National Center for Immunization & Respiratory Diseases



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Advisory Committee on Immunization Practices June 26, 2019

ACIP Evidence to Recommendations Framework

- PICO question and background
- Problem
- Benefits & harms
- Values
- Acceptability
- Resource use
- Feasibility
- Balance of consequences
- Policy option for ACIP consideration

PICO Question

- 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 age 22 through 26 years
- Intervention: Catch-up vaccination with 3 doses of HPV vaccine*
- <u>Comparison</u>: Existing HPV vaccination recommendations
- Outcome: Primary prevention of HPV infection and HPV-related disease

* Data considered for all licensed HPV vaccines, but only 9vHPV is available in the United States

Background

- ACIP routinely recommends HPV vaccination for adolescents; catch-up recommendations apply to people not vaccinated at routine age
 - Since 2006, ACIP has recommended routine vaccination for females at age 11 or 12 years, and catch-up vaccination through age 26 years
 - In 2011, ACIP added routine recommendations for males at age 11 or 12 years, and catch-up vaccination through age 21 years
 - Catch-up vaccination also recommended through age 26 years for MSM, transgender people, and certain immunocompromising conditions
- Coverage is increasing among adolescents but remains low in young adults
 - In 2017, ≥1 dose coverage was 69% in females, 63% in males age 13–17
 - In 2017, ≥1 dose coverage was 51% in females, 15% in males age 22–26

Walker TY, et al. MMWR. 2018;67(33):909-917, and https://www.cdc.gov/nchs/nhis/index.htm

PROBLEM

HPV-ASSOCIATED CANCERS PER YEAR, UNITED STATES

	Percentage	Number probably caused by any HPV type				
Cancer site	attributable to HPV	Women	Men	Total		
Cervix	91%	10,751	0	10,751		
Vagina	75%	635	0	635		
Vulva	69%	2,707	0	2,707		
Penis	63%	0	803	803		
Anus*	91%	4,008	1,949	5,957		
Oropharynx	70%	2,160	10,725	12,885		
TOTAL	_	20,260	13,477	33,737		

Uncertain how much HPV-related morbidity and mortality is related to new HPV infections acquired by men at ages 22 through 26 years

*Includes anal and rectal squamous cell carcinomas. Data for 2011–2015 from https://www.cdc.gov/cancer/hpv/statistics, and Saraiya M, et al. U.S. assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. J Natl Cancer Inst. 2015 Apr 29;107(6):djv086.

Problem



- HPV-related disease is a problem of public health importance
- Preventing new HPV infections among 22–26 year-old males is probably of public health importance

BENEFITS & HARMS

- Desirable anticipated effects
 - Efficacy has been demonstrated in this age group
 - Additional benefit small compared with existing program
 - Under the existing program, number needed to vaccinate (NNV) to prevent one case of anogenital warts, CIN 2+, or cancer, is:

- 9; 22; and 202, respectively

• For expanding recommendations for males through age 26 years to harmonize catch-up vaccination, these NNV would be:

- 40; 450; and 3,260, respectively

Giuliano AR, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. *N Engl J Med*. 2011 Feb 3;364(5):401-11. Palefsky JM, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med*. 2011 Oct 27;365(17):1576-85. Castellsagué X, et al. Immunogenicity and safety of the 9-valent HPV vaccine in men. *Vaccine*. 2015 Nov 27;33(48):6892-901. NNV results from HPV-ADVISE, per Chesson HW, Overview of Health Economic Models for HPV Vaccination of Mid-Adults, presentation to ACIP, June 2019.

- Undesirable anticipated effects
 - In 9vHPV clinical trials (n=3225), no serious vaccine-related events among males aged 9–26 years
 - Other adverse events (injection-site events, headache) generally less common among males than females
- HPV vaccines have an excellent safety profile based on large clinical trials and post-licensure effectiveness data
 - >100 million doses of HPV vaccine given in the United States

Castellsagué X, et al. Immunogenicity and safety of the 9-valent HPV vaccine in men. *Vaccine*. 2015 Nov 27;33(48):6892-901. Moreira ED, et al. Safety profile of the 9-valent HPV vaccine: A combined analysis of 7 phase III clinical trials. *Pediatrics*. 2016 Aug;138(2). Donahue J. Rapid Cycle Analysis of 9vHPV in the Vaccine Safety Datalink. Presentation to ACIP. Atlanta, GA. February 21, 2018. Arana J. Adverse events following 9vHPV reported to VAERS. Presentation to ACIP, Atlanta, GA. February 21, 2018.

How substantial are the desirable anticipated effects?

Minimal	Small ☑	Moder	ate	Large	Don't l	know]	Varies
How substantial are the undesirable anticipated effects?							
Minimal ☑	Small	Moder	ate	Large	Don't l	know]	Varies
Do the desi	Do the desirable effects outweigh the undesirable effects?						
Favors interventio 🗹	intervention comparison		Favors both		Favor neith		Unclear

 Full grading of recommendations, assessment, development and evaluation (GRADE) for use of 4vHPV for males and 9vHPV for males have been publically available since these ACIP recommendations were made in 2011 and 2015

Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) for HPV Vaccine for Males. <u>https://www.cdc.gov/vaccines/acip/recs/grade/hpv-vac-males.html</u> Linked from *MMWR*; December 23, 2011 / 60(50);1705-8. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) for Use of 9-valent Human Papillomavirus Vaccine (9vHPV) in Females and Males. <u>https://www.cdc.gov/vaccines/acip/recs/grade/hpv-9v.html</u> Linked from *MMWR*; March 27, 2015 / 64(11);300-304.

What is the overall certainty of this evidence for the critical outcomes?						
Effectiveness of t	Effectiveness of the intervention					
No included studies	4 Very low □	3 Low	2 Moderate ☑	1 High □		
Safety of the inte	Safety of the intervention					
No included studies	4 Very low □	3 Low	2 Moderate ☑	1 High □		



Values

- Acceptable to target population
 - In a systematic review of 22 studies among men ages 14–79 years (n=8,360), mean acceptability of HPV vaccine was moderate
 - 57 on a 100-point scale
 - In the 9 studies reporting sexual orientation, there was no significant difference in acceptability between gay/bisexual/MSM (n=986) and heterosexual men (n=1713)

Values

Does the target population feel that the desirable effects are large relative to undesirable effects?

No	Probably	Uncertain	Probably	Yes	Varies
	no		yes		

Is there important uncertainty about or variability in how much people value the main outcomes?

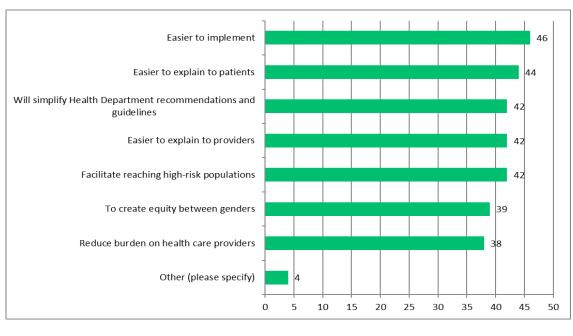
Important	Possibly important	Probably no	No important	No known
uncertainty or	uncertainty or	important	uncertainty or	undesirable
variability	variability	uncertainty or	variability	outcomes
		variability		

ACCEPTABILITY

Acceptability: Programs

- 2018 Association of Immunization Managers (AIM) Survey
 - 51 of 64 immunization programs responded
 - 98% (50 of 51) were in favor of harmonizing the recommended age for catch-up vaccination to include everyone through age 26 years

Reasons programs favor harmonization



Acceptability: Vaccine Providers

- Primary care physician survey in 2018:
 - 820 of 1383 physicians responded, including pediatricians, family physicians, and internal medicine physicians
 - 93% were in favor of a change to harmonize the recommended age for catch-up vaccination to include everyone through age 26 years
 - 27% agreed that current catch-up recommendations with different upper ages for males and females caused challenges or confusion

Acceptability: Vaccine Providers

Reasons why physicians favor harmonization (n=713)		
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%	
To create equity between genders	61%	
Other	5%	

Acceptability

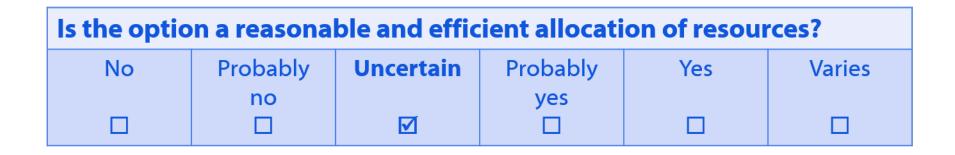
Is the intervention acceptable to key stakeholders?					
No	Probably	Uncertain	Probably	Yes	Varies
	no		yes		

RESOURCE USE

Resource Use

- Health economic analyses were conducted:
 - In the context of the existing program, incremental cost per QALY for expanding male vaccination through age 26 years was \$178,000
 - Although less cost-efficient, absolute costs of vaccination would likely increase by <5% long-term under the expanded recommendation
- Results are not so favorable or unfavorable as to make a strong economic case for or against harmonization through age 26 years

Resource Use



FEASIBILITY

Feasibility

- Modification to an existing vaccination program
- ACIP already recommends catch-up HPV vaccination for people aged 22–26 years who are: female, MSM (including men who identify as gay or bisexual, or who intend to have sex with men), transgender, and/or with certain immunocompromising conditions
- Simplified adult immunization schedule easier to explain and remember

Feasibility

Is the option feasible to implement?					
No	Probably	Uncertain	Probably	Yes	Varies
	no		yes		

BALANCE OF CONSEQUENCES

Balance of Consequences

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 suffi	cient informa	tion to move	forward with	a recommend	dations?
Yes ☑				No □	

Policy Option for ACIP Consideration

Policy option 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				

National Center for Immunization & Respiratory Diseases



Evidence to Recommendations for HPV Vaccination of Adults Older than Age 26 Years

Elissa Meites, MD, MPH

Medical Epidemiologist, Division of Viral Diseases

Advisory Committee on Immunization Practices June 26, 2019

PICO QUESTION

- 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 age 27–45 years
- Intervention: Catch-up vaccination with 3 doses of HPV vaccine*
- <u>Comparison</u>: Persons age 27–45 years with no catch-up HPV vaccination
- Outcome: Primary prevention of HPV infection and HPV-related disease

* Data considered for all licensed HPV vaccines, but only 9vHPV is available in the United States

BACKGROUND

- HPV is a commonly sexually transmitted infection
- Persistent HPV infections can develop into cancers, usually several decades later
- Vaccination against HPV is recommended to prevent new HPV infections and subsequent disease
- In October 2018, FDA approved 9vHPV for use in women and men through age 45 years

Food and Drug Administration. Prescribing information [package insert]. Gardasil 9 [human papillomavirus 9-valent vaccine, recombinant] Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2018.

PROBLEM

HPV-ASSOCIATED CANCERS PER YEAR, UNITED STATES

	Percentage	Number probably caused by any HPV type				
Cancer site	attributable to HPV	Women	Men	Total		
Cervix	91%	10,751	0	10,751		
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Oropharynx	70%	2,160	10,725	12,885		
TOTAL	-	20,260	13,477	33,737		

Uncertain how much HPV-related morbidity and mortality is related to new HPV infections acquired at ages 27 through 45 years

*Includes anal and rectal squamous cell carcinomas. Data for 2011–2015 from https://www.cdc.gov/cancer/hpv/statistics, and 35 Saraiya M, et al. U.S. assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. J Natl Cancer Inst. 2015 Apr 29;107(6):djv086.

PROBLEM

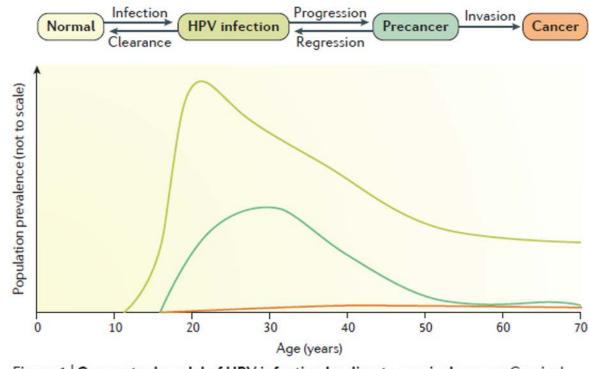


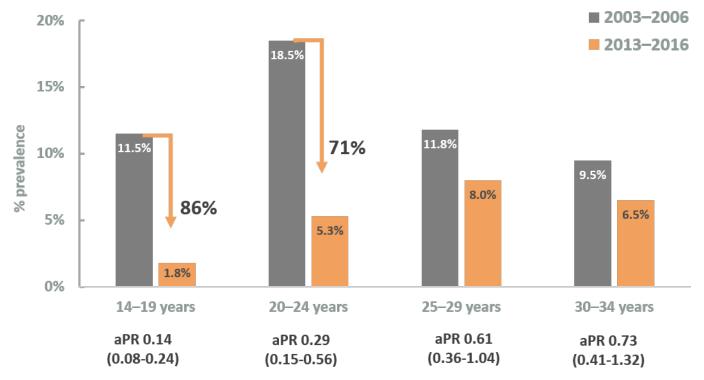
Figure 1 Conceptual model of HPV infection leading to cervical cancer. Cervical cancer arises via a series of necessary steps (infection; persistence, rather than clearance; associated with precancer; and invasive cancer), with each stage mainly occurring at characteristic ages.

PROBLEM

- A new sex partner is a risk factor for new HPV infections
- Exposure to HPV decreases among older age groups
 - Percentage of people reporting a new sex partner within the past year is lower in older age groups than among younger age groups
- The existing U.S. HPV vaccination program has resulted in significant declines in prevalence of vaccine-type HPV infections, anogenital warts, and cervical precancers
- Declines have been observed among both vaccinated and unvaccinated persons, suggesting protective herd effects

Winer RL, et al. Incident Detection of High-Risk HPV in a Cohort of High-Risk Women Aged 25-65 Years. J Infect Dis. 2016 Sep 1;214(5):665-75.Markowitz LE, et al. Ten Years of Human Papillomavirus Vaccination in the United States. Academic Pediatrics. 2018.37

Prevalence of Vaccine-type HPV 6/11/16/18 2013–2016 compared to pre-vaccine era, females



aPR, adjusted prevalence ratio

McClung NM, et al. HPV prevalence among females in the United States, NHANES. 68th EIS Conference; April 2019; Atlanta, GA.

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PROBLEM

Is the problem of public health importance?						
No	Probably	Uncertain	Probably	Yes	Varies	
	no		yes			

- HPV-related disease is a problem of public health importance
- Amount of HPV-related disease that could be prevented by vaccinating 27–45 year-olds is small, compared with vaccinating at younger ages
- Preventing new HPV infections among 27–45 year-olds is of uncertain public health importance

- FUTURE III trial of 4vHPV in women ages 24–45 years (n=3,819)
 - Against a combined endpoint of persistent HPV infection, extragenital lesions, and/or CIN 1+
 - Per-protocol efficacy: 88.7% (95% Cl: 78.1–94.8)
 - Intention-to-treat efficacy: 47.2% (95% CI: 33.5–58.2)
- 9vHPV trial in women ages 27–45 years (n=640)
 - Antibody titers non-inferior compared to women ages 16–26 years
 - >99% of women in both groups seroconverted to all 9vHPV types

Castellsagué X, 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. *British Journal of Cancer*. 2011;105:28-37. Luxembourg A. 9vHPV immunogenicity and safety trial in mid-adult females. Presentation to ACIP, Atlanta, GA. June 26, 2019.

- Desirable anticipated effects vary
 - HPV vaccines are most effective when given before exposure to HPV
 - Population benefit would be minimal, yet some individuals in this age range might be able to benefit from vaccination
- Under the existing program, number needed to vaccinate (NNV) to prevent one case of anogenital warts, CIN 2+, or cancer, is:
 - 9; 22; and 202, respectively
- For expanding vaccination through age 45 years, these NNV would be:
 - 120; 800; and 6,500, respectively

Castellsagué X, 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. *British Journal of Cancer*. 2011;105:28-37.

NNV results from HPV-ADVISE, per Chesson HW, Overview of Health Economic Models for HPV Vaccination of Mid-Adults, presentation to AC42 June 2019

- 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

How substantial are the desirable anticipated effects?

Minimal	Small	Mode	erate	Large	Don	′t know □	Varies ☑
How substantial are the undesirable anticipated effects?							
Minimal ☑	Small	Mode	erate I	Large	Don	′t know □	Varies
Do the desi	Do the desirable effects outweigh the undesirable effects?						
Favors interventio □			Fav	ors both	Favors neither		Unclear

GRADE SUMMARY

- Full GRADE tables were presented to ACIP in October 2018
- Adding results from the 9vHPV observational trial presented today
- Certainty of the evidence on benefits:
 - Efficacy: 3 RCTs of 4vHPV and/or 2vHPV
 - Immunogenicity: 3 RCTs, 6 observational trials
 - GRADE evidence level 2 (moderate quality evidence)
- Certainty of the evidence on harms:
 - Safety: 5 RCTs, 4 observational trials
 - GRADE evidence level 2 (moderate quality evidence)

What is the overall certainty of the evidence for the critical outcomes?							
Effectiveness of the intervention							
No included4321studiesVery lowLowModerateHigh□□□□□							
Safety of the in	Safety of the intervention						
No included studies	4 Very low □	3 Low	2 Moderate ☑	1 High □			



VALUES

- Acceptability to target population
 - 9 published studies of adults (n=2841 women, n=1195 men)
 - Acceptability varied across studies, overall was moderate to high
 - Acceptability was higher when vaccine was assumed to be free, and/or a health care provider made a recommendation
 - Acceptability varied by study population and methodology

VALUES

Does the target population feel that the desirable effects are large relative to undesirable effects?

No	Probably	Uncertain	Probably	Yes	Varies
	no		yes		

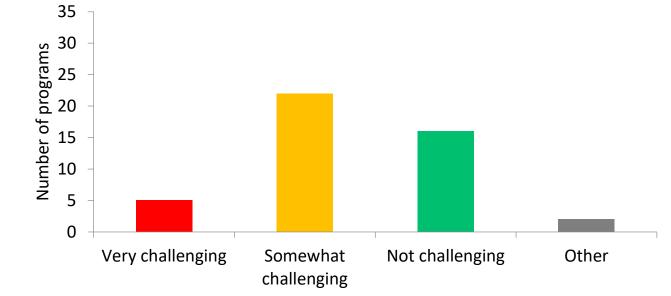
Is there important uncertainty about or variability in how much people value the main outcomes?

Important	Possibly important	Probably no	No important	No known
uncertainty or	uncertainty or	important	uncertainty or	undesirable
variability	variability	uncertainty or	variability	outcomes
		variability		

ACCEPTABILITY

ACCEPTABILITY: PROGRAMS

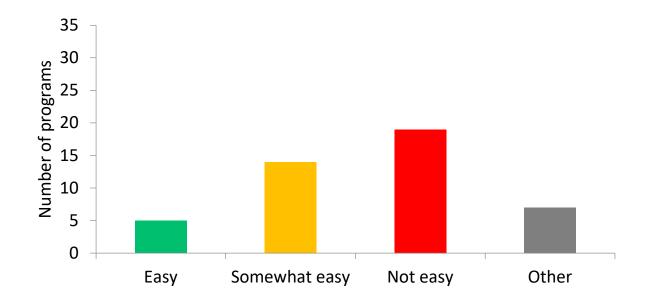
How challenging would it be for your immunization program to communicate a recommendation (for shared clinical decision making) to vaccine providers?



Unpublished data, Association of Immunization Managers (AIM), January–February 2019

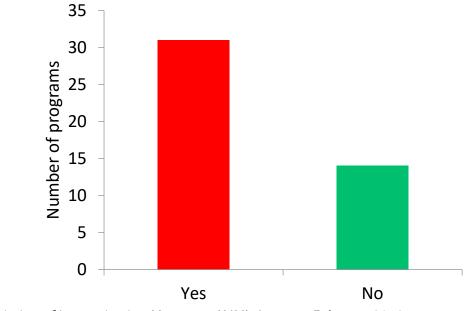
ACCEPTABILITY: PROGRAMS

How easy would it be for vaccine providers to determine patients in this age group who might benefit from vaccination?



ACCEPTABILITY: PROGRAMS

Do you anticipate any challenges to implementing such a recommendation?



Unpublished data, Association of Immunization Managers (AIM), January–February 2019

ACCEPTABILITY



RESOURCE USE

RESOURCE USE: ADULT HPV VACCINATION

- 5 health economic models of HPV vaccination in the U.S. were reviewed:
 - The cost-effectiveness ratio for the current HPV vaccination program ranged from cost-saving to about \$35,000 per QALY gained
 - In the context of the existing program, expanding vaccination to adults through age 45 years would produce relatively small additional health benefits and less favorable costeffectiveness ratios
 - The incremental cost per QALY for also vaccinating adults through age 30 years exceeded \$300,000 in four of five models
 - Variation in results across models was due to factors such as uncertainties about HPV natural history

RESOURCE USE: GLOBAL HPV VACCINE SHORTAGE

- Globally, there is an HPV vaccine shortage as production capacity is not adequate to meet demand currently
- Demand/supply imbalance is expected to last for the next 3–5 years
- In some countries, including those with Gavi and UNICEF support, national introductions and multi-age cohort vaccination are unable to proceed due to lack of vaccine availability
- Although no domestic vaccine shortage is anticipated, some Work Group members had concerns about HPV vaccination recommendations being extended to 27 through 45 year-olds in the United States in this context

RESOURCE USE

Is the option a reasonable and efficient allocation of resources?						
No	Probably	Uncertain	Probably	Yes	Varies	
	no		yes			

- 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
- For shared clinical decision making, identifying individuals likely to benefit from adult HPV vaccination could be challenging
 - Some vaccine providers do not regularly assess sexual behaviors
 - In a 2015 survey of obstetrician/gynecologists (n=353), 81% reported that they stock and administer HPV vaccine

- Health disparities and equity concerns
 - Not clear whether any recommendation for HPV vaccination in this age range would lead to greater uptake among individuals who are <u>likely</u> versus <u>unlikely</u> to benefit
 - Recommending vaccination in this age range might <u>reduce</u> health disparities, by increasing access to vaccination among adults with health insurance coverage
 - Recommending vaccination in this age range might <u>enhance</u> health disparities, as underinsured adults would be less likely to have access to vaccination since states have limited funds for adult vaccination programs

Is the option feasible to implement?						
No	Probably	Uncertain	Probably	Yes	Varies	
	no □		yes ☑			

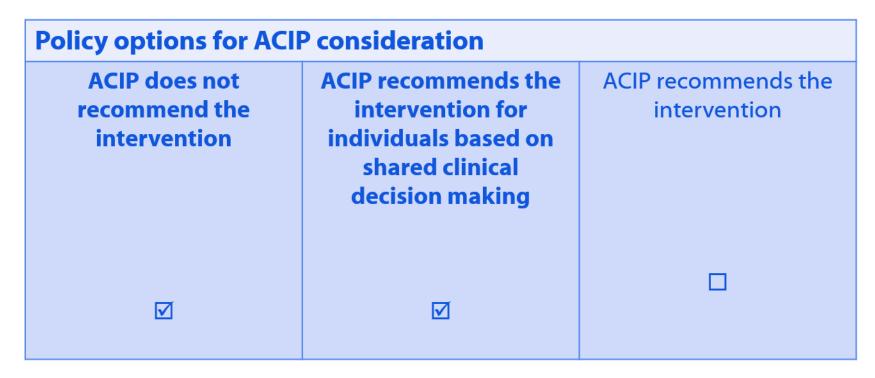
BALANCE OF CONSEQUENCES

BALANCE OF CONSEQUENCES

Balance of consequences

Undesirable consequences <i>clearly</i> <i>outweigh</i> 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 <i>clearly</i> <i>outweigh</i> undesirable consequences in most settings	There is insufficient evidence to determine the balance of consequences		
Is there suffi	Is there sufficient information to move forward with a recommendation?						
Yes ☑				No □			

Policy Options for ACIP Consideration



ACIP HPV Vaccines Work Group

<u>ACIP Members</u> Peter Szilagyi (Chair) Jose Romero Kevin Ault

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

