Overview and Background

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Purpose of presentation

- To provide background for subsequent modeling presentations
- To describe some of the uncertainties regarding HPV epidemiology and natural history that impact considerations for mid-adult HPV vaccination

Mid-adults defined as persons aged 27-45 years
Current recommendations for HPV vaccination in the United States

- **Routine vaccination**
  - Age 11 or 12 years
  - Vaccination can be started at age 9 years

- **Catch-up vaccination**
  - Females through age 26 years
  - Males through age 21 years
  - Certain populations through age 26 years*

- **Males aged 22 through 26 years may be vaccinated**

*Men who have sex with men, transgender persons, and persons with certain immunocompromising conditions

MMWR 2014;63 (RR05)  MMWR 2015;64:300-4  MMWR 2016; 65:2105-8
ACIP HPV Vaccines Work Group discussions

- **Current HPV vaccination program and focus on adolescents**
  - Work Group affirms the importance of adolescent HPV vaccination and the primary focus of the vaccination program on this age group

- **HPV vaccination for mid-adults**
  - Vaccination is safe and effective among mid-adults if they are exposed and susceptible to infection
  - Health economic modeling is addressing the additional health benefit and incremental cost-effectiveness of extending the HPV vaccine program in the United States through age 45 years (or another age between 27 and 45 years)

Mid-adults defined as persons aged 27-45 years
Health economic models examining mid-adult vaccination

- Preliminary results from 3 models presented at ACIP, October 2018
  - US HPV-ADVISE (Laval University/CDC), Simplified model (CDC), Merck model
  - Large differences in cost effectiveness across models

- CDC requested input from another modeling group
  - Cancer Intervention and Surveillance Modeling Network (CISNET) [https://cisnet.cancer.gov/](https://cisnet.cancer.gov/)
  - CISNET is a modeling network funded by the U.S. National Cancer Institute

- Modelers and ACIP/CDC economic reviewers are working to understand reasons for differences
  - Reviewers asked all modelers to include a set of results when using standardized health economic parameters to facilitate comparisons
    - Vaccination costs, medical treatment costs, quality of life impact
Exploration of reasons for differences between HPV vaccine health economic model results for mid-adults

- Health economic parameters
- Vaccination coverage
- Model structures
- HPV epidemiology and natural history

Main question for this policy consideration:
- How much disease is due to incident HPV infections that occur in mid-adults?
HPV natural history considerations for mid-adult vaccination
Understanding the burden of disease due to incident HPV infection in mid-adults

- HPV incidence highest in late teens and early twenties
  - Over 90% of infections clear or become undetectable
- New HPV infections do occur in mid-adults
  - New partner is main risk factor
- Epidemiology of HPV infection differs for males and females
- Some uncertainty about immunity after clearance of natural infection
  - Immunity thought to be low; higher for females than males
- Progression to cancer occurs over years/decades
  - Some high risk HPV types more likely to progress to cancer
- Less known about natural history in males than females

HPV-associated cancers: Rates by age group and median age at diagnosis, United States, 2011–2015

Circles show median age at diagnosis
CDC. Division of Cancer Prevention and Control website: HPV-Associated Cancer Diagnosis by Age (2018)
What proportion of cervical cancers are caused by HPV infections acquired by different ages?

Of women with cervical cancer, an estimated

- 50% of women acquired causal HPV infection by age 21 years
- 75% of women acquired causal HPV infection by age 31 years

Other modeling teams also working to estimate age at causal infection

In the context of no vaccination or screening
Burger at al. CID 2017
Focus on HPV infection and natural history in females

- Incident HPV infection
- Time from infection to cervical precancer
- Time from precancer to cervical cancer

Cervical precancer: cervical intraepithelial neoplasia grade 2 (CIN2), (CIN3), or adenocarcinoma in situ
Conceptual model of HPV infection leading to cervical cancer

- HPV infection highest in late teens/early 20s
- Most infections clear or become undetectable within 1-2 years
- Many precancers clear
- Precancers can progress to cancer after many years/decades

Proportion of women with prevalent HPV infection and newly detected HPV at a cervical cancer screening visit, Kaiser Permanente Northern California

- Prevalent HPV at enrollment and newly detected HPV declined significantly with increasing age
Any high risk 9vHPV type seroprevalence and DNA prevalence, by age group, females, NHANES 2005–2006

DNA prevalence
- Highest in 20–24 year-olds
- Lower in older age groups

Seroprevalence
- 11% by 14–19 years
- 34% by 20–24 years
- Highest in 30–39 year-olds
  - No change from early to late 30s
- Lower in older age groups
Any high risk 9vHPV type seroprevalence by age group, females, NHANES 2005–2006

- Between 14–19 and 20–24 years
  - 23 percentage point increase
- Between 25–29 and 30–34 years
  - 8 percentage point increase

High risk 9vHPV types: HPV 16, 18, 31, 33, 45, 52, 58; NHANES, National Heath and Nutrition Examination Survey; CDC, unpublished data
Estimate of cumulative infection with any high risk 9vHPV type among females, NHANES 2005–2006

By age 20–21 years an estimated 50% of females already had evidence of infection with >1 high risk 9vHPV type

- Assuming 60% of females develop antibody after infection

High risk 9vHPV types: HPV 16, 18, 31, 33, 45, 52, 58

NHANES, National Heath and Nutrition Examination Survey; CDC, unpublished data
What is known about time for progression of incident HPV infection to cervical precancer and cancer?

- **Time from infection to precancer**
  - Estimated from placebo arms of vaccine clinical trials and cohort studies
  - Duration of follow-up and intensity/methods of screening impact findings

- **Time from precancer to invasive cancer**
  - Unethical to follow women prospectively with untreated CIN3
  - Likely decades based on peak age at infection and cancer diagnosis
  - Estimate from statistical model also suggests long interval*
    - Median = 23.5 years; 1.6% progressed within 10 years

*Vink et al. AJE 2013*
Estimated time from incident HPV infection to cervical precancer detection in studies with frequent screening

<table>
<thead>
<tr>
<th>Study/trial</th>
<th>Age (years)</th>
<th>Screening frequency</th>
<th>Duration of follow-up</th>
<th>Median time to CIN2+ detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winer, 2005</td>
<td>18–20</td>
<td>4 months</td>
<td>39 months</td>
<td>14 months</td>
</tr>
<tr>
<td>Insinga, 2011</td>
<td>16–23</td>
<td>6 months</td>
<td>48 months</td>
<td>~ 1 year</td>
</tr>
<tr>
<td>Skinner, 2016</td>
<td>&gt;25</td>
<td>6 months HPV 12 months Pap</td>
<td>48 months</td>
<td>1–2 years</td>
</tr>
</tbody>
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CIN2+, cervical intraepithelial neoplasia grade 2 or worse

Impact of screening frequency on detection of cervical abnormalities

- Cumulative incidence of low grade cervical abnormalities* under the assumption of 4-, 12-, or 24-month screening intervals

<table>
<thead>
<tr>
<th>Screening Interval</th>
<th>At 12 months % (95%CI)</th>
<th>At 24 months % (95%CI)</th>
<th>At 36 months % (95%CI)</th>
<th>At 48 months % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 months</td>
<td>9.1 (6.6, 12.6)</td>
<td>16.7 (13.2, 21.1)</td>
<td>23.3 (19.1, 28.2)</td>
<td>29.0 (24.2, 34.4)</td>
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<tr>
<td>12 months</td>
<td>4.7 (2.9, 7.5)</td>
<td>10.1 (7.4, 14.0)</td>
<td>15.0 (11.5, 19.5)</td>
<td>18.3 (14.1, 23.4)</td>
</tr>
<tr>
<td>24 months</td>
<td>-</td>
<td>7.5 (5.1, 11.0)</td>
<td>-</td>
<td>11.7 (8.3, 16.3)</td>
</tr>
</tbody>
</table>

*low grade squamous intraepithelial neoplasia

Winer et al. JID 2005
Challenges understanding the burden of cervical precancer due to incident HPV infection in mid-adults

- Time from incident infection to CIN2+ diagnosis estimated from studies is impacted by duration of follow-up and screening frequency
- Age at CIN2+ diagnosis depends on age at clinical screening initiation, screening frequency and methods
  - Difficult to use age at CIN2+ diagnosis to estimate when infection occurs
Age distribution of cervical precancers, United States, 2008
Estimates from 5-site surveillance, HPV-IMPACT

- 5-site population-based surveillance in
  - CA, CT, NY, OR, TN

- Used to make projections for U.S. women age ≥18 years

- CIN2+ cases due to any type
  - Annual number: 215,700
  - Median age at diagnosis: 28 years

CIN2+, cervical intraepithelial neoplasia grade 2 or worse, or adenocarcinoma in situ
CDC, unpublished data; based on Gargano et al. CID 2018
Age at precancer detection depends on screening

- **ALTS trial**\(^1\) (1996-1998)
  - Women \(\geq 18\) years, every 6 month screening
  - Median age of CIN3 detection was 23 years

- **5-site HPV-IMPACT surveillance project**\(^2\) (2008)
  - Women \(\geq 18\) years, opportunistic, ‘real life’ screening
  - Median age of CIN2 detection 28 years, CIN3 detection was 30 years

Age at HPV acquisition likely similar in the two populations, but age at precancer detection differed due to screening practices

\(^1\)Sherman et al. CEBP 2003; \(^2\)CDC unpublished data
Summary – selected issues for HPV natural history

- There is rapid acquisition of HPV in late teens and early twenties
- Progression from incident infection to cervical precancer can be within a few years
- Over 90% of infections clear and 30-40% of cervical precancers clear
- Time from progression of precancer to cervical cancer is >20 years – estimate from statistical analysis
- Age at cervical precancer detection depends on screening; difficult to estimate age at causal infection from epidemiologic/surveillance data
- Less is known about the natural history of HPV at non-cervical sites and about progression from infection to cancer in males
- Challenges estimating burden of disease due to incident infections in mid-adults from empiric data
Health economic modeling

- Model-based estimates of the burden of disease due to incident HPV infection in mid-adults depend on assumptions regarding
  - Probability of infection
  - Immunity after clearance of natural infection
  - Sexual behavior and partner mixing
  - Progression and regression of precancer lesions

- Further information on health economic analyses in next 2 presentations
Other Work Group Discussions and Issues
Overview of selected Work Group discussions

- **Mid-adult HPV vaccination recommendations**
  - *Individual decision making* in mid-olds is one of the options being considered by Work Group - presented to ACIP in October 2018
  - Acceptability and values among key stakeholders - to be presented later in session

- **Harmonization of HPV vaccination catch-up recommendations**
  - In February 2018, before awareness of FDA application for expanded age range, Work Group was considering harmonization of catch-up recommendations across genders
  - Work Group members support harmonization
  - Work Group has continued to focus on harmonization while considering mid-adult vaccination
  - Results from provider and program surveys will be presented later in session
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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.