pooled analyses of randomized clinical trials. Data from multiple meta-analyses show that CIN2+ after surgical treatment occurred at a rate of 1.72% to 4.0% in the vaccinated group compared with 4.76% to 5.9% in the unvaccinated cohort, an overall risk reduction of recurrent CIN2+ of 57% to 66%.[13–17] Meta-analyses that reported on the risk of recurrence of HPV 16/18-associated CIN2+ (the HPV types targeted by the bivalent and quadrivalent vaccine) found a similar risk reduction (59% to 74%) in recurrence of HPV16/18-associated CIN2+.[14–17] These preliminary data suggest that the prophylactic HPV vaccine may provide some benefit to immunocompetent individuals undergoing treatment of CIN2+ who have not previously received the vaccine. However, there is a high likelihood of bias in these studies because of the study designs. Large, randomized controlled trials are currently underway.

ROLE OF ADJUVANT HPV VACCINATION IN PREVIOUSLY UNVACCINATED INDIVIDUALS TREATED FOR OTHER HPV-RELATED DISEASES

Limited studies have examined the risk of recurrence of HPV disease after treatment and adjuvant HPV vaccination in individuals with vulvar intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia, high-grade anal intraepithelial neoplasia, and anogenital warts. Some studies suggest a possible benefit in reducing the risk of recurrence in individuals surgically treated for high-grade VIN,[18] in individuals surgically or topically treated for VIN or vaginal intraepithelial neoplasia ,[19] and in men who have sex with men treated for high-grade anal intraepithelial neoplasia.[20] A systematic review including 2 randomized controlled trials evaluating the role of adjuvant HPV vaccination in the prevention of recurrence of anogenital warts did not find a benefit.[21] Multiple randomized, placebo-controlled, clinical trials examining the risk of recurrence of HPV disease with and without adjuvant HPV vaccination at the time of treatment for VIN, anal neoplasia, and anogenital warts are currently ongoing.[22,23]

LACK OF EVIDENCE FOR A ROLE OF ADJUVANT HPV VACCINATION IN PREVIOUSLY UNVACCINATED INDIVIDUALS LIVING WITH HIV UNDERGOING TREATMENT FOR CIN2+ AND HIGH-GRADE ANAL INTRAEPITHELIAL NEOPLASIA

Adjuvant HPV vaccination has also been studied in individuals living with HIV. Recent randomized, double-blind, placebo-controlled studies of individuals living with HIV found no benefit for prophylactic HPV vaccination in individuals undergoing treatment for CIN2+ or high-grade anal intraepithelial neoplasia.[24,25] Findings from these studies suggest that treatment for CIN2+ or high-grade anal intraepithelial neoplasia are not indications for adjuvant HPV vaccination in individuals living with HIV.

ASCCP RECOMMENDATIONS FOR CONSIDERATION OF ADJUVANT VACCINATION IN PREVIOUSLY UNVACCINATED INDIVIDUALS UNDERGOING TREATMENT FOR CIN2+

Based on these findings, ASCCP recommends consideration of the possible benefit of adjuvant HPV vaccination in shared decision making regarding HPV vaccination for previously unvaccinated, immunocompetent individuals aged 27 to 45 years who are undergoing treatment for CIN2+ (Figure 1). The optimal timing of HPV vaccination in these individuals is not known. These individuals should be well counseled that the prophylactic vaccine will not treat existing HPV disease or prevent all future HPV-related disease. All individuals treated for CIN2+ are at risk for persistent or recurrent disease and require continued surveillance and management as per the 2019 risk-based management guidelines. The ASCCP recommendations may change based on findings from ongoing and future clinical trials.

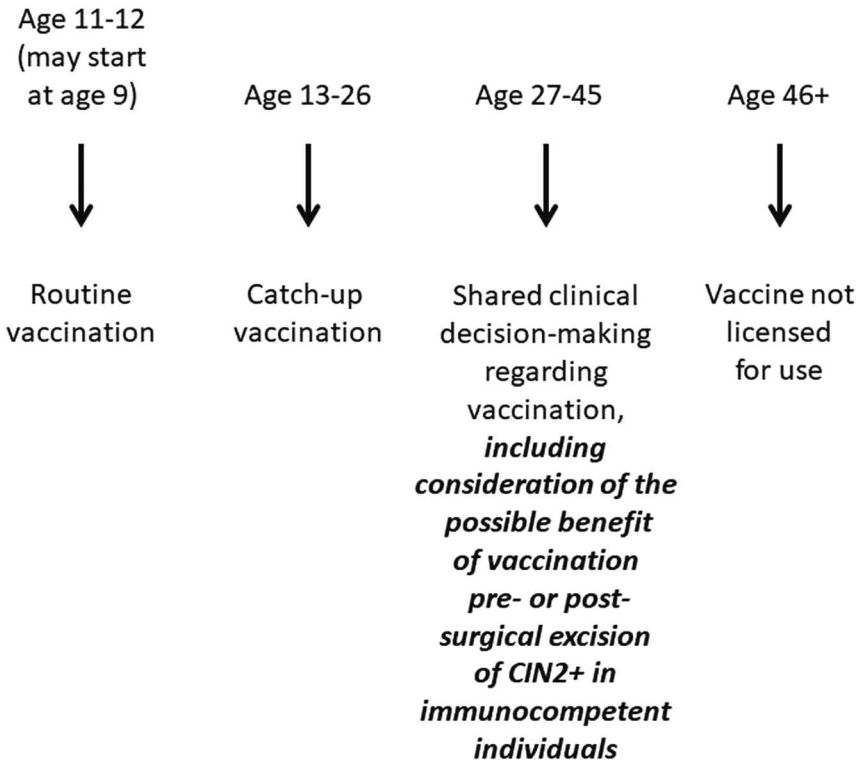

FIGURE 1. Recommendations for HPV vaccination based on age and shared clinical decision making.

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