

ACIP Evidence to Recommendations Framework

Question 1: Should catch-up HPV vaccination be recommended for primary prevention of HPV infection and HPV-related disease for all persons through age 26 years?

Population: Males aged 22 through 26 years

Intervention: Catch-up vaccination with 3 doses of HPV vaccine

Comparison: Existing HPV vaccination recommendations

Outcome: Primary prevention of HPV infection and HPV-related disease

Background:

Vaccination against human papillomavirus (HPV) is recommended to prevent HPV infections and HPV-associated diseases, including cancers.

The Advisory Committee on Immunization Practices (ACIP) has recommended routine HPV vaccination since 2006 for females and 2011 for males. Routine HPV vaccination is recommended at age 11 or 12 years; vaccination can be given starting at age 9 years. Catch-up vaccination has been routinely recommended since 2006 for females through age 26 years, and since 2011 for males through age 21 years. Catch-up vaccination also has been routinely recommended through age 26 years for men who have sex with men (including men who identify as gay, bisexual, or who intend to have sex with men), transgender persons, and persons with certain immunocompromising conditions.

There has been interest in simplifying the immunization schedule and having the same catch-up age range for all genders.

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.

HPV vaccination coverage has been increasing in the United States, but is still below Healthy People 2020 target of 80% of adolescents, and coverage in males is lower than coverage in females. In 2017, coverage with ≥1 dose of HPV vaccine was 65% among 13–17 year-olds; 69% in females and 63% in males.

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
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PROBLEM	<p>Is the problem of public health importance?</p> <p> <input type="checkbox"/> No <input type="checkbox"/> Probably no <input type="checkbox"/> Uncertain <input checked="" type="checkbox"/> Probably yes <input type="checkbox"/> Yes <input type="checkbox"/> Varies </p>	<p>Approximately 33,700 cancers are caused by HPV annually in the United States, including cervical, vaginal, vulvar cancers in females; penile cancers in males; and anal and oropharyngeal cancers in males and females. Of HPV-attributable cancers annually, approximately 20,200 occur in females and 13,500 occur in males.</p> <p>First HPV infections occur soon after first sexual activity. HPV prevalence is high among both males and females.</p>	<p>HPV vaccination coverage has been increasing among adolescents, but remains low among young adults. Coverage in males is lower than coverage in females. Among persons aged 22–26 years in 2017, coverage with ≥1 dose of HPV vaccine was 15% in males and 51% in females.</p>
BENEFITS & HARMS	<p>How substantial are the desirable anticipated effects?</p> <p> <input type="checkbox"/> Minimal <input checked="" type="checkbox"/> Small <input type="checkbox"/> Moderate <input type="checkbox"/> Large <input type="checkbox"/> Don't know <input type="checkbox"/> Varies </p>	<p>Efficacy has been demonstrated in this age group.</p> <p>HPV vaccines are most effective when given before exposure to any HPV. 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.</p> <p>Additional benefit of vaccinating males in this age range would be small compared with the benefit of the existing program. 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 40; 450; and 3,260 for expanding</p>	

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		recommendations for males through age 26 years to harmonize catch-up vaccination across genders.	
CRITERIA	WORK GROUP JUDGMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
How substantial are the undesirable anticipated effects?	<p><i>Minimal</i> <i>Small</i> <i>Moderate</i> <i>Large</i> <i>Don't know</i> <i>Varies</i></p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>	<p>HPV vaccines have an excellent safety profile based on large clinical trials and post-licensure effectiveness data. Over 100 million doses of HPV vaccine have been given in the United States.</p> <p>In 9vHPV clinical trials (n=3225), there were no serious vaccine-related events among males aged 9–26 years.</p>	<p>Adverse events following 4vHPV vaccination in 2009–2015 and following 9vHPV in 2014–2017 reported to the Vaccine Adverse Event Reporting System (VAERS), have been analyzed for both males and females. Syncope and injection site reactions were commonly reported in both males and females. Headache, fatigue and nausea were commonly reported serious AEs. More than 60 million 4vHPV doses and 29 million doses of 9vHPV were distributed during the study periods. There were no new or unexpected safety concerns.</p>
Do the desirable effects outweigh the undesirable effects?	<p><i>Favors intervention</i> <i>Favors comparison</i> <i>Favors both</i> <i>Favors neither</i> <i>Unclear</i></p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>	Small desirable effects outweigh minimal undesirable effects of HPV vaccination	
What is the overall certainty of this evidence for the critical outcomes?	<p>Effectiveness of the intervention</p> <p><i>No included studies</i> <i>4 Very low</i> <i>3 Low</i> <i>2 Moderate</i> <i>1 High</i></p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/></p> <p>Safety of the intervention</p> <p><i>No included studies</i> <i>4 Very low</i> <i>3 Low</i> <i>2 Moderate</i> <i>1 High</i></p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/></p>	<p>Refer to 2011 GRADE tables for use of 4vHPV for males and 2015 GRADE tables 9vHPV in females and males for detailed assessment of the certainty of the evidence.</p> <p>For males through age 26 years, GRADE evidence level is 2 (moderate) for benefits of 4vHPV, 2 (moderate) for harms of 4vHPV, 3 (low) for benefits of 9vHPV, and 2 (moderate) for harms of 9vHPV.</p>	<p>Full grading of recommendations, assessment, development, and evaluation (GRADE) for use of 4vHPV and 9vHPV in males have been available since these ACIP recommendations were made in 2011 and 2015, respectively.</p>

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VALUES	<p>Does the target population feel that the desirable effects are large relative to undesirable effects?</p> <p style="text-align: center;"> <i>No</i> <i>Probably no</i> <i>Uncertain</i> <i>Probably yes</i> <i>Yes</i> <i>Varies</i> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> </p>	<p>In a 2013 systematic review of 22 published studies among men aged 14–79 years (N=8360), overall mean acceptability of HPV vaccine was moderate at 57 on a 100-point scale, and median acceptability of HPV vaccine was 62 (range: 8–94).</p>		
	CRITERIA	WORK GROUP JUDGMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	<p>Is there important uncertainty about or variability in how much people value the main outcomes?</p> <p style="text-align: center;"> <i>Important uncertainty or variability</i> <i>Possibly important uncertainty or variability</i> <i>Probably no important uncertainty or variability</i> <i>No important uncertainty or variability</i> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> </p>		<p>In the same 2013 systematic review, in the 9 studies reporting sexual orientation, there was no significant difference in acceptability between gay/bisexual/MSM (n=986) and heterosexuals (n=1713).</p>	
ACCEPTABILITY	<p>Is the intervention acceptable to key stakeholders?</p> <p style="text-align: center;"> <i>No</i> <i>Probably no</i> <i>Uncertain</i> <i>Probably yes</i> <i>Yes</i> <i>Varies</i> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> </p>	<p>In a 2018 survey of 51 immunization programs, 98% were in favor of harmonizing the recommended age for catch-up vaccinations to include everyone through age 26 years. Reasons reported by the majority of programs included: easier to implement (92%), easier to explain to patients (88%), and will simplify health department recommendations and guidelines (84%), easier to explain to providers (84%), facilitate reaching high-risk populations (84%), to create equity between genders (78%), and to reduce the burden on health care providers (76%).</p> <p>In a 2018 survey of 820 primary care physicians, 93% were in favor of a change to harmonize the recommended age for catch-up vaccinations to include everyone</p>		

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			through age 26 years, and 27% agreed that current catch-up recommendations with different upper ages for males and females have caused challenges or confusion. Reasons reported by the majority of physicians included: simplify the vaccination schedule (99%), easier to implement (97%), easier to explain to patients (96%), facilitate reaching high-risk populations (88%), reduce burden on health care providers (80%), and create equity between genders (61%).				
RESOURCE USE	Is the intervention a reasonable and efficient allocation of resources?	<p style="text-align: center;"> <i>No</i> <i>Probably no</i> <i>Uncertain</i> <i>Probably yes</i> <i>Yes</i> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> </p>	<p>In the context of the existing program, the incremental cost per QALY of expanding male vaccination through age 26 was \$178,000 in a subset of analyses in the HPV-ADVISE model with more favorable model assumptions for adult vaccination.</p> <p>Although less cost-efficient, absolute costs of vaccination would likely increase by <5% in the long-term under the expanded recommendation.</p>				Results of health economic analyses are not so favorable or unfavorable as to make a strong economic case for or against harmonization through age 26 years.
FEASIBILITY	Is the intervention feasible to implement?	<p style="text-align: center;"> <i>No</i> <i>Probably no</i> <i>Uncertain</i> <i>Probably yes</i> <i>Yes</i> <i>Varies</i> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> </p>	As a simplifying modification to an existing vaccination program, this intervention is considered feasible to implement. ACIP already recommends catch-up vaccination for females aged 22–26 years and some special populations.				A simplified HPV vaccine schedule is expected to be easier to explain and remember.
	Balance of consequences	Undesirable consequences <i>clearly outweigh</i> desirable consequences in most settings <input type="checkbox"/>	Undesirable consequences <i>probably outweigh</i> desirable consequences in most settings <input type="checkbox"/>	The balance between desirable and undesirable consequences <i>is closely balanced or uncertain</i> <input type="checkbox"/>	Desirable consequences <i>probably outweigh</i> undesirable consequences in most settings <input checked="" type="checkbox"/>	Desirable consequences <i>clearly outweigh</i> undesirable consequences in most settings <input type="checkbox"/>	There is insufficient evidence to determine the balance of consequences <input type="checkbox"/>

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Is there sufficient information to move forward with a recommendation?			
Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>			
Policy option for ACIP consideration	ACIP does not recommend the intervention <input type="checkbox"/>	ACIP recommends the intervention for individuals based on shared clinical decision-making <input type="checkbox"/>	ACIP recommends the intervention <input checked="" type="checkbox"/>
Recommendation (text)	<p><i>Routine and catch-up age groups</i> ACIP recommends routine HPV vaccination at age 11 or 12 years; vaccination can be given starting at age 9 years.* ACIP also recommends catch-up vaccination for persons through age 26 years who are not adequately vaccinated.†</p> <p><i>Special populations and medical conditions</i> The above recommendations for routine and catch-up age groups also apply to MSM;‡ transgender people; and people with immunocompromising conditions.</p>		
Additional considerations (optional)	<p>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.</p>		

*Recommended 2-dose and 3-dose schedules and intervals are unchanged from prior recommendation (Meites et al, MMWR 2016).

†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

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Final deliberation and decision by the ACIP

Final ACIP recommendation	ACIP does not recommend the intervention <input type="checkbox"/>	ACIP recommends the intervention for individuals based on shared clinical decision-making <input type="checkbox"/>	ACIP recommends the intervention <input checked="" type="checkbox"/>
ACIP considerations	Fourteen ACIP members voted unanimously to recommend harmonization across genders of the upper age for catch-up vaccination through age 26 years. ACIP placed high value on prevention of HPV infections and related disease; simplification of the immunization schedule to improve acceptability and feasibility for programs and vaccine providers; and gender equality, according to the Healthy People 2020 goal to achieve health equity, eliminate disparities, and improve the health of all groups.		

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-etc-framework>. Framework last updated 19 June 2019.