ACIP Evidence to Recommendations Framework

Question 2: Should catch-up HPV vaccination be recommended for primary prevention of HPV infection and HPV-related disease for all persons ages 27 through 45 years?

Population: Persons aged 27 through 45 years at initiation of vaccination
Intervention: Catch-up vaccination with 3 doses of HPV vaccine
Comparison: Persons aged 27 through 45 years with no catch-up HPV vaccination
Outcome: Primary prevention of HPV infection and HPV-related disease

Background:

Human papillomavirus (HPV) is a common sexually transmitted infection of the epithelium. Persistent HPV infections can develop into cervical, vaginal, vulvar, penile, anal, and oropharyngeal cancers, usually after several decades.

Vaccination against HPV is recommended to prevent HPV infections and HPV-associated diseases, including cancers. HPV vaccination was introduced in the United States in 2006 for females and 2011 for males aged 9–26 years. The Advisory Committee on Immunization Practices (ACIP) recommends routine HPV vaccination at age 11 or 12 years; vaccination can be given starting at age 9 years. Catch-up vaccination has been recommended through age 26 years.

Three prophylactic HPV vaccines are licensed for use in the United States: 9-valent and quadrivalent HPV vaccines (9vHPV and 4vHPV, Gardasil 9 and Gardasil, Merck & Co., Inc., Kenilworth, NJ) and bivalent HPV vaccine (2vHPV, Cervarix, GlaxoSmithKline, Rixensart, Belgium). As of late 2016, only 9vHPV is being distributed in the United States.

The majority of all HPV-associated cancers are caused by HPV 16 or 18, types targeted by all three vaccines. In addition, 4vHPV targets HPV 6 and 11, types that cause anogenital warts. 9vHPV protects against these and five additional types: HPV 31, 33, 45, 52, and 58. In October 2018, based on results from 4vHPV clinical trials in women through age 45 years and bridging immunogenicity and safety data in women and men, the Food and Drug Administration (FDA) approved 9vHPV for use in women and men through age 45 years.

Additional background information can be found in the relevant publication of the recommendation referenced on the ACIP website.

	CRITERIA	WORK GROUP JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION

ACIP Evidence to Recommendations Framework

PROBLEM	Is the problem of public health importance?	*No* ☐ *Probably no* ☐ *Uncertain* ☒ *Probably yes* ☐ *Yes* ☐ *Varies* ☐	Approximately 33,700 cancers are caused by HPV annually in the United States, including 12,900 oropharyngeal cancers among men and women, 10,800 cervical cancers among women, and 6,000 anal cancers among men and women; vaginal, vulvar, and penile cancers are less common. The existing HPV vaccination program for U.S. adolescents has the potential to prevent the majority of these cancers. Mean age of acquisition of causal HPV infection for cancers is unknown, but estimated to be decades before cancer is diagnosed. It is uncertain how much HPV-related morbidity and mortality is related to HPV infections acquired at ages 27 through 45 years. HPV incidence is highest among people in the age range of teens to early twenties. First HPV infections are acquired soon after first sexual activity. Most sexually active adults have been exposed to HPV, but a new sex partner is a risk factor for new HPV infections. The percentage of people reporting a new sex partner within the past year is lower in older age groups than among younger age groups.	In 2017, coverage with ≥1 dose of HPV vaccine was 65.5% among 13–17 year-olds. Coverage remains below the Healthy People 2020 target of 80% of adolescents. Even so, the existing U.S. HPV vaccination program has resulted in significant declines in prevalence of vaccine-type HPV infections, anogenital warts, and cervical precancers. Among 14–19 and 20–24 year-old females, prevalence of 4vHPV vaccine-type infection declined from 11.5% to 1.8% and from 18.5% to 5.3%, respectively, in 2013–2016 compared with the prevaccine era. Declines have been observed among both vaccinated and unvaccinated persons, suggesting protective herd effects.
BENEFITS & HARMS	How substantial are the desirable anticipated effects?	*Minimal* ☐ *Small* ☐ *Moderate* ☐ *Large* ☐ *Don't know* ☐ *Varies* ☒	Desirable anticipated effects vary since population benefit would be minimal, yet some individuals in this age range might be able to benefit from vaccination. HPV vaccines are most effective when given before exposure to any HPV.	HPV vaccines are prophylactic (i.e., they prevent new HPV infections) and do not prevent progression of infection to disease, decrease time to clearance of HPV infection, or treat HPV-related disease. Since HPV is commonly acquired soon after first sex, vaccine effectiveness

			Compared with the benefit of the existing HPV vaccination program for adolescents and young adults through age 26 years, the additional benefit of vaccinating people age 27 through 45 years would be minimal. Based on modeling data, the number needed to vaccinate (NNV) to prevent one case of anogenital warts, cervical intraepithelial neoplasia (CIN) grade 2+, or cancer, is 9, 22, and 202, respectively, under the existing program. In a subset of analyses in the HPV-ADVISE model with more favorable model assumptions for adult vaccination, these NNV would be 120; 800; and 6,500 for expanding vaccination to include adults through age 45 years. Clinical trials have shown that HPV vaccines are effective against infection and related disease due to HPV types that recipients are not infected with at the time of vaccination. In per-protocol analyses of efficacy results from 4vHPV and 2vHPV trials among adults older than age 26 years who were HPV-naïve, across 10 trials, HPV vaccines showed significant efficacy against a combined endpoint of persistent vaccine-type HPV infections, anogenital warts, and/or cervical intraepithelial neoplasia grade 1 or worse. Seroconversion rates to vaccine-type HPV following 3 doses of any HPV vaccine were 93.6–100% at 7 months post first dose.	will be much lower in adults than among young adolescents. In clinical trials, intention-to-treat (ITT) results had lower observed efficacy than per-protocol analyses, since ITT analyses included participants with previous exposures and prevalent vaccine-type HPV infections at baseline before initial vaccination. In the FUTURE III trial in 3,819 women age 24–45 years, ITT efficacy of 4vHPV was 47.2% (95% CI 33.5, 58.2) against a combined endpoint of persistent HPV infection, extragenital lesions, and/or CIN 1+. No significant efficacy was observed against CIN 2+, although the study was not powered to evaluate for this endpoint specifically.

			In the FUTURE III trial in 3,819 women age 24 through 45 years, per-protocol efficacy of 4vHPV was 88.7% (95% CI 78.1, 94.8) against a combined endpoint of persistent HPV infection, extragenital lesions, and/or CIN 1+. When analysis was restricted to women age 27 through 45 years, efficacy was 87.7% (95% CI, 75.4, 94.6). No significant efficacy was observed against CIN 2+, although the study was not powered to evaluate for this endpoint specifically. Ten-year follow-up of a subset of women in this study found no waning protection. In a 9vHPV immunogenicity trial, geometric mean antibody titers to 7 high-risk HPV types were non-inferior in 642 women age 27–45 years compared to 570 women age 16–26 years; >99% of women in both groups seroconverted to all 9vHPV types.	
	CRITERIA	WORK GROUP JUDGMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	How substantial are the undesirable anticipated effects?	*Minimal* ☒ *Small* ☐ *Moderate* ☐ *Large* ☐ *Don't know* ☐ *Varies* ☐	There is abundant evidence for safety of HPV vaccines. In 9 clinical trials of 9vHPV, 4vHPV or 2vHPV in adults older than age 26 years (n=14,057), there were few serious adverse events and no vaccine-related deaths.	Some Work Group members felt that adult vaccination might detract from the adolescent vaccination program, which remains the main focus for HPV prevention.

ACIP Evidence to Recommendations Framework

	Do the desirable effects outweigh the undesirable effects?	Favors intervention ☐ Favors comparison ☐ Favors both ☐ Favors neither ☐ Unclear ☒	Given abundant evidence for safety of HPV vaccines, undesirable anticipated effects are minimal. Also, anticipated population-level benefits are minimal for vaccinating adults over age 26 years. In this scenario, other considerations including cost-effectiveness play an important role in guiding policy-making.	
	What is the overall certainty of this evidence for the critical outcomes?	Effectiveness of the intervention: No included studies ☐ 4 Very low ☐ 3 Low ☐ 2 Moderate ☒ 1 High ☐ Safety of the intervention: No included studies ☐ 4 Very low ☐ 3 Low ☐ 2 Moderate ☒ 1 High ☐	Refer to GRADE tables for detailed assessment of the certainty of the evidence. Overall evidence on benefits in the per-protocol population was GRADE evidence level 2 (moderate quality evidence). Overall evidence on harms was also GRADE evidence level 2 (moderate quality evidence).	Evidence in the GRADE tables has to do with individual-level outcomes on vaccine safety and effectiveness; outcomes in GRADE do not speak to population-level outcomes or programmatic concerns.
VALUES	Does the target population feel that the desirable effects are large relative to undesirable effects?	No ☐ Probably no ☐ Uncertain ☐ Probably yes ☒ Yes ☐ Varies ☐	In 9 published studies of adults (N=2841 women and N=1195 men), acceptability varied across studies, although was moderate to high overall. Acceptability was higher when the vaccine was assumed to be free and/or a health care provider made a recommendation.	
	CRITERIA	WORK GROUP JUDGMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	Is there important uncertainty about or variability in how much people value the main outcomes?	Important uncertainty or variability ☐ Possibly important uncertainty or variability ☒ Probably no important uncertainty or variability ☐ No important uncertainty or variability ☐ No known undesirable outcomes ☐	Acceptability of HPV vaccine among adults varied by study population and methodology.	

Updated June 26, 2019

ACIP Evidence to Recommendations Framework

ACCEPTABILITY	Is the intervention acceptable to key stakeholders?	*No* ☐ *Probably no* ☐ *Uncertain* ☒ *Probably yes* ☐ *Yes* ☐ *Varies* ☐	There are no recently published data assessing U.S. stakeholder acceptability of routine HPV vaccination among 27 through 45 year-olds. However, vaccines for other conditions are routinely given to adults in this age range.	In a 2019 survey about HPV vaccination recommendations based on clinical decision making for individuals among 45 immunization programs, the majority (60%) anticipated that it would be very or somewhat challenging to communicate a recommendation for clinical decision-making to vaccine providers in their jurisdiction. Almost half (42%) thought it would be easy or somewhat easy for vaccine providers to determine patients in this age group who might benefit from vaccination. Most (69%) anticipated challenges to implementing such a recommendation.
RESOURCE USE	Is the intervention a reasonable and efficient allocation of resources?	*No* ☐ *Probably no* ☒ *Uncertain* ☐ *Probably yes* ☐ *Yes* ☐	Five health economic models of HPV vaccination in the United States were reviewed. The cost-effectiveness ratio for the current HPV vaccination program ranged from cost-saving to about $35,000 per quality-adjusted life year (QALY). In the context of the existing program, vaccinating adults aged 30 years or older would produce relatively small additional health benefits. The incremental cost per QALY gained by also vaccinating adults through age 30 years exceeded $300,000 in four of five models. In most models, expanding vaccination to older ages would result in less favorable cost-effectiveness ratios. Variation in results across models was likely due to uncertainties about HPV natural history (e.g., burden of HPV-	Globally, there is an HPV vaccine shortage as production capacity is not adequate to meet demand currently. The demand/supply imbalance is expected to remain over the next 3–5 years. In some countries, including those with Gavi and UNICEF support, cohort expansion efforts and vaccination of multi-age cohorts of girls are not able to proceed due to lack of vaccine availability. Although no domestic vaccine shortage is anticipated, some Work Group members had equity concerns about HPV vaccination recommendations being extended to 27 through 45 year-olds in the United States in this context.

			associated disease caused by new HPV infections after age 26 years, and prevalence of immunity following clearance of natural infections) and level of herd protection from the existing HPV vaccination program.	It is not clear whether any recommendation for HPV vaccination in this age range would lead to greater uptake among individuals who are likely versus unlikely to benefit.
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☒ *Yes* ☐ *Varies* ☐	Delivering any adult vaccination can be challenging in the United States. Programs and funding for adult vaccination are not available in all jurisdictions. Adult immunization is performed primarily in the private sector. In a 2015 survey of 353 obstetrician/gynecologists, 81% reported that they stock and administer HPV vaccine.	Routine recommendations are easier to implement than shared clinical decision making. Identifying individual patients likely to benefit from adult HPV vaccination could be challenging for vaccine providers, especially those who do not regularly assess sexual risk behaviors. Some Work Group members felt that recommending vaccination in this age range might reduce health disparities, by increasing access to vaccination among adults with health insurance coverage. Others felt that recommending vaccination in this age range might enhance health disparities, as underinsured adults would be less likely to have access to vaccination since states have limited funds for adult vaccination programs.

ACIP Evidence to Recommendations Framework

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced* or *uncertain* ☒	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐	There is insufficient evidence to determine the balance of consequences ☐
Is there sufficient information to move forward with a recommendation? Yes ■ No ☐						

Policy options for ACIP consideration	ACIP does not recommend the intervention ☒	ACIP recommends the intervention for individuals based on shared clinical decision-making ☒	ACIP recommends the intervention ☐
Recommendation (text)	<u>Option for "ACIP does not recommend the intervention":</u> *Individuals older than the catch-up age group* ACIP does not recommend HPV vaccination for adults older than age 26 years. <u>Option for "ACIP recommends the intervention for individuals based on shared clinical decision making":</u> *Individuals older than the catch-up age group* ACIP recommends HPV vaccination based on shared clinical decision making for individuals ages 27 through 45 years who are not adequately vaccinated.* HPV vaccines are not licensed for use in adults older than age 45 years. *Special populations and medical conditions* The above recommendations for individuals older than the catch-up age group also apply to MSM;† transgender people; and people with immunocompromising conditions.		

*Definitions of persons considered adequately vaccinated are unchanged from prior publication (Meites et al, MMWR 2016).

†Men who have sex with men; includes men who identify as gay or bisexual, or who intend to have sex with men

ACIP Evidence to Recommendations Framework

Additional considerations (optional)	The HPV Vaccines Work Group was unanimous that routine or catch-up HPV vaccination should not be recommended for 27 through 45 year-olds. A majority felt that ACIP should recommend the intervention for adults based on shared clinical decision making, while a large minority felt that ACIP should not recommend the intervention in this age range. Thus two policy options were presented to ACIP for consideration. No prevaccination physical examination (e.g., Pap and/or HPV testing) is required to establish the appropriateness of HPV vaccination. Cervical cancer screening guidelines and recommendations should be followed. CDC continues to monitor HPV vaccine safety and impact of the vaccination program on HPV-attributable outcomes, including prevalence of HPV infections, anogenital warts, precancers, and cancers. ACIP reviews results from ongoing studies, vaccine trials, and health economic analyses as data become available, and updates vaccine policy as appropriate.

ACIP Evidence to Recommendations Framework

Final deliberation and decision by the ACIP

Final ACIP recommendation	ACIP does not recommend the intervention ☐	ACIP recommends the intervention for individuals based on shared clinical decision-making ☒	ACIP recommends the intervention ☐
ACIP considerations	ACIP members voted 10:4 in favor of shared clinical decision making for adults aged 27 through 45 years, recognizing that some individuals who are at risk for new HPV infection might benefit from vaccination in this age range. ACIP members in favor of shared clinical decision making cited data on vaccine safety and efficacy, and data suggesting that some adults in this age range might benefit from vaccination against HPV. ACIP members not in favor noted that little public health benefit is expected from vaccinating adults in this age range, compared to benefits of the existing vaccination program for adolescents. ACIP noted that most U.S. adults ages 27 through 45 years will not need to be vaccinated against HPV, since most people are unlikely to benefit from vaccination in this age range.		

This Evidence to Recommendation table is based on the GRADE Evidence to Decision framework developed through the *DECIDE* project. Further information is available at http://www.decide-collaboration.eu/evidence-decision-etd-framework. Framework last updated 19 June 2019.