Expanded age range for 9-valent HPV vaccine
Background for policy considerations

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Division of Viral Diseases

Advisory Committee on Immunization Practices
October 24–25, 2018
Outline

- Expanded age range for 9vHPV
  - Data submitted in support of application

- Data from the United States
  - Vaccine coverage and impact, HPV epidemiology and sexual behavior

- Post-licensure vaccine effectiveness evaluations
  - By age at vaccination

- Update on global HPV vaccination
### HPV vaccine licensure and availability, United States
#### Before October 2018

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>HPV types</th>
<th>Manufacturer</th>
<th>Licensure ages</th>
</tr>
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<tr>
<td>Bivalent (2vHPV)</td>
<td>16,18</td>
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</tr>
<tr>
<td>Quadrivalent (4vHPV)</td>
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<td>Merck &amp; Co</td>
<td>Females and males 9–26 yrs</td>
</tr>
<tr>
<td>9-valent (9vHPV)</td>
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<td>Merck &amp; Co</td>
<td>Females and males 9–26 yrs</td>
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### Availability
- Since end of 2016, only 9vHPV has been available in the United States
- 2vHPV and 4vHPV continue to be available in other countries
# HPV vaccine licensure and availability, United States

## October 2018

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### Availability
- Since end of 2016, only 9vHPV has been available in the United States
- 2vHPV and 4vHPV continue to be available in other countries

### Vaccine licensure and use in mid-adults in other countries
- HPV vaccines have been licensed through age 45 years or older in other countries
- No country has a public health HPV vaccine program targeting mid-adults
Current recommendations for HPV vaccination in the United States

- **Routine HPV vaccination at age 11 or 12 years**
  - The vaccination series can be started beginning at age 9 years

- **HPV vaccination is also recommended for the following persons if not adequately vaccinated previously**
  - 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
Expanded age range for use of 9vHPV
FDA Summary Basis for Regulatory Action

- Results of a randomized, double-blind, placebo-controlled trial (base study) of 4vHPV that included women 27–45 years of age
  
  Munoz et al. Lancet 2009
  Castellsague et al. Br J Cancer 2011 (end of study results)

- Observational follow-up of a subset of women in the base study showing effectiveness against anogenital warts and CIN up to 10 years post-vaccination
  
  Luna et al. PLoS One 2013 (6 year follow-up)
  Luxembourg (10 year follow-up presented at ACIP June 2018)

CIN, cervical intraepithelial neoplasia

Expanded age range for use of 9vHPV
FDA Summary Basis for Regulatory Action

- A cross-study immunogenicity analysis showing statistical non-inferiority of immune responses to 4vHPV in males aged 27–45 years compared with males aged 16–26 years, the age in which efficacy was demonstrated

  Antibody data from open label, single arm study of 150 men aged 27–45 years
  Giuliano et al. Vaccine 2015

  Compared with antibody data in males aged 16–26 years in 4vHPV efficacy trial

Expanded age range for use of 9vHPV
FDA Summary Basis for Regulatory Action

- Extrapolation of effectiveness against the additional 5 HPV types covered by 9vHPV in individuals 27–45 years of age
  - Based on understanding of HPV pathophysiology and immune responses to those types elicited by 9vHPV in individuals 9–26 years of age

- Extrapolation of safety of 9vHPV in individuals 27–45 years of age
  - Based on safety experience with 4vHPV in individuals 9–45 years of age and safety experience with 9vHPV in individuals 9–26 years of age

### 4vHPV randomized controlled efficacy, safety and immunogenicity trial in mid-adult women, FUTURE III

<table>
<thead>
<tr>
<th><strong>Population</strong></th>
<th>Women aged 24–45 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>Multi-national – 7 countries</td>
</tr>
<tr>
<td><strong>Number enrolled</strong></td>
<td>3,819</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>Vaccine type 6-month persistent infection or vaccine-type related CIN1 or worse, external genital lesions</td>
</tr>
<tr>
<td><strong>Duration of follow-up</strong></td>
<td>4 years</td>
</tr>
</tbody>
</table>

CIN1, cervical intraepithelial neoplasia, grade 1
4vHPV randomized controlled efficacy, safety and immunogenicity trial in mid-adult women, FUTURE III

<table>
<thead>
<tr>
<th>HPV 6,11,16,18-related Outcomes</th>
<th>Cases</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Vaccine</td>
<td>Control</td>
<td>Efficacy</td>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per-protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent infection, CIN, EGL</td>
<td>10</td>
<td>86</td>
<td></td>
<td>88.7%</td>
<td>(78.1, 94.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN2+</td>
<td>1</td>
<td>6</td>
<td></td>
<td>83.3%</td>
<td>(-37.6, 99.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention-to-treat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent infection, CIN, EGL</td>
<td>116</td>
<td>214</td>
<td></td>
<td>47.2%</td>
<td>(33.5, 58.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN2+</td>
<td>21</td>
<td>27</td>
<td></td>
<td>22.4%</td>
<td>(-42.5, 58.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This analysis includes 24–45 year old women; per-protocol: received 3 doses PCR negative and seronegative to relevant vaccine type at day 1 and through month 7
CIN, cervical intraepithelial neoplasia, EGL, external genital lesions; CIN2+: CIN grade 2 or worse
Mean follow-up time 46 months

Castellsague et al. Br J Cancer 2011
Mid-adult long term follow-up study

- After base study, placebo-recipients were offered vaccine
- 685 Colombian subjects who received 4vHPV in the base study consented to participate in a long-term follow-up for 10 years
- Vaccine effectiveness was evaluated by incidence probability
  - Primary effectiveness endpoint: HPV6/11/16/18-related CIN or condyloma in per-protocol population
  - No vaccine-type CIN or condyloma during follow-up
  - Cases (few) of non-vaccine type outcomes during follow-up, suggesting ongoing exposure to HPV.
Evidence for expanding range for use of 9vHPV

- Data considered for regulatory approval, as well as data from other studies, included in GRADE
- There are no efficacy or immunogenicity data on 9vHPV in persons older than age 27 years
- Manufacturer is conducting a study of immunogenicity and safety of 9vHPV in women aged 16–45 years*
  - Primary Objective: Compare antibody titers and adverse events at month 7 in women aged 16–26 years to women aged 27–45 years
  - Results expected in Q2 2019

*NCT 03158220
Data from the United States

HPV vaccine coverage and impact

HPV epidemiology and sexual behavior
Estimated HPV vaccination coverage among adolescents aged 13–17 years, NIS-Teen, United States, 2006–2017

![Graph showing estimated HPV vaccination coverage among adolescents from 2006 to 2017. The graph includes data for females and males.]

Adapted from Walker et al. MMWR 2018; NIS-Teen, National Immunization Survey-Teen; UTD, Up-to-date

Note: revised definition of adequate provider data in 2013
Estimated HPV vaccination coverage among adolescents aged 13–17 years, NIS-Teen, United States, 2006–2017

Adapted from Walker et al. MMWR 2018; NIS-Teen, National Immunization Survey-Teen; UTD, Up-to-date
Note: revised definition of adequate provider data in 2013
HPV vaccination coverage of ≥1 dose among females
NHANES, 2015–2016

Vaccination Coverage, %

Age, years


Adapted from Lewis and Markowitz, Vaccine 2018

NHANES, National Heath and Nutrition Examination Survey
HPV vaccination coverage of ≥1 dose, females and males
NHANES, 2015–2016

Adapted from Lewis and Markowitz, Vaccine 2018

NHANES, National Heath and Nutrition Examination Survey
Impact of the HPV vaccination program
Vaccine type prevalence (HPV 6,11,16,18), NHANES

Early vaccine era compared to pre-vaccine era, females

- **Pre-vaccine era 2003–2006**
- **Early vaccine era 2007–2010**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Pre-vaccine</th>
<th>Early Vaccine</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>14–19 years</td>
<td>11.5%</td>
<td>5.0%</td>
<td>56%</td>
</tr>
<tr>
<td>20–24 years</td>
<td>18.5%</td>
<td>19.9%</td>
<td></td>
</tr>
<tr>
<td>25–29 years</td>
<td>11.8%</td>
<td>13.1%</td>
<td></td>
</tr>
<tr>
<td>30–34 years</td>
<td>9.5%</td>
<td>8.9%</td>
<td></td>
</tr>
</tbody>
</table>
Impact of the HPV vaccination program
Vaccine type prevalence (HPV 6,11,16,18), NHANES

Later vaccine era compared to pre-vaccine era, females

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>14–19 years</td>
<td>11.5</td>
<td>5.0</td>
<td>3.3</td>
</tr>
<tr>
<td>20–24 years</td>
<td>18.5</td>
<td>19.9</td>
<td>7.2</td>
</tr>
<tr>
<td>25–29 years</td>
<td>11.8</td>
<td>13.1</td>
<td>8.8</td>
</tr>
<tr>
<td>30–34 years</td>
<td>9.5</td>
<td>8.9</td>
<td>7.1</td>
</tr>
</tbody>
</table>

61% decrease
71% decrease
Anogenital wart prevalence among 15–39 year-olds females with private insurance, United States, 2006–2014
Estimated cervical precancer incidence rates per 100,000 screened women, HPV IMPACT Project

- CIN2+ rates decreased significantly in estimated screened women aged 18-20 and 21-24 years
- CIN2+ rates increases in screened women aged 25-29, 30-34, and 35-39 years
  - Could be attributable to longer screening intervals and/or increased sensitivity of screening or diagnostic tests

CIN2+, cervical intraepithelial neoplasia, grade 2 or worse or adenocarcinoma in situ

Gargano et al. CID in press
# Estimated HPV-attributable cancers per year

**United States, 2011–2015**

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Percentage attributable to HPV</th>
<th>Estimated number attributable to any HPV type per year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Female</td>
</tr>
<tr>
<td>Cervix</td>
<td>91%</td>
<td>10,800</td>
</tr>
<tr>
<td>Vagina</td>
<td>75%</td>
<td>600</td>
</tr>
<tr>
<td>Vulva</td>
<td>69%</td>
<td>2,700</td>
</tr>
<tr>
<td>Penis</td>
<td>63%</td>
<td>0</td>
</tr>
<tr>
<td>Anus*</td>
<td>91%</td>
<td>4,000</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>70%</td>
<td>2,200</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td>20,300</td>
</tr>
</tbody>
</table>

*Includes anal and rectal squamous cell carcinomas

HPV natural history

Schiffman et al. NEJM 2005
What proportion of cervical cancers are caused by HPV infections acquired by different ages?

Modeling estimate:

- 50% of women acquired causal HPV infection by age 21 years
- 75% of women acquired causal HPV infection by age 31 years
Benefit and potential impact of HPV vaccination in mid-adults is influenced by

- Likelihood of already having had vaccine-type infection
- Immunity after natural infection
- Risk of incident infection
- Risk of development of disease from incident infection
- Vaccine efficacy against reinfection with a type previously cleared
Any HPV type prevalence by age group and sex
NHANES, 2013–2014

Weighted Prevalence (%)

Age group (years)

Females

Males

CDC, unpublished data; adapted from Lewis et al. JID 2018; NHANES, National Heath and Nutrition Examination Survey
Any 9vHPV-type DNA prevalence and seroprevalence 20–59 year-old females, NHANES, 2005–2006

- DNA and antibody detection are imperfect measures of current and past infection
- Not all persons develop antibody after HPV infection; varies by HPV type
  - Females 50–70%
  - Males 4–36%

Antibody measured by competitive Luminex immunoassay
Adapted from Liu et al. JID 2016 and Liu et al. STD 2016

Carter et al, JID 2000
Edelstein et al. JID 0211
Any 9vHPV-type DNA prevalence and seroprevalence 20–59 year-olds, NHANES, 2005–2006

Females

Males

Antibody measured by competitive Luminex immunoassay
Adapted from Liu et al. JID 2016 and Liu et al. STD 2016
### U.S. studies of HPV incidence in mid-adult women

<table>
<thead>
<tr>
<th></th>
<th>Major U.S. cities</th>
<th>Baltimore, MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>On-line daters</td>
<td>OB/GYN clinic attendees</td>
</tr>
<tr>
<td>Age range, yrs</td>
<td>25–65</td>
<td>35–60</td>
</tr>
<tr>
<td>New male partner</td>
<td>50%</td>
<td>10%</td>
</tr>
<tr>
<td>Incident HPV detection</td>
<td>High risk HPV 29.5/100 women-yrs</td>
<td>Any HPV 14/100 women-yrs</td>
</tr>
</tbody>
</table>

In women with new partners, 64-82% of new detections attributed to newly acquired infection.
>1 new sex partner in past year, by age group and sex

Females

- 20-24: 31.9%
- 25-29: 18.7%
- 30-34: 15.4%
- 35-39: 9.9%
- 40-44: 8.4%
- 45-49: 5.4%
- 50-54: 2.9%

Males

- 20-24: 39.6%
- 25-29: 30.5%
- 30-34: 20.6%
- 35-39: 14.6%
- 40-44: 14.5%
- 45-49: 9.1%
- 50-54: 6.8%

CDC, NHANES unpublished data; ≥1 past year new partner among those who reported ever having sex
Marital status, by age group, females

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>never married</th>
<th>married</th>
<th>living with partner</th>
<th>widowed/separated/divorced</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-24</td>
<td>60.8</td>
<td>19.5</td>
<td>17</td>
<td>2.7</td>
</tr>
<tr>
<td>25-29</td>
<td>38.1</td>
<td>38.4</td>
<td></td>
<td>4.1</td>
</tr>
<tr>
<td>30-34</td>
<td>23</td>
<td>54.7</td>
<td></td>
<td>9.8</td>
</tr>
<tr>
<td>35-39</td>
<td>14.6</td>
<td>59.7</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>40-44</td>
<td>9.5</td>
<td>62.3</td>
<td></td>
<td>20.7</td>
</tr>
<tr>
<td>45-49</td>
<td>8.6</td>
<td>67.6</td>
<td></td>
<td>19.4</td>
</tr>
<tr>
<td>50-54</td>
<td>11.3</td>
<td>57.2</td>
<td></td>
<td>27.1</td>
</tr>
</tbody>
</table>

Source: CDC, NHANES unpublished data
≥1 new partner in past year, by sex, age group and marital status, United States, 2013–2016

Females

- Married or living with partner
- Not married or living with partner

Males

- Married or living with partner
- Not married or living with partner

CDC, NHANES unpublished data; ≥1 past year new partner, among those who reported ever having sex
Understanding the potential benefit of vaccination in mid-adults is complex

- HPV infection is common, infection occurs soon after first sexual activity

- Challenges in studies of HPV incidence
  - HPV DNA detection can not distinguish between new, persistent, or redetection of infection

- New HPV infections occur in adults and sex with a new partner remains a risk for infections
  - Percent of adults with a new sex partner in past year is lower with increasing age

- Not all infected individuals develop antibody: males < females
  - Uncertainly about immunity after clearance of infection
  - No protective antibody level identified
Vaccine effectiveness studies
Background

- High efficacy found in clinical trials in mid-adult women in per-protocol analyses, but lower efficacy in intent-to-treat analyses
- Vaccine effectiveness studies can provide information on real world effectiveness of vaccine and vaccination programs
- Studies in countries with catch-up vaccination have been able to evaluate effectiveness by age at vaccination
Review of HPV vaccine effectiveness studies

- Reviewed post-licensure effectiveness studies that included analyses by age at vaccination
  - Limited to evaluations of 3 vaccine doses
  - Extracted basic information on
    - Study design, age at outcome, age at vaccination
    - Buffer period: time between vaccination and case counting
    - Relative risk or other measure
HPV vaccine effectiveness studies that included analyses by age at vaccination

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of studies</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV vaccine-type prevalence</td>
<td>2</td>
<td>United States, Scotland</td>
</tr>
<tr>
<td>Anogenital warts</td>
<td>5</td>
<td>United States, Sweden, Belgium, Canada</td>
</tr>
<tr>
<td>Cervical lesions</td>
<td>4</td>
<td>United States, Sweden, Australia</td>
</tr>
</tbody>
</table>
Studies evaluating effectiveness against HPV vaccine-type prevalence

<table>
<thead>
<tr>
<th>Publication</th>
<th>Country</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dunne, 2015</td>
<td>United States</td>
<td>Women screened for cervical cancer at an integrated health care delivery system</td>
</tr>
<tr>
<td>Kavanagh, 2017</td>
<td>Scotland</td>
<td>Women screened for cervical cancer and national registries</td>
</tr>
</tbody>
</table>
# Risk reduction for vaccine-type prevalence, by age at vaccination

<table>
<thead>
<tr>
<th>Publication</th>
<th>Vaccine</th>
<th>Buffer</th>
<th>Age (years) at follow-up*</th>
<th>Age (years) at vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dunne, 2015</td>
<td>4vHPV</td>
<td>1 month</td>
<td>20–29</td>
<td>&lt;19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥19</td>
</tr>
<tr>
<td>Kavanagh, 2017*</td>
<td>2vHPV</td>
<td>None</td>
<td>20–21</td>
<td>12–13</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>14</td>
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<td>15</td>
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<td>16</td>
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<td></td>
<td>17</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥18</td>
</tr>
</tbody>
</table>

*Follow-up or outcome

*Odds ratio presented

Relative risk - measured as prevalence ratio, hazard ratio or incidence rate ratio

Dunne, J Infect Dis 2015; Kavanagh, Lancet 2017
### Studies evaluating effectiveness against anogenital wart by age at vaccination

<table>
<thead>
<tr>
<th>Publication</th>
<th>Country</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leval, 2013</td>
<td>Sweden</td>
<td>Retrospective cohort study using population-based health registries</td>
</tr>
<tr>
<td>Herweijer, 2014</td>
<td>Sweden</td>
<td>Retrospective cohort study using population-based health registries</td>
</tr>
<tr>
<td>Dominiak-Felden, 2015</td>
<td>Belgium</td>
<td>Retrospective cohort study using sick-fund/ insurance data</td>
</tr>
<tr>
<td>Zeybek, 2018</td>
<td>United States</td>
<td>Retrospective matched cohort study using health insurance claims data</td>
</tr>
<tr>
<td>Willows, 2018</td>
<td>Canada</td>
<td>Retrospective matched cohort study using population-based health registries</td>
</tr>
</tbody>
</table>

Leval, JNCI 2013; Herweijer, JAMA 2014; Dominiak-Felden, Plos One 2015; Zeybek, JLGTD 2018; Willows, Sex Trans Dis 2018
Risk reduction for anogenital warts, by age at vaccination

- **Relative risk** - measured as prevalence ratio, hazard ratio or incidence rate ratio
- Leval, JNCI 2013; Herweijer, JAMA 2014; Dominiak-Felden, Plos One 2015; Zeybek, JLGTD 2018; Willows, Sex Trans Dis 2018

### Table of Results

<table>
<thead>
<tr>
<th>Publication</th>
<th>Buffer</th>
<th>Age (years) at follow-up†</th>
<th>Age (years) at vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leval, 2013*</td>
<td>None</td>
<td>10–27+</td>
<td>10–13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14–16</td>
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<td>17–19</td>
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<td>20–22</td>
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<td>23–26</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>≥27</td>
</tr>
<tr>
<td>Herweijer, 2014</td>
<td>3 months</td>
<td>10–24</td>
<td>10–16</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17–19</td>
</tr>
<tr>
<td>Dominiak-Felden, 2015</td>
<td>1 month</td>
<td>Median, 20</td>
<td>&lt;15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥18</td>
</tr>
<tr>
<td>Zeybek, 2018</td>
<td>3 months</td>
<td>9–31</td>
<td>&lt;15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15–19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥20</td>
</tr>
<tr>
<td>Willows, 2018†</td>
<td>12 months</td>
<td>≥15</td>
<td>9–18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥19</td>
</tr>
</tbody>
</table>

†Follow-up or outcome

#78% received 3 doses, including 81% of those ≥27 years

*Manitoba’s catchup program specifically targeted high risk women

**Relative Risk (95% CI)**

Leval, JNCI 2013; Herweijer, JAMA 2014; Dominiak-Felden, Plos One 2015; Zeybek, JLGTD 2018; Willows, Sex Trans Dis 2018
Studies evaluating effectiveness against cervical intraepithelial neoplasia grade 2 or worse (CIN2+), by age at vaccination

<table>
<thead>
<tr>
<th>Publication</th>
<th>Country</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crowe, 2014</td>
<td>Australia</td>
<td>Case control study using linked data from registries</td>
</tr>
<tr>
<td>Brotherton, 2015</td>
<td>Australia</td>
<td>Retrospective cohort using linked regional data registries</td>
</tr>
<tr>
<td>Herweijer, 2016</td>
<td>Sweden</td>
<td>Retrospective cohort using linked national registries</td>
</tr>
<tr>
<td>Silverberg, 2018</td>
<td>United States</td>
<td>Nested case-control study using electronic medical records from integrated health-care delivery system</td>
</tr>
</tbody>
</table>
### Risk reduction for CIN2+, by age at vaccination

<table>
<thead>
<tr>
<th>Publication</th>
<th>Vaccine</th>
<th>Buffer</th>
<th>Age (years) at follow-up*</th>
<th>Age (years) at vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crowe, 2014*</td>
<td>4vHPV</td>
<td>12 months</td>
<td>11–31</td>
<td>15–18, 19–22, 23–27</td>
</tr>
<tr>
<td>Brotherton, 2015*</td>
<td>4vHPV</td>
<td>None</td>
<td>Mean, 23</td>
<td>&lt;16, 17–19, 20–23, 24–26</td>
</tr>
<tr>
<td>Herweijer, 2016</td>
<td>4vHPV</td>
<td>None</td>
<td>23–29</td>
<td>&lt;17, 17–19, 20–29</td>
</tr>
<tr>
<td>Silverberg, 2018</td>
<td>4vHPV</td>
<td>6 months</td>
<td>Age at index, 26</td>
<td>14–17, 18–20, ≥21</td>
</tr>
</tbody>
</table>

*Follow-up or outcome

*Odds ratio is presented

*Data for those vaccinated before first cervical cancer screen

Relative risk - measured as prevalence ratio, hazard ratio or incidence rate ratio

Relative Risk* (95% CI)
Summary

- 11 studies reviewed, conducted in 6 different countries
- All found lower effectiveness with increasing age at vaccination
  - 7 found no significant effectiveness in the oldest age group evaluated
Intention-to-treat analyses in HPV vaccine clinical trials

- Intention-to-treat population includes
  - Individuals with vaccine type infection at time of vaccination

- No efficacy observed in first year
  - Most cases had evidence of infection or disease that was prevalent at enrollment

- During second year, incidence of vaccine-type disease
  - Placebo group - continued to increase
  - Vaccine group - began to plateau

Conclusions

- Estimated vaccine effectiveness lower with increasing age at vaccination
  - Due to higher HPV prevalence at time of vaccination

- Methodological challenges for evaluating vaccine effectiveness
  - Biases due to differences in vaccinated and unvaccinated persons
  - Some findings could be result of higher risk persons in older age groups being targeted for vaccination at beginning of vaccine program (reported in one study)
  - Time between vaccination and case counting in published studies likely impacts ability to observe vaccine effectiveness among persons vaccinated at older ages

- Data support importance of vaccination in early adolescence
Global HPV vaccine issues
Countries with HPV vaccine in the national immunization program, 2018

- Introduced* to date (80 countries or 41%)
- Not Available, Not Introduced/No Plans (114 countries or 59%)
- Not applicable

* Includes partial introduction

Data source: WHO/IVB Database, as of 15 May 2018
Map production Immunization Vaccines and Biologicals (IVB), World Health Organization

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. ©WHO 2018. All rights reserved.
HPV Vaccine Introduction Status

Middle income countries (MICs) and Gavi countries lag far behind high income countries (HICs) and PAHO procuring countries

- Countries that have introduced account for only 25% of the global target population
- Only 13 of 73 Gavi countries have introduced HPV, but have >50% of HPV disease burden
- MICs, of which only 39% have introduced, account for greater disease burden than HICs and PAHO combined

Global demand/supply balance – HPV vaccine

- Vaccine supply is currently insufficient to meet demand; some countries have or will have to postpone introductions
- Demand/supply imbalance is forecasted to grow and remain through 2023
- From 2024 onward supply is expected to support demand

MACs, multi-age cohorts (ages 9-13 years)
World Health Organization/Global Market, September 2018
http://www.who.int/immunization/programmes_systems/procurement/v3p/platform/module2/WHO_HPV_market_study_public_summary.pdf?ua=1
Summary

- Data submitted to FDA in support of expanded age range through age 45 years
  - Include a RCT: efficacy high in women naïve to vaccine type; lower efficacy in intent-to-treat population

- United States data to inform the policy considerations
  - HPV vaccine coverage is increasing in adolescents
  - Impact of the vaccination program has been observed among females in teens and twenties
  - Most adults have already been exposed to a 9vHPV type, but not all 9vHPV types
  - HPV incidence is lower at older ages, but new infections can occur in adults
  - New sex partner is a risk factor for incident HPV infection

- Post-licensure vaccine effectiveness evaluations
  - Vaccine effectiveness is lower with increasing age at vaccination

- Update on global HPV vaccination
  - Less than 50% of countries have introduced HPV vaccination
  - Global vaccine shortage is limiting introductions in some countries
  - No current HPV vaccine shortage in the United States
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