Evidence to Recommendations for Harmonization of Catch-Up HPV Vaccination through Age 26 Years

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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

Framework last updated 19 June 2019
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*
- **Comparison**: 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

# HPV-ASSOCIATED CANCERS PER YEAR, UNITED STATES

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Percentage attributable to HPV</th>
<th>Number probably caused by any HPV type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Women</td>
</tr>
<tr>
<td>Cervix</td>
<td>91%</td>
<td>10,751</td>
</tr>
<tr>
<td>Vagina</td>
<td>75%</td>
<td>635</td>
</tr>
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<td>Vulva</td>
<td>69%</td>
<td>2,707</td>
</tr>
<tr>
<td>Penis</td>
<td>63%</td>
<td>0</td>
</tr>
<tr>
<td>Anus*</td>
<td>91%</td>
<td>4,008</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>70%</td>
<td>2,160</td>
</tr>
<tr>
<td>TOTAL</td>
<td>-</td>
<td>20,260</td>
</tr>
</tbody>
</table>

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

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

NNV results from HPV-ADVISE, per Chesson HW, Overview of Health Economic Models for HPV Vaccination of Mid-Adults, presentation to ACIP, June 2019.
Benefits & Harms

- 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
# Benefits & Harms

## How substantial are the desirable anticipated effects?

<table>
<thead>
<tr>
<th>Minimal</th>
<th>Small</th>
<th>Moderate</th>
<th>Large</th>
<th>Don’t know</th>
<th>Varies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</table>

## Do the desirable effects outweigh the undesirable effects?

<table>
<thead>
<tr>
<th>Favors intervention</th>
<th>Favors comparison</th>
<th>Favors both</th>
<th>Favors neither</th>
<th>Unclear</th>
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<tbody>
<tr>
<td>✓</td>
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</table>
Benefits & Harms

- 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.
https://www.cdc.gov/vaccines/acip/recs/grade/hpv-vac-males.html 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.
https://www.cdc.gov/vaccines/acip/recs/grade/hpv-9v.html Linked from MMWR; March 27, 2015 / 64(11);300-304.
## Benefits & Harms

### What is the overall certainty of this evidence for the critical outcomes?

<table>
<thead>
<tr>
<th>Effectiveness of the intervention</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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</thead>
<tbody>
<tr>
<td>No included studies</td>
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<td>Moderate</td>
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</table>
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?

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<th>Yes</th>
<th>Varies</th>
</tr>
</thead>
<tbody>
<tr>
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<td><img src="true" alt="Uncertain" /></td>
<td><img src="true" alt="Probably yes" /></td>
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### Is there important uncertainty about or variability in how much people value the main outcomes?

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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

- Easier to implement: 46
- Easier to explain to patients: 44
- Will simplify Health Department recommendations and guidelines: 42
- Easier to explain to providers: 42
- Facilitate reaching high-risk populations: 42
- To create equity between genders: 39
- Reduce burden on health care providers: 38
- Other (please specify): 4
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

<table>
<thead>
<tr>
<th>Reasons why physicians favor harmonization (n=713)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simplify the vaccination schedule</td>
<td>99%</td>
</tr>
<tr>
<td>Easier to implement</td>
<td>97%</td>
</tr>
<tr>
<td>Easier to explain to patients</td>
<td>96%</td>
</tr>
<tr>
<td>Facilitate reaching high-risk populations</td>
<td>88%</td>
</tr>
<tr>
<td>Reduce burden on health care providers</td>
<td>80%</td>
</tr>
<tr>
<td>To create equity between genders</td>
<td>61%</td>
</tr>
<tr>
<td>Other</td>
<td>5%</td>
</tr>
</tbody>
</table>

Unpublished data, Children’s Outcomes Research, University of Colorado, 2018
<table>
<thead>
<tr>
<th>Acceptability</th>
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</table>

Is the intervention acceptable to key stakeholders?

<table>
<thead>
<tr>
<th></th>
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<th>Uncertain</th>
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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.

QALY, quality-adjusted life year
Chesson HW. Overview of Health Economic Models for HPV Vaccination of Mid-Adults. Presentation to ACIP, Atlanta, GA. June 26, 2019.
## Resource Use

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<thead>
<tr>
<th></th>
<th>No</th>
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<th>Yes</th>
<th>Varies</th>
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<tbody>
<tr>
<td><strong>Is the option a reasonable and efficient allocation of resources?</strong></td>
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<td>✔️</td>
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</table>
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

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</tr>
</tbody>
</table>

Is the option feasible to implement?
BALANCE OF CONSEQUENCES
## Balance of Consequences

<table>
<thead>
<tr>
<th>Undesirable consequences clearly outweigh desirable consequences in most settings</th>
<th>Undesirable consequences probably outweigh desirable consequences in most settings</th>
<th>The balance between desirable and undesirable consequences is closely balanced or uncertain</th>
<th>Desirable consequences probably outweigh undesirable consequences in most settings</th>
<th>Desirable consequences clearly outweigh undesirable consequences in most settings</th>
<th>There is insufficient evidence to determine the balance of consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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</tbody>
</table>

**Is there sufficient information to move forward with a recommendations?**

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>☑</td>
<td>☐</td>
</tr>
</tbody>
</table>
## Policy Option for ACIP Consideration

<table>
<thead>
<tr>
<th>Policy option for ACIP consideration</th>
<th>ACIP does not recommend the intervention</th>
<th>ACIP recommends the intervention for individuals based on shared clinical decision making</th>
<th>ACIP recommends the intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
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<td></td>
</tr>
</tbody>
</table>
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*
- **Comparison**: 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
### HPV-ASSOCIATED CANCERS PER YEAR, UNITED STATES

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Percentage attributable to HPV</th>
<th>Women</th>
<th>Men</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>91%</td>
<td>10,751</td>
<td>0</td>
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<td>Vagina</td>
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<td>635</td>
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<td>Vulva</td>
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<td>2,707</td>
<td>0</td>
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<tr>
<td>Penis</td>
<td>63%</td>
<td>0</td>
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<td>Anus*</td>
<td>91%</td>
<td>4,008</td>
<td>1,949</td>
<td>5,957</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>70%</td>
<td>2,160</td>
<td>10,725</td>
<td>12,885</td>
</tr>
<tr>
<td>TOTAL</td>
<td>-</td>
<td>20,260</td>
<td>13,477</td>
<td>33,737</td>
</tr>
</tbody>
</table>

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

PROBLEM

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

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

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

- 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

<table>
<thead>
<tr>
<th>Is the problem of public health importance?</th>
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<tbody>
<tr>
<td>No</td>
</tr>
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- Preventing new HPV infections among 27–45 year-olds is of uncertain public health importance

39
BENEFITS & HARMs

- 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% CI: 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

BENEFITS & HARMs

- 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


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

- 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.

Meites E, GRADE for HPV Vaccination of Mid-Adults. ACIP. October 2018, Atlanta, GA, and [http://www.cdc.gov/vaccines/acip/recs/grade/table-refs.html](http://www.cdc.gov/vaccines/acip/recs/grade/table-refs.html)
### BENEFITS & HARMs

<table>
<thead>
<tr>
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<td>Favors intervention [ ]</td>
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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)

Meites E, GRADE for HPV Vaccination of Mid-Adults. ACIP. October 2018, Atlanta, GA, and http://www.cdc.gov/vaccines/acip/recs/grade/table-ref-s.html. RCTs, Randomized Controlled Trials
### BENEFITS & HARMs

What is the overall certainty of the evidence for the critical outcomes?

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VALUES
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?**

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

- Very challenging
- Somewhat challenging
- Not challenging
- Other

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?

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

- Do you anticipate any challenges to implementing such a recommendation?

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

### Is the option acceptable to key stakeholders?

<table>
<thead>
<tr>
<th>No</th>
<th>Probably no</th>
<th>Uncertain</th>
<th>Probably yes</th>
<th>Yes</th>
<th>Varies</th>
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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 cost-effectiveness 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.

QALY, quality-adjusted life year.

Chesson HW. Overview of Health Economic Models for HPV Vaccination of Mid-Adults. Presentation to ACIP, Atlanta, GA. June 26, 2019.
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
<table>
<thead>
<tr>
<th>No</th>
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FEASIBILITY
FEASIBILITY

- 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

FEASIBILITY

- 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 likely versus unlikely to benefit
  - Recommending vaccination in this age range might reduce health disparities, by increasing access to vaccination among adults with health insurance coverage
  - 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
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<td><strong>FEASIBILITY</strong></td>
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BALANCE OF CONSEQUENCES
### Balance of Consequences

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<tr>
<th>Undesirable consequences clearly outweigh desirable consequences in most settings</th>
<th>Undesirable consequences probably outweigh desirable consequences in most settings</th>
<th>The balance between desirable and undesirable consequences is closely balanced or uncertain</th>
<th>Desirable consequences probably outweigh undesirable consequences in most settings</th>
<th>Desirable consequences clearly outweigh undesirable consequences in most settings</th>
<th>There is insufficient evidence to determine the balance of consequences</th>
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**Is there sufficient information to move forward with a recommendation?**

<table>
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## Policy Options for ACIP Consideration

<table>
<thead>
<tr>
<th>Policy options for ACIP consideration</th>
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<tbody>
<tr>
<td><strong>ACIP does not recommend the intervention</strong></td>
</tr>
<tr>
<td>✓</td>
</tr>
<tr>
<td><strong>ACIP recommends the intervention for individuals based on shared clinical decision making</strong></td>
</tr>
<tr>
<td>✓</td>
</tr>
<tr>
<td><strong>ACIP recommends the intervention</strong></td>
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</table>
ACIP HPV Vaccines
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Kevin Ault

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Joohee Lee (FDA)

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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.