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CDC did not accept commercial support for this continuing education activity.
Human papillomavirus (HPV) and HPV vaccination in the United States

Update on HPV-associated cancers, HPV vaccination policy, vaccine safety, and impact

Lauri E. Markowitz, MD
Division of Viral Diseases

Atlanta, Georgia
May 15, 2018
Introduction and purpose of session

- 12 years since HPV vaccine introduced into the U.S. immunization program
- Since 2006, there has been
  - Further understanding of HPV-associated cancers
  - Changes in vaccination recommendations
  - Substantial data on vaccine safety
  - Evidence of impact of the vaccination program
Countries with HPV vaccine in the national immunization program, 2010

Source: WHO/IVB database, 193 WHO Member States.
Data as of April 2011
Date of slide: 03 August 2011

No (156 countries or 81%)
Yes (33 countries or 17%)
Yes (Part of the country) (4 countries or 2%)
Countries with HPV vaccine in the national immunization program, 2018

Data source: WHO/IVB Database, as of 26 January 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.

* Includes partial introduction

Introduced* to date (79 countries or 40.7%)
Not Available, Not Introduced/No Plans (115 countries or 59.3%)
Not applicable
Overview

  - Dr. Mona Saraiya, Division of Cancer Prevention and Control, CDC

- Current HPV vaccination policy: Preventing cancers just got easier
  - Dr. Elissa Meites, Division of Viral Diseases, CDC

- Post-licensure monitoring of 9-valent HPV vaccine safety, United States
  - Ms. Julianne Gee, Immunization Safety Office, CDC

- Impact of HPV vaccination program in the United States: Data from cervical precancer monitoring
  - Dr. Julia Gargano, Division of Viral Diseases, CDC
Thank you

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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.

Mona Saraiya, MD, MPH
Division of Cancer Prevention and Control
Epidemiology and Applied Research Branch

National Immunization Conference
May 15, 2018
Background

- Human papillomavirus (HPV) is a known cause of cervical cancer, some oropharyngeal, vulvar, vaginal, penile, and anal cancers
- Cervical cancer is the only HPV-associated cancer with screening guidelines
Objective

- Provide an update on the epidemiology and burden of HPV-associated cancers
- Examine trends of HPV-associated cancer types in the U.S. population from 1999–2014
  - Age
  - Sex
  - Race
  - Ethnicity
HPV-Associated Cancer

- Cancer registries do not routinely collect HPV genotyping information
- Cell types in which HPV DNA is frequently found
  - Carcinomas of the cervix:
    - Squamous cell carcinomas (SCCs)
    - Adenocarcinomas
    - Other carcinomas
  - SCCs of the:
    - Oropharynx, vulva, vagina, penis, anus*
- Malignant/invasive
- Histologically confirmed

*includes rectal SCC

Cases were classified by anatomic site (topographical) and morphology using the International Classification of Diseases for Oncology, 3rd Edition
HPV-associated vs HPV-attributable

- **HPV-associated cancer**: a specific cellular type of cancer that is diagnosed in a part of the body where HPV is often found.

- **HPV-attributable cancer**: a cancer probably caused by HPV, and is estimated by multiplying the number of HPV-associated cancers by the percentage attributable to HPV.
  
  - Based on a CDC study that used population-based data to genotype HPV types from cancer tissue
    - 90% of cervical and anal cancers
    - 70% of oropharyngeal, vaginal, and vulvar cancers
    - 60% of penile cancers
Data Source

- All 50 states, the District of Columbia, and Puerto Rico
- For 1999–2014, registry data that met specific quality standards covered approximately 97% of the U.S. population
Methods and Data Analysis

- Average annual percent change (AAPC): weighted average of percent change per year of cancer incidence rates
  - Statistically significant AAPCs were different from zero at the alpha 0.05 level
- Rates and trends were estimated by sex, age group, race, and ethnicity
- Age-adjusted to the 2000 U.S. standard population
- Data were suppressed for rates if cases were <16 per period
Results

- 34,864 cases of HPV-associated cancer were diagnosed annually from 1999–2014

- Incidence rate 11.4 per 100,000 person per year:
  - Males 9.1/100,000
  - Females 13.7/100,000
HPV-Associated Cancers by Site and Sex

1999
29,760 cases

- Cervix: 44%
- Oropharynx (M): 23%
- Anus (M): 4%
- Penis: 3%
- Oropharynx (F): 8%
- Anus (F): 7%
- Vulva: 9%
- Vagina: 2%

2014
42,394 cases

- Cervix: 27%
- Oropharynx (M): 35%
- Anus (M): 5%
- Penis: 3%
- Oropharynx (F): 8%
- Anus (F): 11%
- Vulva: 9%
- Vagina: 2%

HPV-associated cancers among males: 1999: 34% → 2014: 44%

M = male; F = female
Rates were considered to increase if annual average percentage change (AAPC) >0 (p<0.05) and to decrease if AAPC <0 (p<0.05); otherwise rates were considered stable. * = p<0.05

Analyses limited to cervical carcinomas. Rates were considered to increase if annual average percentage change (AAPC) >0 (p<0.05) and to decrease if AAPC <0 (p<0.05); otherwise rates were considered stable. * = p<0.05.
Cervical Cancer Trends by Age — United States, 1999–2014

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>AAPC</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–19</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>20–24</td>
<td>-3.8*</td>
<td>-4.9</td>
</tr>
<tr>
<td>25–29</td>
<td>-2.7*</td>
<td>-4.0</td>
</tr>
<tr>
<td>30–34</td>
<td>-1.9*</td>
<td>-2.3</td>
</tr>
<tr>
<td>35–39</td>
<td>-1.2</td>
<td>-2.4</td>
</tr>
<tr>
<td>40–44</td>
<td>-1.1*</td>
<td>-1.5</td>
</tr>
<tr>
<td>45–49</td>
<td>-1.4*</td>
<td>-2.3</td>
</tr>
<tr>
<td>50–54</td>
<td>-1.7*</td>
<td>-2.5</td>
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<tr>
<td>55–59</td>
<td>-2.2*</td>
<td>-3.1</td>
</tr>
<tr>
<td>60–64</td>
<td>-2.8*</td>
<td>-3.7</td>
</tr>
<tr>
<td>65–69</td>
<td>-3.0*</td>
<td>-3.6</td>
</tr>
<tr>
<td>≥70</td>
<td>-3.2*</td>
<td>-3.9</td>
</tr>
</tbody>
</table>

Analyses limited to cervical carcinomas. Rates were considered to increase if annual average percentage change (AAPC) >0 (p<0.05) and to decrease if AAPC <0 (p<0.05); otherwise rates were considered stable. * = p<0.05. ** Data suppressed.

Analyses limited to cervical carcinomas. Rates were considered to increase if annual average percentage change (AAPC) >0 (p<0.05) and to decrease if AAPC <0 (p<0.05); otherwise rates were considered stable. * = p<0.05.
Cervical Cancer Trends by Histology — United States, 1999–2014

Analyses limited to cervical carcinomas. Rates were considered to increase if annual average percentage change (AAPC) >0 (p<0.05) and to decrease if AAPC <0 (p<0.05); otherwise rates were considered stable. * = p<0.05.

Limited to anal squamous cell carcinomas. Rates were considered to increase if annual average percentage change (AAPC) >0 (p<0.05) and to decrease if AAPC <0 (p<0.05); otherwise rates were considered stable. * = p<0.05.
Anatomy of the Oropharynx

- The parts of the oropharynx are:
  - Soft palate
  - Side and back walls of the throat
  - Tonsils
  - Back one-third of tongue (base of tongue)
Analyses limited to oropharyngeal squamous cell carcinomas. Rates were considered to increase if annual average percentage change (AAPC) >0 (p<0.05) and to decrease if AAPC <0 (p<0.05); otherwise rates were considered stable. * = p<0.05.
Analyses limited to oropharyngeal squamous cell carcinomas. Rates were considered to increase if annual average percentage change (AAPC) >0 (p<0.05) and to decrease if AAPC <0 (p<0.05); otherwise rates were considered stable. * = p<0.05.

Analyses limited to oropharyngeal squamous cell carcinomas. Rates were considered to increase if annual average percentage change (AAPC) >0 (p<0.05) and to decrease if AAPC <0 (p<0.05); otherwise rates were considered stable. * = p<0.05.
Oropharyngeal Cancer among Men by Primary Site — United States, 1999–2014

Analyses limited to oropharyngeal squamous cell carcinomas. Rates were considered to increase if annual average percentage change (AAPC) >0 (p<0.05) and to decrease if AAPC <0 (p<0.05); otherwise rates were considered stable. * = p<0.05.

Analyses limited to oropharyngeal squamous cell carcinomas. Trends were measured with AAPC in annual rates (per 100,000, age-adjusted to the 2000 U.S. standard population). Rates were considered to increase if AAPC >0 (p<0.05) and to decrease if AAPC <0 (p<0.05); otherwise rates were considered stable. *Data suppressed for American Indian/Alaska due to counts. * = p<0.05.
Oropharyngeal Cancer among Men and Cervical Cancer by Age — United States, 2010–2014

Strengths and Limitations

- Systematic population-based approach to monitor HPV-associated cancers in the United States
- High quality data from cancer registries
- Covers the entire U.S. population, so can be used to look at rare cancers
- Assesses trends among age groups and race/ethnicity

- HPV status not routinely collected
Summary

HPV-associated cancer rates are changing from 1999–2014

- **Increased:**
  - Oropharyngeal cancer among men and women
  - Anal cancer among men and women
  - Vulvar cancer

- **Decreased:**
  - Cervical cancer

- **Stable:**
  - Penile cancer
  - Vaginal cancer
Conclusion

- Oropharyngeal cancer is now the most common HPV-associated cancer and increasing, particularly among males.
- In the future, the HPV vaccine should decrease the burden of HPV-associated cancers, but it may take decades to see population-level impact due to the length of time between the initial HPV infection and the development of cancer.
US Cancer Statistics Data Briefs (2010-2014)

- Cancers associated with human papillomavirus, United States—2010–2014—
- Annual rate and number of HPV-associated cancer cases by sex, cancer type, and state, 2010–2014
Quarterly Updates on HPV-associated and attributable cancers

- Brief 2-page report with state-specific data on number of HPV vaccine doses ordered and HPV-associated cancers

![Estimated number of HPV-associated cancers by cancer type and HPV type, State X, 2010–2014](chart.png)

- Cancers caused by HPV types 16/18/31/33/45/52/58 can be prevented by 9-valent vaccine
- Cancers caused by other HPV types
- HPV negative cancers

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Total, All Anatomic Sites</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>514</td>
<td>41</td>
<td>147</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>199</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Germ</td>
<td>169</td>
<td>19</td>
<td>20</td>
</tr>
</tbody>
</table>
You Are the Key to HPV Cancer Prevention – 2018

- Web-on-demand video
- [https://www.cdc.gov/vaccines/ed/hpv/you-are-key-2018.html](https://www.cdc.gov/vaccines/ed/hpv/you-are-key-2018.html)
- Continuing education is available until April 11, 2020
Thank you
yzs2@cdc.gov
HPV vaccination policy: Preventing cancer just got easier

Elissa Meites, MD, MPH
Medical Epidemiologist, Division of Viral Diseases

National Immunization Conference
May 15, 2017
Conflicts of interest

- None
Background
Background

- National vaccination recommendations are made by the Advisory Committee on Immunization Practices (ACIP)
- The first vaccine against human papillomavirus (HPV) was licensed and recommended in the United States in 2006
- Since then, ACIP recommendations for HPV vaccination have evolved based on additional data and considerations
HPV vaccines

- Three vaccines have been licensed and recommended for use in the United States:
  - Quadrivalent HPV vaccine (4vHPV), licensed since 2006
  - Bivalent HPV vaccine (2vHPV), licensed since 2009
  - 9-valent HPV vaccine (9vHPV), licensed since 2014

- All were initially FDA-approved as a 3-dose series for females and males ages 9–26 years; in late 2016, 9vHPV was FDA-approved as a 2-dose series for females and males ages 9–14 years

- As of late 2016, only 9vHPV is being distributed in the United States
Objectives

- To review current HPV vaccination policy in the United States
- To summarize issues in HPV vaccination recently considered by ACIP
Methods used by ACIP
Methods

- We reviewed current recommendations for use of HPV vaccine based on 1 ACIP Statement and 2 Policy Notes published in 2014–2016:

- We also reviewed recent presentations to ACIP addressing current issues for HPV vaccine policy
Evidence-based recommendation process

- 2010: Grading of Recommendations Assessment, Development and Evaluation (GRADE)
  - Evaluate quality of evidence for benefits and harms
  - HPV vaccine recommendations evaluated using this process included:
    - Use of 9-valent HPV vaccine
    - 2-dose schedules of HPV vaccine

- 2018: Evidence to Recommendations framework
  - Incorporates additional key factors
  - Future recommendations will be evaluated this way
<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Study design (number of studies*)</th>
<th>Findings</th>
<th>Evidence type</th>
<th>Overall evidence type</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 doses of HPV vaccine (age 9-14) versus 3 doses of HPV vaccine (age 15-26)</td>
<td>Immunogenicity to 9vHPV types</td>
<td>Observational (1)</td>
<td>Non-inferior immunogenicity</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Immunogenicity to 4vHPV types</td>
<td>Observational (2)</td>
<td>Non-inferior immunogenicity</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Immunogenicity to 2vHPV types</td>
<td>Observational (4)</td>
<td>Non-inferior immunogenicity</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

* Supplemental data reviewed for additional available analyses from each study
ACIP Evidence to Recommendations framework

- Statement of problem
  - Public health importance, burden of disease
- Benefits and harms
  - Balance of desirable and undesirable effects
  - Certainty in evidence (evidence profiles)
- Values and preferences of target populations
- Acceptability to stakeholders
- Resource use
  - Health economic analyses
- Feasibility
  - Implementation considerations
### Evidence to Recommendations judgment example

**Is the problem a public health priority?**

<table>
<thead>
<tr>
<th>No</th>
<th>Probably no</th>
<th>Uncertain</th>
<th>Probably yes</th>
<th>Yes</th>
<th>Varies</th>
</tr>
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</tbody>
</table>
Current ACIP Recommendations
Recommendations for use of HPV vaccines

- 2014 ACIP Statement
  - Provides detailed summary of background, prevention approaches, HPV vaccines and evaluation, economic burden, program description, and recommendations for use of HPV vaccines

- 2015 Policy Note
  - Adds use of 9-valent vaccine

- 2016 Policy Note
  - Adds 2-dose schedules
  - Clarifies special populations and medical conditions
Routine and catch-up age groups

- ACIP recommends routine HPV vaccination for girls and boys at age 11 or 12 years. Vaccination can be given starting at age 9 years.
- ACIP also recommends vaccination for females through age 26 years and for males through age 21 years who were not adequately vaccinated previously. Males aged 22 through 26 years may be vaccinated.
- Additional details: Special populations, Medical conditions
Dosing schedules

- For persons initiating vaccination before the 15th birthday:
  - The recommended immunization schedule is 2 doses of HPV vaccine. The second dose should be administered 6–12 months after the first dose (0, 6–12 month schedule).*

- For persons initiating vaccination on or after the 15th birthday:
  - The recommended immunization schedule is 3 doses of HPV vaccine. The second dose should be administered 1–2 months after the first dose, and the third dose should be administered 6 months after the first dose (0, 1–2, 6 month schedule).

* Minimum interval between first and second dose in a 2-dose schedule is 5 months.
Interrupted series

- If the vaccine schedule is interrupted, the vaccination series does not need to be restarted.
- 9vHPV may be used to continue or complete a series started with 4vHPV or 2vHPV.
- Number of recommended doses is based on age at administration of the first dose.
Special populations

- For men who have sex with men (MSM)*, ACIP recommends routine HPV vaccination as for all males, and initiation of vaccination through age 26 years for those who were not adequately vaccinated previously.
- For transgender persons, ACIP recommends routine HPV vaccination as for all adolescents, and initiation of vaccination through age 26 years for those who were not adequately vaccinated previously.

* Including those who identify as gay or bisexual, or who intend to have sex with men
ACIP recommends vaccination with 3 doses* of HPV vaccine for females and males aged 9–26 years with primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity, such as B lymphocyte antibody deficiencies, T lymphocyte complete or partial defects, HIV infection, malignant neoplasms, transplantation, autoimmune disease, or immunosuppressive therapy, because immune response to vaccination might be attenuated.

* The recommendation for a 3-dose schedule of HPV vaccine does not apply to children aged <15 years with asplenia, asthma, chronic granulomatous disease, chronic liver disease, chronic lung disease, chronic renal disease, central nervous system anatomic barrier defects (e.g., cochlear implant), complement deficiency, diabetes, heart disease, or sickle cell disease.
### Recommended number of doses and dosing schedule for HPV vaccine

<table>
<thead>
<tr>
<th>Recommended number of doses</th>
<th>Recommended dosing schedule</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0, 6–12 months*</td>
<td>Persons initiating vaccination at ages 9 through 14 years, except immunocompromised persons</td>
</tr>
<tr>
<td>3</td>
<td>0, 1–2, 6 months†</td>
<td>Persons initiating vaccination at ages 15 through 26 years, and immunocompromised persons initiating vaccination at ages 9 through 26 years</td>
</tr>
</tbody>
</table>

* In a 2-dose schedule of HPV vaccine, the minimum interval is 5 months between the first and second dose
† In a 3-dose schedule of HPV vaccine, the minimum intervals are 4 weeks between the first and second dose, 12 weeks between the second and third dose, and 5 months between the first and third dose
Programmatic considerations

- 2-dose schedule is considered easier to implement and more acceptable
- 2-dose (0, 6–12 month) schedule allows flexibility for vaccination to occur during other health care visits
- Remains to be seen whether 2-dose recommendation will impact vaccination initiation or series completion
Current issues

- Discussions regarding simplification of immunization schedules
Summary
Evolution of ACIP recommendations for HPV vaccination

4vHPV
- **Females** 11 or 12 yrs* and 13–26 yrs not previously vaccinated
  - June 2006

4vHPV or 2vHPV
- **Females** 11 or 12 yrs* and 13–26 yrs not previously vaccinated
  - October 2009

4vHPV
- **May be given**, males 9–26 yrs*
  - October 2011

4vHPV
- **Males** 11 or 12 yrs* and 13–21 yrs not previously vaccinated
  - May be given, 22–26 yrs*
  - October 2016

9vHPV
- Recommended as 1 of 3 vaccines for females and 1 of 2 for males
  - February 2015

9vHPV, 4vHPV or 2vHPV
- **2-dose schedules**
  - October 2016

* Can be given starting at age 9 years; see also: special populations, medical conditions
Conclusions

- During the first 12 years of the HPV vaccination program in the United States, new scientific evidence has resulted in evolving vaccine indications, target populations, and recommendations for use.
- Current policy statements summarize evidence base through 2014, with updates to add 9-valent vaccine and 2-dose schedules.
- In 2018, ACIP is considering information on harmonizing the upper age range for males and females for catch-up vaccination.
Human Papillomavirus (HPV) ACIP Vaccine Recommendations

Advisory Committee on Immunization Practices (ACIP)

as Published in Morbidity and Mortality Weekly Report (MMWR)

The Advisory Committee on Immunization Practices (ACIP) provides advice and guidance to the Director of the CDC regarding use of vaccines and related agents for control of vaccine-preventable diseases in the civilian population of the United States. Recommendations made by the ACIP are reviewed by the CDC Director and, if adopted, are published as official CDC/HHS recommendations in the Morbidity and Mortality Weekly Report (MMWR).

CURRENT HPV Vaccine Recommendations

• Marcos E, Kampo A, Markowitz LE. Use of a 2-Dose Schedule for Human Papillomavirus Vaccination — Updated Recommendations of the Advisory Committee on Immunization Practices. MMWR. 2016;65(19);1405-8.
  Print version

  Print version

• MMWR. August 29, 2014. Vo1 63, RR05

Human Papillomavirus Vaccination: Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Additional guidance

9-valent HPV Vaccine

https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html
ACKNOWLEDGMENTS

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Cynthia Pellegrini
Jose Romero

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Amy Middleman (SAHM)
Chris Nyquist (AAP)
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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.
GRADE components

- Develop a policy question
- Consider critical outcomes
- Review and summarize evidence of benefits and harms
- Evaluate quality of evidence
- Assess population benefit
- Evaluate values and preferences
- Review health economic data
- Considerations for formulating recommendations
- ACIP recommendation and GRADE category
<table>
<thead>
<tr>
<th></th>
<th>Bivalent (2vHPV) (Cervarix)</th>
<th>Quadrivalent (4vHPV) (Gardasil)</th>
<th>9-valent (9vHPV) (Gardasil 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>L1 VLP types</strong></td>
<td>16, 18</td>
<td>6, 11, 16, 18</td>
<td>6, 11, 16, 18, 31, 33, 45, 52, 58</td>
</tr>
<tr>
<td><strong>Manufacturer</strong></td>
<td>GlaxoSmithKline</td>
<td>Merck</td>
<td>Merck</td>
</tr>
<tr>
<td><strong>Adjuvant</strong></td>
<td>AS04</td>
<td>AAHS</td>
<td>AAHS</td>
</tr>
<tr>
<td></td>
<td>500 µg aluminum hydroxide</td>
<td>225 µg amorphous aluminum</td>
<td>500 µg amorphous aluminum</td>
</tr>
<tr>
<td></td>
<td>50 µg 3-O-desacyl-4'-monophosphoryl</td>
<td>hydroxyphosphate sulfate</td>
<td>hydroxyphosphate sulfate</td>
</tr>
<tr>
<td></td>
<td>lipid A</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Licensed</strong></td>
<td>2009</td>
<td>2006</td>
<td>2014</td>
</tr>
</tbody>
</table>

L1, major capsid protein; VLP, virus-like particle
Key stakeholders

- Patients
  - Men, men at high risk for HPV-related diseases
- Providers
  - Primary care providers, health care providers, vaccine providers
- Programs
  - Immunization programs, health departments
- Policymakers
  - ACIP, HPV vaccines workgroup
Feasibility

- Modification to an existing vaccination program
- ACIP already recommends catch-up vaccination for people aged 22–26 years who are: female, transgender, men who have sex with men (including men who identify as gay or bisexual, or who intend to have sex with men), and/or have certain immunocompromising conditions
- Feasible to implement:
  - Simplified adult vaccine schedule is easier to explain and remember
  - Reduce burden on clinicians by not requiring risk assessments
  - Increase coverage by not requiring risk disclosure from men

Figure 1. Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger—United States, 2018.

For those who fall behind or start late, see the catch-up schedule (Figure 2).

To determine minimum intervals between doses, see the catch-up schedule (Figure 2). School entry and adolescent vaccine age groups are shaded in gray.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Month 4</th>
<th>Month 5</th>
<th>Month 6</th>
<th>Month 7</th>
<th>Month 8</th>
<th>Month 9</th>
<th>Month 10</th>
<th>Month 11</th>
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<tr>
<td>Hepatitis A (Hepa)</td>
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<tr>
<td>Rotavirus (RV)</td>
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<tr>
<td>Pneumococcal Conjugate (PCV)</td>
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<tr>
<td>Inactivated polio (IPV)</td>
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<td>Inactivated influenza (IIV)</td>
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<tr>
<td>Measles, mumps, rubella (MMR)</td>
<td>See footnote III</td>
<td>1st dose</td>
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<td>Varicella (VZV)</td>
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<tr>
<td>Hepatitis B (Hepb)</td>
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<tr>
<td>Human papillomavirus (HPV)</td>
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<td>Meningococcal 4v (MenACWY)</td>
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<td>Haemophilus influenza type b (Hib)</td>
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<tr>
<td>Pneumococcal polyvalent D (PPVD)</td>
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<td>2nd dose</td>
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NOTE: The above recommendations must be read along with the footnotes of this schedule.
Post-licensure Monitoring of 9-valent Human Papillomavirus Vaccine Safety in the United States

Julianne Gee, MPH
Immunization Safety Office

National Immunization Conference
May 15, 2018
Outline

- Background on HPV vaccines
- US Vaccine Safety Systems
- Findings from 9-valent HPV vaccine safety monitoring
- Ongoing and planned 9-valent HPV monitoring and evaluation activities
Background: HPV vaccines

- Three HPV vaccines licensed and recommended for use in United States
- 9-valent HPV vaccine (9vHPV) licensed in United States – December 2014
- ACIP recommended 9vHPV as 1 of 3 HPV vaccines for routine vaccination of females and 1 of 2 for males – February 2015
- HPV vaccination recommendations in the United States:
  - Routine vaccination at age 11 or 12 years*
  - Through age 26 years for females and age 21 years for males, if not vaccinated
  - Through age 26 for MSM and for immunocompromised persons, if not vaccinated
- 9vHPV only available HPV vaccine in United States since end of 2016

*Can be started at age 9 years
ACIP, Advisory Committee on Immunization Practices; MSM, men who have sex with men
Background: 9vHPV pre-licensure trial data

- Safety evaluated in ~ 15,000 subjects
- Vaccine was well-tolerated; most adverse events were injection site-related pain, swelling, and erythema
- Safety profiles were similar in quadrivalent HPV vaccine (4vHPV) and 9vHPV vaccines
  - Among inadvertent vaccination during pregnancy:
    - An imbalance in spontaneous abortions (SAB) among 9vHPV group as compared to those who received 4vHPV
      - Rates of SAB in 9vHPV group not elevated as compared to background rates

## U.S. vaccine safety systems

<table>
<thead>
<tr>
<th>System</th>
<th>Collaboration</th>
<th>Description</th>
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<tbody>
<tr>
<td>Vaccine Adverse Event Reporting System (VAERS)</td>
<td>CDC and FDA</td>
<td>Frontline spontaneous reporting system to detect potential vaccine safety issues</td>
</tr>
<tr>
<td>Vaccine Safety Datalink (VSD)</td>
<td>CDC and 8 Integrated Health Care Systems</td>
<td>Large linked database system used for active surveillance and research</td>
</tr>
<tr>
<td></td>
<td></td>
<td>~11.3 million members (~3% of US pop.)</td>
</tr>
<tr>
<td>Clinical Immunization Safety Assessment (CISA) Project</td>
<td>CDC and 7 Medical Research Centers</td>
<td>Expert collaboration that conducts individual clinical vaccine safety assessments and clinical research</td>
</tr>
<tr>
<td>Post-Licensure Rapid Immunization Safety Monitoring Program (PRISM)</td>
<td>FDA and 6 partner organizations</td>
<td>Large distributed database system used for active surveillance and research</td>
</tr>
<tr>
<td></td>
<td></td>
<td>~170 million individuals</td>
</tr>
<tr>
<td>System</td>
<td>Collaboration</td>
<td>Description</td>
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<tr>
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</tr>
</tbody>
</table>
Vaccine Adverse Event Reporting System (VAERS)

Strengths
- National data; accepts reports from anyone
- Rapid signal detection
- Can detect rare adverse events
- Collects information about vaccine, characteristics of vaccinee, adverse event*
- Data available to public

Limitations
- Reporting bias
- Inconsistent data quality and completeness
- Lack of unvaccinated comparison group
- Generally cannot assess if vaccine caused an AE

A hypothesis generating system, VAERS identifies potential vaccine concerns that can be studied in more robust data systems.

VAERS website: http://vaers.hhs.gov; *Some reports have no adverse event
9-valent HPV Vaccine Safety
Monitoring and Evaluation
VAERS: Methods

- U.S. 9vHPV reports received from December 1, 2014 – December 31, 2017
  - Excluded pregnancy reports
- Automated analysis of 9vHPV reports
  - Serious\(^1\) report defined as death, life-threatening illness, hospitalization, prolongation of hospitalization, or permanent disability
  - Signs and symptoms of the adverse event coded using Medical Dictionary for Regulatory Activities (MedDRA)\(^2\) Preferred Terms (PTs)
- Clinical review of reports for select conditions of clinical interest
  - Historical interest: anaphylaxis, Guillain-Barré syndrome, and death
  - Recent interest: complex regional pain syndrome, postural orthostatic tachycardia syndrome, and primary ovarian insufficiency

\(^1\) Based on the Code of Federal Regulations 21 CFR 600.80
\(^2\) Medical Dictionary for Regulatory Activities (https://www.meddra.org/)
Summary of U.S. 9vHPV reports to VAERS  
12/1/2014 – 12/31/2017

Doses distributed in the United States: ~29 million

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total reports</td>
<td>7,244</td>
</tr>
<tr>
<td>Female</td>
<td>2,258 (31)</td>
</tr>
<tr>
<td>Male</td>
<td>1,566 (22)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3,420 (47)</td>
</tr>
<tr>
<td>Serious reports</td>
<td>186 (3)</td>
</tr>
<tr>
<td>Deaths</td>
<td>7 (0.1)</td>
</tr>
<tr>
<td>Reported by manufacturer</td>
<td>4,650 (64)</td>
</tr>
<tr>
<td>Age range, years [median]</td>
<td>0-73 [14]</td>
</tr>
<tr>
<td>Onset interval, days [median]</td>
<td>0-751[0]</td>
</tr>
<tr>
<td>Received 9vHPV alone</td>
<td>5,411 (75)</td>
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</tbody>
</table>

1 Arana J. Adverse events following 9-valent human papillomavirus vaccine (9vHPV) reported to the Vaccine Adverse Event Reporting System (VAERS). ACIP. Feb 2018
2 US primary reports (foreign reports excluded)
3 Based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization or permanent disability
Top 10 reported signs and symptoms\(^1\) after 9vHPV in VAERS, 12/1/14 – 12/31/17: All Reports

<table>
<thead>
<tr>
<th>Reported Signs and Symptoms</th>
<th>N (%)</th>
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</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>579 (8)</td>
</tr>
<tr>
<td>Syncope</td>
<td>517(7)</td>
</tr>
<tr>
<td>Headache</td>
<td>418(6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>361(5)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>324(5)</td>
</tr>
<tr>
<td>Pyrexia (fever)</td>
<td>318 (4)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>317 (4)</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>299 (4)</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>268 (4)</td>
</tr>
<tr>
<td>Pallor</td>
<td>252 (3)</td>
</tr>
</tbody>
</table>

\(^1\) As coded using the MedDRA preferred terms (PT); more than one code may be assigned to a single event

\(^2\) Based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization or permanent disability
VAERS clinical review of select conditions

- Conditions of historical interest
  - Anaphylaxis: 9 reports
    - 3 confirmed¹
      - 2 received 9vHPV only
  - Guillain-Barré Syndrome (GBS): 8 reports
    - 4 confirmed²
      - 3 describe a viral respiratory illness two to four weeks prior to presentation of GBS symptoms
  - Death: 7 reports
    - 5 “hearsay” reports based on indirect information
    - 2 verified by autopsy and/or certificate of death
      - Cause of death: cardiac arrest; cerebellar aneurysm

 VAERS clinical review of select conditions (cont.)

- Conditions of recent interest
  - Complex regional pain syndrome (CRPS)
    - 1 report of possible\(^1\) CRPS; insufficient information
  - Postural orthostatic tachycardia syndrome (POTS)
    - 17 reports of possible POTS cases
      - 6 partially met diagnostic criteria\(^2\)
      - No pattern of concern was noted
  - Primary ovarian insufficiency (POI)
    - 3 reports of possible POI cases did not meet diagnostic criteria\(^3\); insufficient information

---

\(^1\)Harden et al. Validation of proposed diagnostic criteria (the “Budapest Criteria”) for Complex Regional Pain Syndrome. Pain. 2010; 150(2):268-274


\(^3\)The American College of Obstetricians and Gynecologists. Committee on Adolescent Health. Primary Ovarian Insufficiency in Adolescents and Young Adults. Committee Opinion. July 2014 Number 605
Vaccine Safety Datalink (VSD) 9vHPV Rapid Cycle Analysis (RCA)\(^1\)

- Near-real time active monitoring of pre-specified outcomes
- Automated patient level data collected at VSD’s participating health plans
  - Ability to review medical records to verify condition
- Study population:
  - Persons aged 9-26 years who received a 9vHPV dose
- Study period:
  - October 4, 2015 - October 3, 2017

\(^1\) Donahue, J. Rapid Cycle Analysis of the 9-valent Human Papillomavirus Vaccine (9vHPV) in the Vaccine Safety Datalink. ACIP. Feb 2018
VSD 9vHPV RCA

Methods

- Weekly sequential monitoring to detect statistically significant findings using the automated data (e.g. signals)
  - Each outcome; subgroups are defined by age, sex and dose

Analytic methods

- Sequential probability ratio tests
  - Rare outcomes: Historical VSD comparison group (January 2007 to December 2014)
- Exact sequential analysis
  - Common outcomes: Comparison groups include persons 9-26 years old with a visit during the surveillance period for a non-HPV adolescent vaccination (e.g. Td, meningococcal, HAV, or varicella)

Pre-specified outcomes

- GBS, appendicitis, injection site reaction, anaphylaxis, stroke, syncope, VTE, allergic reaction, CIDP, pancreatitis, seizures (1st ever, 1st in 42 days)

VTE, venous thromboembolism; GBS, Guillain-Barre Syndrome; CIDP, chronic inflammatory demyelinating polyneuropathy
Near real-time monitoring completed in October 2017
- ~900,000 doses

Statistically significant RCA findings detected for several adverse events after 9vHPV
- Syncope and local injection site reactions were expected
  - Both are identified in 9vHPV package insert\(^1\)
  - Syncope is a known adverse event following any injectable vaccine\(^2\)
- Statistically significant findings for allergic reaction, pancreatitis, and appendicitis were not confirmed after further evaluation

\(^1\)https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm426457.pdf
Ongoing and planned 9vHPV monitoring and evaluation activities

- **VAERS**
  - Ongoing monitoring of U.S. reports following HPV vaccine
    - Clinical review of deaths and other pre-specified events* by physicians at CDC and FDA
  - Completion of the 3 year 9vHPV surveillance summary and publication of findings

- **VSD**
  - Completion of 9vHPV Rapid Cycle Analysis manuscript and publication of findings
  - Epidemiologic study evaluating spontaneous abortion following inadvertent 4vHPV and 9vHPV administration
  - Tree-temporal scan data mining for 4vHPV and 9vHPV

*Pre-specified adverse events include anaphylaxis, autoimmune disorders, GBS, multiple sclerosis, POTS, CRPS, and POI
Other 9vHPV safety monitoring and evaluation activities

- Post-marketing commitments conducted by the manufacturer\(^1\)
  - Completion of 10-year study extensions for long-term safety, immunogenicity, effectiveness
    - Males and females 9-15 years
    - Females 16-26 years
  - Observational study to further characterize safety profile in approximately 10,000 persons
  - Pregnancy registry
    - Exposures occurring within 30 days prior to the last menstrual period or any time during pregnancy

- FDA PRISM: General safety study\(^2\)

\(^1\)http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm426520.htm
\(^2\)http://www.brookings.edu/~/media/events/2015/02/05%20fda%20sentinel%20initiative%20workshop/2015%20sentinel%20initiative%20annual%20meeting%20slide%20deck.pdf
Conclusions

- There is a robust, multicomponent safety monitoring system in the United States for all vaccines, including HPV vaccines.

- Based on VAERS review, no 9vHPV safety concerns to date; safety profile is consistent with data from pre-licensure trials and similar to post-licensure safety data from 4vHPV monitoring in VAERS.

- No concerning signals from near-real time 9vHPV safety monitoring in VSD.

- Safety monitoring and evaluation continues for 9vHPV, as for all vaccines in the United States, even after enhanced monitoring for new vaccines.
Acknowledgements

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  Jorge Arana
  Frank DeStefano
  Lauri Markowitz
  Tom Shimabukuro

Marshfield Clinic:
  James Donahue
  Burney Kieke
Thank you

jgee@cdc.gov
For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333
Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov Web: http://www.cdc.gov

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.
Backup
Reports to VAERS following human papillomavirus, meningococcal, and Tdap vaccines by year, 2006-2017

4vHPV: 4-valent human papillomavirus vaccine
9vHPV: 9-valent human papillomavirus vaccine
MCV: meningococcal conjugated vaccine
Tdap: tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine.
VAERS: Vaccine Adverse Event Reporting System
Vaccine Safety Datalink (VSD)

- Collaboration between CDC and 8 integrated healthcare plans
- Data on over 11 million persons per year (~3% of US population)
- Conducts traditional epidemiologic studies and Rapid Cycle Analysis (RCA)
- Links vaccination data to health outcome data

Data are linked and kept at each site, not at CDC