Presenters

• Lauri E. Markowitz, MD
  Centers for Disease Control and Prevention

• Tom Shimabukuro, MD
  Centers for Disease Control and Prevention
Webinar Logistics

- **Audio**: All participant lines are muted.

- **Webinar Recording**: We are recording this webinar. We will notify all participants when the recording and presentation are available online.

- **Q&A Session**: Type your question into the “Questions” panel. We will read selected questions out loud for the presenters to answer.
HPV Vaccination Update - 2015

Lauri E. Markowitz, MD
Centers for Disease Control and Prevention

#PreteenVaxScene Webinar Series
April 3, 2015
Outline

- Overview of HPV vaccines
- HPV-associated cancers due to HPV types
- Data from 9-valent HPV vaccine trials
- Updated recommendations of the Advisory Committee on Immunization Practices
Available prophylactic HPV vaccines

- Virus-like particle (VLP) vaccines
- The L1 major capsid protein expressed using recombinant technology
- L1 proteins self-assemble into VLPs
- Non infectious
### Available HPV vaccines

<table>
<thead>
<tr>
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<th>Bivalent 2vHPV (Cervarix)</th>
<th>Quadrivalent 4vHPV (Gardasil)</th>
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<tr>
<td>L1 VLP types</td>
<td>16, 18</td>
<td>6, 11, 16, 18</td>
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<tr>
<td>Manufacturer</td>
<td>GlaxoSmithKline</td>
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</tr>
<tr>
<td>Adjuvant</td>
<td>AS04:</td>
<td>AAHS:</td>
</tr>
<tr>
<td></td>
<td>500 µg aluminum hydroxide</td>
<td>225 µg amorphous aluminum</td>
</tr>
<tr>
<td></td>
<td>50 µg 3-O-desacyl-4'-</td>
<td>hydroxyphosphate sulfate</td>
</tr>
<tr>
<td></td>
<td>monophosphoryl lipid A</td>
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</tr>
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L1, Major capsid protein; VLP, virus like particle
# Available HPV vaccines

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L1, Major capsid protein; VLP, virus like particle
Percentage of cervical cancers attributed to high risk HPV types, worldwide

- HPV 16: 60.6%
- HPV 18: 10.2%
- HPV 45: 5.9%
- HPV 33: 3.8%
- HPV 31: 3.7%
- HPV 52: 2.8%
- HPV 58: 2.3%
- HPV 35: 1.9%
- HPV 39: 1.6%
- HPV 51: 1.3%
- HPV 59: 1.1%
- HPV 56: 0.8%
Estimated number of HPV-attributable cancer cases per year, United States

http://www.cdc.gov/cancer/hpv/statistics/cases.htm
## Estimated percentages of cancers attributed to HPV in the U.S.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>HPV attributable % (95% CI)</th>
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Adapted from Saraiya, presented at AIN Conference, March 13–15, 2015, Atlanta, GA.
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Adapted from Saraiya, presented at AIN Conference, March 13–15, 2015, Atlanta, GA.
Estimated numbers of HPV-associated cancers attributable to HPV 16/18 and 5 additional types in 9-valent vaccine, U.S.*

*Based on years 2006-2010 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6349a11.htm and data from Saraiya, presented at AIN Conference, March 2015
Summary: attribution of HPV 16/18 and HPV 31/33/45/52/58, United States

- **HPV-associated cancers**
  - ~33,000 per year
  - 64% of cancers attributable to HPV 16/18
    - 66% of cervical cancer
    - Other cancers: range, 48% penile -80% anal
  - 10% of cancers attributable to additional 5 types
    - 15% of cervical cancer
    - Other cancers: range, 4% oropharyngeal -18% vaginal
    - Differences by sex: 14% for females; 4% for males

- **≥CIN2 lesions**
  - ~50% attributable to HPV 16/18
  - ~25% attributable to 5 additional types

≥CIN, cervical intraepithelial neoplasia grade 2 or worse
% among all HPV-associated cancers
9-valent HPV vaccine

- Licensed by FDA in December 2014

- Clinical development program
  - Efficacy trial
  - Immunogenicity/immunobridging trials
  - Concomitant use trials
9-valent HPV vaccine efficacy trial

- **Design**
  - ~14,000 women aged 16-26 years
  - Randomized trial: 9vHPV or 4vHPV

- **Objectives**
  - Demonstrate efficacy for HPV 31,33,45,52,58
  - Demonstrate non-inferior immunogenicity for HPV 6,11,16,18

Joura, et al. NEJM 2015
9-valent HPV vaccine efficacy trial
per protocol population results

<table>
<thead>
<tr>
<th>HPV 31,33,45,52,58 related outcomes</th>
<th>9vHPV n/total</th>
<th>4vHPV n/total</th>
<th>Vaccine efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥CIN2, VIN2/3, VaIN2/3</td>
<td>1/6016</td>
<td>30/6017</td>
<td>96.7 (80.9, 99.8)</td>
</tr>
<tr>
<td>6 month persistent infection</td>
<td>35/5939</td>
<td>810/5953</td>
<td>96.0 (94.4, 97.2)</td>
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- High efficacy against HPV 31,33,45,52,58 outcomes

≥CIN2 = cervical intraepithelial neoplasia grade 2 or 3, or adenocarcinoma in situ; VIN = vulvar intraepithelial neoplasia; VaIN = vaginal intraepithelial neoplasia
### 9-valent HPV vaccine efficacy trial

per protocol population results

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<td>3/5898</td>
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- Few high grade outcomes due to HPV 6,11,16,18
- Non-inferiority immunogenicity for HPV 6,11,16,18
  - ≥99% seroconversion; GMTs non-inferior

≥CIN2 = cervical intraepithelial neoplasia grade 2 or 3, or adenocarcinoma in situ; VIN = vulvar intraepithelial neoplasia; VaIN = vaginal intraepithelial neoplasia

Joura, et al.  NEJM 2015
9-valent HPV vaccine adult-to-adolescent immunobridging trial

Data from per protocol population; Antibody measured by cLIA at month 7

9-valent HPV vaccine trials

- **Efficacy**
  - ~97% protection against HPV 31,33,45,52,58-related outcomes
  - Similar protection against HPV 6,11,16,18-related disease

- **Non-inferior immunogenicity**
  - For HPV 6,11,16,18 compared with 4vHPV in 16–26 and 9–15 year olds
  - For all 9 HPV vaccine types in adolescent females and males compared to adult females and in adult males compared to adult females

- **Concomitant use**
  - No impact on immunogenicity or safety administered concomitantly with quadrivalent meningococcal conjugate vaccine (Menactra) and tetanus, diphtheria, acellular pertussis vaccine (Adacel)

9-valent HPV vaccine safety

- Trials included >15,000 9vHPV vaccinees
- Generally well tolerated; safety profile similar to 4vHPV
  - 9vHPV - more injection-site reactions
    - swelling (40.3% vs 29.1%)
    - erythema (34.0% vs 25.8%)
  - Injection-site erythema and swelling increased with number of doses
- Concomitant use
  - No difference in safety profile when co-administered with quadrivalent meningococcal conjugate vaccine (Menactra) and tetanus, diphtheria, acellular pertussis vaccine (Adacel)
RECOMMENDATIONS
Recommendations for HPV vaccination in the United States (before February 2015)

- Routine vaccination at age 11 or 12 years*
- Vaccination recommended through age 26 for females and through age 21 for males not previously vaccinated
- Vaccination recommended for immunocompromised persons (including persons HIV-infected) and for men who have sex with men through age 26
- 3-dose schedule (0, 1-2 and 6 months)
- Vaccines
  - 2vHPV or 4vHPV for females
  - 4vHPV for males

*vaccination series can be started at age 9 years
Available HPV vaccines

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<tr>
<td>Licensed for</td>
<td>Females 9-25 years</td>
<td>Females 9-26 years Males 9-26 years</td>
<td>Females 9-26 years Males 9-15 years</td>
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</table>

- At the time of the first application to FDA, 9vHPV trials in males 16-26 years had not been completed
- Immunogenicity data now are available for males 16-26 years, reviewed by ACIP and submitted to FDA
- ACIP recommended use of 9vHPV in the currently recommended age groups

L1, major capsid protein; VLP, virus like particle
Updated ACIP recommendations

- Routine vaccination at age 11 or 12 years*
- Vaccination recommended through age 26 for females and through age 21 for males not previously vaccinated
- Vaccination recommended for men who have sex with men and immunocompromised men (including persons HIV-infected) through age 26
- Vaccination of females is recommended with 2vHPV, 4vHPV (as long as this formulation is available), or 9vHPV
- Vaccination of males is recommended with 4vHPV (as long as this formulation is available) or 9vHPV

*Vaccination series can be started at 9 years of age
Updated ACIP recommendations

2vHPV, 4vHPV and 9vHPV all protect against HPV 16 and 18, types that cause about 66% of cervical cancers and the majority of other HPV-attributable cancers in the United States. 9vHPV targets five additional cancer causing types, which account for about 15% of cervical cancers. 4vHPV and 9vHPV also protect against HPV 6 and 11, types that cause genital warts.

MMWR 2015;64:300-4
Updated ACIP recommendations: Interchangeability

If vaccination providers do not know or do not have available the HPV vaccine product previously administered, or are in settings transitioning to 9vHPV, for protection against HPV 16 and 18, any HPV vaccine product may be used to continue or complete the series for females; 4vHPV or 9vHPV may be used to continue or complete the series for males.

MMWR 2015;64:300-4
Updated ACIP recommendations: Administration

- 2vHPV, 4vHPV and 9vHPV are each administered in a 3-dose schedule
- The second dose is administered at least 1 to 2 months after the first dose, and the third dose at least 6 months after the first dose
- If the vaccine schedule is interrupted, the vaccination series does not need to be restarted

MMWR 2015;64:300-4
Updated ACIP recommendations: HPV vaccination during pregnancy

- No change in recommendations
- HPV vaccine not recommended for use in pregnancy

A new vaccine in pregnancy registry has been established for 9vHPV. Registries for 4vHPV and 2vHPV have been closed with concurrence from FDA.

4vHPV registry closed in 2012
2vHPV registry closed in 2015  http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm434787.htm
9vHPV vaccination for persons who completed a HPV vaccination series

- The manufacturer did not seek an indication for 9vHPV vaccination for persons who previously completed a HPV vaccination series
- A study of 9vHPV in prior 4vHPV vaccinees was conducted
- Due time limitations (abbreviated ACIP meeting), this was not discussed; will be discussed at a future ACIP meeting
**Summary: 9-valent HPV vaccine**

- Licensed by FDA in December 2014
- Recommended by ACIP in February 2015
- One of 3 HPV vaccines that can be used for routine vaccination of females and one of 2 for males
- Targets 5 additional high risk types
  - Overall 14% of HPV-associated cancers in females; 4% in males attributable to these 5 types
  - 15% of cervical cancers attributable to these 5 types
Next steps

- 9vHPV available from manufacturer starting in February 2015
- CDC awarded a Vaccines for Children (VFC) contract for 9vHPV
- Efforts need to continue to increase HPV vaccination coverage
National estimated vaccination coverage levels among adolescents 13-17 years
NIS-Teen, 2006-2013

Routine recommendation for females

Routine recommendation for males

Tdap

MCV4

≥1 HPV (girls)

3 HPV (girls)

≥1 HPV (boys)

3 HPV (boys)

NIS-Teen = National Immunization Survey-Teen
MMWR 2014:63;625-33
Resources

ACIP website with slides, minutes and recommendations
http://www.cdc.gov/vaccines/acip/index.html

Additional resources for providers/patients/clients
http://www.cdc.gov/vaccines/vpd-vac/hpv/
www.cdc.gov/vaccines/YouAreTheKey
www.cdc.gov/hpvwww.cdc.gov/vaccines/teens
Thank you

For more information please contact Centers for Disease Control and Prevention

lem2@cdc.gov
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.
Human Papillomavirus (HPV) Vaccine Safety Update

Tom Shimabukuro, MD
Immunization Safety Office
Centers for Disease Control and Prevention

April 3, 2015
Disclaimer

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

Disclosure: No conflicts of interest
Outline

- Update of HPV vaccine safety monitoring and publications*
- Ongoing HPV vaccine safety-related activities
- 9-valent HPV (9vHPV) vaccine safety monitoring plans

* Predominately quadrivalent human papillomavirus vaccine (4vHPV)
# CDC Immunization Safety Office Post-licensure Vaccine Safety Monitoring Infrastructure

<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>US frontline spontaneous reporting system to detect potential vaccine safety problems</td>
</tr>
<tr>
<td>Vaccine Safety Datalink (VSD)</td>
<td>CDC and 9 Managed Healthcare Plans</td>
<td>Large linked database system used for active surveillance and research ~9.4 million members (~3% of US pop.) -Conducts monitoring &amp; evaluation -Rates &amp; risk estimates can be calculated</td>
</tr>
<tr>
<td>Clinical Immunization Safety Assessment (CISA) Project</td>
<td>CDC and 7 Academic Centers</td>
<td>Expert collaboration that conducts individual clinical vaccine safety assessments and clinical research</td>
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Postlicensure HPV Vaccine Safety Publications: General Safety

- **VAERS Postlicensure safety summary**
  - Initial review in 2009\(^1\)--Proportion of reports for venous thromboembolism (VTE) and syncope after 4vHPV were higher than expected
  - No other signals identified through passive surveillance
  - Updated reviews in 2013 and 2014--no new concerns identified\(^2,^3\)

- **VSD Rapid Cycle Analysis (RCA) conducted near-real time monitoring following 600,558 4vHPV doses (2011)\(^4\)**
  - No statistically significant associations with Guillain-Barré Syndrome, stroke, VTE, appendicitis, seizures, syncope, allergic reactions, and anaphylaxis
  - Non-significant elevated risk (RR=1.98) for VTE in females 9-17 years

- **General safety assessment from two large US health plans with 189,629 female vaccinees (2012)\(^5\)**
  - 4vHPV associated with syncope and skin infections in the two weeks following immunization

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\(^1\) Slade et al, Post-licensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA 2009


\(^3\) Stokely et al, HPV vaccination coverage among adolescents 2007-13 and post-licensure vaccine safety monitoring 2006-14. MMWR 2014

\(^4\) Gee et al, Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the VSD. Vaccine 2011

\(^5\) Klein et al, Safety of quadrivalent human papillomavirus vaccine administered routinely to females, Arch Ped Adolesc Med 2012
HPV vaccine and Venous Thromboembolism (VTE)

- Possible association found in VAERS and VSD RCA studies\(^1,\ 2\)
  - VAERS: Proportion of reports were higher than expected
  - VSD RCA: Elevated non-significant risk identified among females ages 9-17 years

- Two national register-based cohort studies found no elevated risk for VTE following 4vHPV:
  - 296,826 vaccinated females aged 10-17 years (Denmark and Sweden)\(^3\)
  - 500,345 vaccinated females aged 10-44 years (Denmark)\(^4\)

- Preliminary VSD study results using self-controlled case series method found no increased risk of VTE following 4vHPV among persons aged 9-26 years\(^5\)

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2. Gee et al., Monitoring the safety of 4vHPV: findings from the VSD. Vaccine 2011
3. Arnheim-Dahlstrom et al, Autoimmune, neurological, and venous thromboembolic adverse events following immunization of adolescent girls with 4vHPV in Denmark and Sweden. BMJ 2013
4. Scheller et al, 4vHPV and the risk of venous thromboembolism. JAMA 2014
Postlicensure HPV Vaccine Safety Publications: Autoimmune and Neurologic Diseases

- No evidence for causal association observed between 4vHPV and autoimmune and/or neurologic conditions
  - 16 autoimmune conditions at two health plans among 189,629 vaccinated females aged 9-26 years (US)\(^1\)
  - 23 autoimmune, 5 neurologic conditions and VTE among 296,826 vaccinated females aged 10-17 years (Denmark and Sweden)\(^2\)
  - 6 autoimmune outcomes among 1,365 (269 cases, 1,096 controls) 14-27 year olds (France)\(^3\)
  - Multiple sclerosis and demyelinating diseases among 789,082 vaccinated females aged 10-44 years (Denmark)\(^4\)

\(^1\)Chao C et al, Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. J Intern Med 2012
\(^2\)Arnheim-Dahlstrom et al, Autoimmune, neurological, and venous thromboembolic adverse events following immunzation of adolescent girls with HPV4 in Denmark and Sweden. BMJ 2013
\(^4\)Scheller NM et al, Quadrivalent HPV vaccination and the risk of multiple sclerosis and other demyelinating diseases of the central nervous system. JAMA 2015
2011 Institute of Medicine (IOM) Report on Adverse Effects of Vaccines

• Syncope following vaccination
  • IOM concluded that, “the injection of a vaccine was a contributing cause of syncope.”

• Anaphylaxis following vaccination
  • IOM concluded that, “the evidence favors acceptance of a causal relationship between HPV vaccine and anaphylaxis.”
CDC’s Immunization Safety Office: Current HPV Vaccine Safety-Related Activities

- **VAERS:**
  - Ongoing monitoring of US reports (2vHPV and 4vHPV)
  - Clinical review of deaths (and other pre-specified adverse outcomes as needed)
  - FDA data mining

- **CISA:**
  - Assessing feasibility and impact of implementing an oral water hydration strategy to prevent post-vaccination presyncope and syncope in adolescents and young adults receiving any intramuscular vaccines (including HPV vaccine)
    - Interventional clinical trial registered at Clinical.Trials.gov (NCT02353390)
CDC’s Immunization Safety Office: HPV Vaccine Safety-Related Activities

**VSD:**

- Addressing HPV vaccine safety in special populations:
  - Safety of 4vHPV among males
  - Inadvertent 4vHPV vaccination during pregnancy

- Addressing HPV vaccine safety concerns from case reports and/or media:
  - Autoimmune disease risk following 4vHPV
  - Premature ovarian insufficiency following 4vHPV
  - Mortality following 4vHPV and other adolescent vaccines
9vHPV Vaccine Safety

- 7 prelicensure studies
- Generally well tolerated in > 15,000 subjects
  - Adverse event profile similar to that of 4vHPV across age, gender, race, and ethnicity
  - More injection site-related swelling and erythema in 9vHPV group
  - Among inadvertent pregnancies occurring during clinical studies:\(^1,^2\)
    - The proportion of adverse outcomes observed were consistent with pregnancy outcomes observed in the general population
    - In sub-analyses, pregnancies within 30 days of 9vHPV vaccination resulted in spontaneous abortion more frequently than after 4vHPV:
      - 9vHPV group 27.4% (17/62) vs. 4vHPV group 12.7% (7/55)
      - Spontaneous abortion background rate: 31% \(^3\)

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1. 9vHPV is FDA Category B for pregnancy, [http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf](http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf)
9vHPV Vaccine Safety Monitoring and Evaluation: CDC

- **VAERS:**
  - Monitor reports using automated data
  - Clinical review of deaths (and other pre-specified adverse outcomes as needed)
  - FDA data mining

- **VSD:**
  - Near real-time monitoring for several pre-specified outcomes through Rapid Cycle Analysis
  - Evaluation of spontaneous abortion following 9vHPV
    - Label indicates possible increase relative to 4vHPV
9vHPV Vaccine Safety Monitoring and Evaluation: Manufacturer and FDA

- **Postmarketing commitments by manufacturer:**¹
  - Completion of two 10-year study extensions evaluating the long-term safety, immunogenicity, and effectiveness in:
    - males and females 9-15 years
    - females 16-26 years
  - Observational study to further characterize the safety profile in approximately 10,000 persons
  - Pregnancy registry to prospectively collect data on spontaneously reported exposures occurring within 30 days prior to the last menstrual period or any time during pregnancy

- **FDA’s Sentinel Initiative pharmacovigilance plan:**²
  - General safety study
  - Pregnancy outcomes study

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

- 4vHPV has a good safety profile as demonstrated by:
  - VAERS and VSD safety monitoring data
  - Published and preliminary data from many sources
- Safety monitoring and evaluation continue for all HPV vaccines
Thank you!
Thank you for participating!

For more information, visit www.cdc.gov/vaccines/teens