JAMA Clinical Guidelines Synopsis

Human Papillomavirus Vaccination for Adults
Updated Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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GUIDELINE TITLE Human Papillomavirus Vaccination for Adults: Updated Recommendations From the Advisory Committee on Immunization Practices

DEVELOPER Advisory Committee on Immunization Practices (ACIP)

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PRIOR VERSION August 29, 2014

FUNDING SOURCE Centers for Disease Control and Prevention

TARGET POPULATION Males and females aged 9 through 45 years

MAJOR RECOMMENDATIONS

- Clinicians should use shared decision-making to offer human papillomavirus (HPV) vaccination to adults aged 27 to 45 years who have not started or completed the vaccine series based on individual risk factors and likelihood of benefit.
- All males and females through age 26 years who did not start or complete routine vaccination by age 11 to 12 years should receive catch-up vaccination.
- HPV vaccination is administered in a 3-dose schedule, with a second dose 1 to 2 months after the first and a third dose 6 months after the first, when initiated after the 15th birthday. When initiated before the 15th birthday, the vaccine is administered in a 2-dose schedule.
- Persons with HIV and other immunocompromising conditions should receive the 3-dose schedule regardless of age.
- HPV vaccination can be offered to persons who are breastfeeding or lactating. Vaccination should not be given during pregnancy, but a pregnancy test is not required before vaccination.

Summary of the Clinical Problem

Human papillomavirus is a highly prevalent sexually transmitted infection. Prior to vaccination programs, 1 large study of US female individuals documented an overall HPV prevalence of 26.8%, with the highest prevalence of 44.8% in women aged 20 to 24 years.[1] Although many HPV infections are transient and asymptomatic, HPV types 6 and 11 cause about 90% of genital warts. Types 16, 18, 31, 33, 45, 52, and 58 are considered high-risk oncogenic types and are responsible for an estimated 44 000 US cases of cancer each year. HPV causes 90% of US cervical cancers and 70% of US oropharyngeal cancers, and less commonly, anal, vaginal, vulvar, and penile cancer.[2]

Characteristics of the Guideline Source

This guideline[3] update was published by the ACIP, which is under the jurisdiction of the Secretary of the US Department of Health and Human Services. The ACIP uses the evidence-based GRADE approach to review evidence. The ACIP screens potential members for vaccine-related conflicts of interest. The ACIP has liaison relationships with federal agencies responsible for immunization programs, as well as organizations with immunization expertise, such as the American Academy of Pediatrics, the American Academy of Family Physicians, and the American College of Physicians.

Evidence Base

Human papillomavirus vaccines work by preventing new infections. They do not prevent progression of HPV infection to disease, improve clearance of HPV infection, or treat HPV-related disease. This guideline update (**Table**) reviewed 16 publications and unpublished clinical reports to answer 2 major questions pertinent to adults: (1) who should receive catch-up vaccination through age 26 and (2) which persons older than 26 years should receive vaccination.

Efficacy data supporting the expansion of HPV vaccination to adults aged 27 to 45 years were derived from 12 trials of the 2-valent (2v) HPV, 4vHPV, and/or 9vHPV vaccine involving 18 280 individuals, of which 5 were randomized trials and 7 were observational trials. In 9 trials reporting immunogenicity, seroconversion rates after 3 doses ranged from 93.6% to 100% after 7 months.[3] Efficacy of the 4vHPV vaccine in women aged 24 to 45 years against a combined end point of cervical intraepithelial neoplasia grades 1, 2, or 3, persistent HPV infection, or extragenital lesions in per-protocol analysis was 88.7% (95% CI, 78.1%-94.8%).[4] The potential longer-term benefits of effective population-wide HPV vaccination were suggested in a recent study in Scotland of women vaccinated with the 2vHPV vaccine at age 12 to 13 years. It showed an 89% (95% CI, 91%-94%) reduction in CIN grade 3 or higher, considered the best predictor of future invasive cervical cancer, as well as strong evidence of herd immunity in unvaccinated individuals.[5]

Benefits and Harms

Benefits of HPV vaccine in adults aged 26 to 45 years include prevention of HPV infection, HPV-related genital warts, and vaccine

Table. Guideline Rating

Establishing transparency	Good
Management of conflict of interest in the guideline development group	Good
Guideline development group composition	Fair
Clinical practice guideline-systematic review intersection	Good
Establishing evidence foundations and rating strength for each of the guideline recommendations	Fair
Articulation of recommendations	Good
External review	Fair
Updating	Fair
Implementation issues	Fair

serotype–related cancers. Harms appear to be minimal. In 9 clinical trials with 7816 patients that reported harms, patients in the vaccine group experienced no vaccine-related deaths and less than 1% serious adverse events, similar to placebo. In observational data, women aged 27 to 45 years had similar rates of mild adverse events as women aged 16 to 26 years, including injection site pain, swelling, and erythema.[6]

Discussion

The HPV vaccine is highly effective and well tolerated. Existing studies demonstrate high levels of immunogenicity for patients up to age 45 years. Trials show effectiveness against cervical and anal intraepithelial neoplasia, condyloma, and persistent HPV infection. Studies included both sexes, as well as male and female cohorts with HIV. A 2014 guideline recommended vaccination for males aged 13 to 21 years and catch-up vaccination through age 26 years for all women, men who have sex with men, transgender persons, and immunocompromised persons up to age 26 years. This guideline significantly simplifies recommendations for catch-up vaccination by including both sexes aged 21 to 26 years and suggests an approach for selective vaccination in individuals aged 27 to 45 years.

The HPV vaccine is most cost-effective when administered prior to virus exposure, and it can be given starting at age 9 years. Given that many adults aged 27 to 45 years will have been exposed to HPV earlier in life, universal vaccination for all adults aged 27 to 45 years is not cost-effective. The number needed to vaccinate all adults through age 45 years to prevent 1 case of cervical cancer was estimated to be 6500.[3] Thus, selective vaccination of adults aged 27 to 45 years is advised, both for cost-effectiveness and given the public policy concern that indiscriminate vaccination of adults older than 26 years could divert focus and vaccine supply from effective adolescent vaccination programs.

So how should clinicians discuss this issue with patients potentially eligible for HPV vaccination in the 27- to 45-year age range? Persons who are in a long-term, mutually monogamous sexual partnership are not likely to acquire a new HPV infection or benefit from vaccination. The vaccine may be more beneficial for persons who have had few prior sex partners *and* who are at greater risk of acquiring unencountered strains of HPV from new sex partners. Individuals with multiple prior sex partners are likely to have been exposed to the vaccine serotypes in the past, reducing usefulness.

Unfortunately, there are no clinical antibody tests available to guide this decision because most male individuals do not develop an antibody response after natural infection, and seroconversion is inconsistent in female individuals. More importantly, even when antibodies are present, no antibody titer has been established that predicts immunity to HPV. Clinicians should obtain a thorough sexual history and educate patients about the potential value of the vaccine for their circumstances using shared decision-making.

Areas in Need of Future Study or Ongoing Research

While screening programs have reduced rates of cervical cancer, it remains the fourth most common cancer in women worldwide. Much work remains to reduce its overall burden and associated racial and socioeconomic disparities. Countries with vaccination strategies that target multiple age groups and achieve higher coverage benefit from direct as well as herd immunity.[5,7] Beyond cervical cancer, oropharyngeal cancer has now become the most common US HPV-related cancer, with a recent study estimating that the 9vHPV vaccine could prevent 92% (32 100) of US HPV-related cancers each year.[8] Studies proving this benefit in noncervical cancers are needed.

Studies of outcomes in adults vaccinated at age 27 to 45 years are needed to refine future guidelines. However, strategies to increase adolescent vaccination are foundational for population-wide benefit. The Healthy People 2020 goal is 80% HPV vaccination by age 13 to 15 years; in 2018, only 51% of all US adolescents aged 13 to 17 years had completed vaccination. Ongoing research on educational approaches, clinic delivery methods, and population health strategies should improve vaccine uptake. Some effective techniques include moving from a 3-dose to a 2-dose series when vaccination is initiated prior to age 15 years, clinician communication training, and quality improvement and practice transformation programs that focus on missed opportunities and vaccine-positive messages.[9]

ARTICLE INFORMATION

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Conflict of Interest Disclosures: Dr Oshman reported currently holding less than $5000 in stock from Merck, the manufacturer of the HPV Gardasil vaccine. No other disclosures were reported.

REFERENCES

1. Dunne EF, Unger ER, Sternberg M, et al. Prevalence of HPV infection among females in the United States. *JAMA*. 2007;297(8):813-819. doi:10.1001/jama.297.8.813

2. Centers for Disease Control and Prevention. Cancers associated with human papillomavirus, United States—2012–2016. August 2019. https://www.cdc.gov/cancer/uscs/about/data-briefs/no10-hpv-assoc-cancers-UnitedStates-2012-2016.htm. Accessed September 23, 2019.

3. Meites E, Szilagyi PG, Chesson HW, et al. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2019;68(32):698-702. doi:10.15585/mmwr.mm6832a3

4. Castellsagué X, Muñoz N, Pitisuttithum P, et al. End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. *Br J Cancer*. 2011;105(1):28-37. doi:10.1038/bjc.2011.185

5. Palmer T, Wallace L, Pollock KG, et al. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland. *BMJ*. 2019;365(l1161):l1161. doi:10.1136/bmj.l1161

6. Luxembourg A. 9-valent (9vHPV) vaccine program safety and immunogenicity study in women 27-45 years. Presented at: ACIP; June 26, 2019; Atlanta, GA. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2019-06/HPV-3-Luxembourg-508.pdf. Accessed September 23, 2019.

7. Drolet M, Bénard É, Pérez N, Brisson M. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes. *Lancet*. 2019;394(10197):497-509. doi:10.1016/S0140-6736(19)30298-3

8. Senkomago V, Henley SJ, Thomas CC, et al. Human papillomavirus-attributable cancers—United States, 2012-2016. *MMWR Morb Mortal Wkly Rep*. 2019;68(33):724-728. doi:10.15585/mmwr.mm6833a3

9. Markowitz LE, Gee J, Chesson H, Stokley S. Ten years of human papillomavirus vaccination in the United States. *Acad Pediatr*. 2018;18(2S):S3-S10. doi:10.1016/j.acap.2017.09.014