Human Papillomavirus (HPV) Vaccine Safety

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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
Introduction

• HPV vaccines are a powerful public prevention tool for reducing the burden of cervical cancer and other HPV-related diseases

• Used in 129 countries since 2006

• Substantial safety data accumulated to date have been reassuring

• Vaccine safety concerns persist
  • In US, safety concerns reported by parents as one of the top 5 reasons for not initiating the HPV vaccination series

Estimated HPV Vaccination Coverage among Adolescents Aged 13-17 Years, NIS-Teen, United States, 2006-2014

MMWR 64(29);784-792  * APD = Adequate provider data
Outline

- Background of HPV vaccine
- Overview of US vaccine safety systems
- Review of HPV vaccine safety findings*
- Current and planned US HPV vaccine safety-related activities

* Predominately quadrivalent human papillomavirus vaccine (4vHPV)
HPV Prophylactic Vaccines

- Recombinant L1 capsid proteins that form “virus-like” particles (VLP)
- Non-infectious and non-oncogenic
- Produce higher levels of neutralizing antibody than natural infection
## HPV Vaccines Currently Licensed in the United States

<table>
<thead>
<tr>
<th></th>
<th>2vHPV (Cervarix)</th>
<th>4vHPV (Gardasil)</th>
<th>9vHPV (Gardasil 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
<td>GlaxoSmithKline</td>
<td>Merck &amp; Co.</td>
<td>Merck &amp; Co.</td>
</tr>
<tr>
<td><strong>HPV Types Included</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>Contraindications</strong></td>
<td>Hypersensitivity to latex*</td>
<td>Hypersensitivity to yeast</td>
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</tr>
<tr>
<td><strong>Dose Schedule</strong></td>
<td>3-dose series: 0, 1, 6 months</td>
<td>3-dose series: 0, 2, 6 months</td>
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*May be present in tip of pre-filled syringes*
HPV Vaccine Comparison

<table>
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<th>HPV Types Included in Vaccine</th>
</tr>
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<tbody>
<tr>
<td>6</td>
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- **Bivalent**
  - Genital warts
  - ~66% of Cervical Cancers

- **Quadrivalent**

- **9-valent**
  - ~15% of Cervical Cancers
ACIP HPV Vaccine Recommendation

Girls & Boys can start HPV vaccination at age 9

Preteens should finish HPV vaccine series by 13th birthday

Plus girls 13-26 years old who haven’t started or finished HPV vaccine series

Plus boys 13-21 years old who haven’t started or finished HPV vaccine series
ACIP HPV Vaccine Recommendations: A Closer Look

Age

• 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 through age 26 who have sex with men (MSM) or are immunocompromised (including HIV-infected persons)

Formulation by gender (assuming availability)

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<th>9vHPV</th>
<th>4vHPV</th>
<th>2vHPV</th>
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<td><strong>Females</strong></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td><strong>Males</strong></td>
<td>✔</td>
<td>✔</td>
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* vaccination series can be started at 9 years of age

MMWR 2015;64:300-4
VACCINE SAFETY

Vaccine efficacy: Ability of a vaccine to work as intended to protect from illness.

Vaccine-associated risk: Probability increased adverse event that harm the individuals or population.
How a Vaccine is Developed and Approved for Licensure

Food and Drug Administration (FDA) sets rules for the three phases of clinical trials to ensure the safety of the volunteers. Researchers test vaccines with adults first.

**PHASE 1**
- **20-100 healthy volunteers**
  - Is this vaccine safe?
  - Does this vaccine seem to work?
  - Are there any serious side effects?
  - How is the size of the dose related to side effects?

**PHASE 2**
- **several hundred volunteers**
  - What are the most common short-term side effects?
  - How are the volunteers' immune systems responding to the vaccine?

**PHASE 3**
- **HUNDREDS or THOUSANDS of volunteers**
  - How do people who get the vaccine and people who do not get the vaccine compare?
  - Is the vaccine safe?
  - Is the vaccine effective?
  - What are the most common side effects?

**FDA licenses the vaccine only if:**
- It’s safe and effective
- Benefits outweigh risks
HPV Vaccines: Clinical Trials

- 2vHPV: 23,952 females
- 4vHPV: 18,083 males and females
- 9vHPV: 23,081 males and females

Based on favorable safety findings from the clinical trials, vaccines were licensed by FDA and recommended for use in the US by the Advisory Committee on Immunization Practices
US Post-licensure vaccine safety monitoring and evaluation

- FDA post-marketing commitments by the manufacturer
  - Routine evaluation of clinically significant post-licensure adverse event reports
  - Requested post-licensure safety studies
  - Pregnancy registries
- US Public health authorities and regulatory agencies fund and/or conduct large population-based studies including:
  - Passive surveillance
  - Active surveillance
  - Traditional epidemiologic studies
## US Post-licensure Vaccine Safety System

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Vaccine Adverse Event Reporting System (VAERS)

- National spontaneous reporting system jointly administered by CDC and FDA since 1990 for adverse events (AE) following vaccination
  - Signal detection and hypothesis generation
    - Not designed to assess causality
  - Signs/symptoms of adverse event are coded using MedDRA* terms and entered into database
  - More than one code may be assigned to a single event
  - Coded as serious if one of the following is reported:
    - Death, life-threatening illness, hospitalization, prolongation of hospitalization, or permanent disability

* † Any untoward medical occurrence following vaccination and which does not necessarily have a causal relationship with vaccination
VAERS Reports

- Accepted from healthcare providers, manufacturers and the public
- Submission of reports:
  - Mailed written hardcopy of paper form
  - Faxed hardcopy
  - Secure online submission (~30% of reports in recent years)
  - Via telephone through a VAERS customer service representative
- VAERS staff follow up with health care providers on serious reports and certain selected reports of interest by phone to obtain medical records and autopsy reports
- CDC and FDA clinicians review medical records and VAERS reports
# Vaccine Adverse Event Reporting System (VAERS)

<table>
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<tr>
<th>Strengths</th>
<th>Limitations</th>
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<td>National data; accepts reports from anyone</td>
<td>Reporting bias</td>
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<tr>
<td>Rapid signal detection</td>
<td>Inconsistent data quality and completeness</td>
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<tr>
<td>Can detect rare adverse events</td>
<td>Lack of unvaccinated comparison group</td>
</tr>
<tr>
<td>Collects information about vaccine, characteristics of vaccinée, adverse event</td>
<td>Generally cannot assess if vaccine caused an AE</td>
</tr>
<tr>
<td>Data available to public</td>
<td>Pregnancy inconsistently reported</td>
</tr>
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1. VAERS website: [http://vaers.hhs.gov](http://vaers.hhs.gov)
2. Some reports have no adverse event
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  ~9.4 million members (~3% of US pop.)  
  -Conducts monitoring & evaluation                   |
| Clinical Immunization Safety Assessment (CISA) Project | CDC and 7 Academic Centers            | Expert collaboration that conducts individual clinical vaccine safety assessments and clinical research                                      |
| Post-Licensure Rapid Immunization Safety Monitoring Program (PRISM) | FDA and 4 partner organizations       | Large distributed database system used for active surveillance and research  
  ~170 million individuals                           |
Vaccine Safety Datalink (VSD)

- Established in 1990
- Collaboration between CDC and 9 integrated healthcare plans
- Data on over 9 million persons per year (~3% of US population)
- Links vaccination data to health outcome data

Vaccination Records

Health Outcomes
- (Hospital)
- (Emergency Dept)
- (Outpatient)

Patient Characteristics

Linked by Study IDs

Data are linked and kept at each site, not at CDC
VSD administrative data sources

- Ambulatory visit diagnosis codes
- Hospital discharge diagnosis codes
- Birth and death certificate information
- Laboratory
- Immunizations
- Enrollment and demographics
- Pharmacy

Large Linked Database
Vaccine Safety Datalink Sites in 2016

- Group Health Cooperative
- Kaiser Permanente Northwest
- Kaiser Permanente Northern CA
- Kaiser Permanente Colorado
- Health Partners
- Marshfield Clinic
- Harvard Pilgrim
- CDC
Types of VSD Evaluations

- **Traditional epidemiologic studies**
  - Descriptive epidemiology, case series, cohort study, case-control study

- **Rapid Cycle Analysis (RCA)**
  - Developed to provide weekly near real-time assessment of the safety of newly licensed vaccines or change in recommendations for current vaccines
  - Adverse events being monitored are pre-specified
  - Adverse events can also be added if a signal for an event (not already pre-specified) is identified from another system
  - Hypothesis testing, not data mining
  - Findings of association using RCA are considered safety signals and further refinement of the analysis needs to occur once a signal is identified
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Clinical Immunization Safety Assessment (CISA) Project

- Collaboration between CDC and 7 medical research centers
- Serves as a vaccine safety resource for consultation on clinical vaccine safety issues
- Develop strategies to assess individuals who may be at increased risk for adverse events following immunization (AEFI)
- Conduct studies to identify risk factors and preventive strategies for AEFI, particularly in special populations
CISA evaluation for patient vaccine safety questions

- Healthcare provider email requests accepted at CISAeval@cdc.gov
- Providers notified within 1-2 weeks if case will be reviewed
- Whether a case is accepted for a CISA consultation or not, it is recommended that provider submit a report to VAERS
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Post-Licensure Rapid Immunization Safety Monitoring Program (PRISM)

- Initiated in 2009
- Component of FDA’s Sentinel System
  - National, integrated, electronic system that allows for monitoring medical product safety
- Specifically focuses on vaccines
- 6 data partners
- Distributed database
  - Links health plan claims data with state and city immunization data
- Data on over 170 million individuals
Review of
HPV Vaccine Safety Findings
HPV vaccine

• Doses distributed in the US since licensure through March 31, 2016:
  – 4vHPV: ~79 Million doses
  – 9vHPV: ~10 Million doses
  – 2vHPV: 720,000 doses

• US Manufacturer plans:
  – GSK will no longer be offering 2vHPV in US
  – Merck will withdraw 4vHPV from the US market by the end of 2016
    • 9vHPV will be available for use for females and males aged 9-26 yrs

1 Kuter B, Personal Communication, June 2016
2 Seifert H, Personal Communication, July 2016
Reasons parents won’t initiate HPV vaccination for children

- Safety concern/Side effects
- Not recommended
- Not needed or necessary
- Lack of knowledge
- Not sexually active

MMWR 2014; 63(29);625-633;
4vHPV General Safety Studies

- VAERS post-licensure safety summary (2009)\(^1\)
  - Analyzed all reports with detailed review of select outcomes
  - Safety profile consistent with pre-licensure data
    - Proportion of reports for venous thromboembolism (VTE) and syncope after 4vHPV were higher than expected
  - Updated reviews in 2013 and 2014 with no new concerns identified\(^2,3\)

- General safety assessment from two large US health plans with 189,629 female vaccinees (2012)\(^4\)
  - Post-marketing manufacturer commitment to FDA
  - 4vHPV associated with syncope on the day of vaccination and skin infections in the two weeks following vaccination
  - No other safety signals following 4vHPV exposure

\(^1\) Slade et al, Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA 2009
\(^4\) Klein et al, Safety of quadrivalent human papillomavirus vaccine administered routinely to females, Arch Ped Adolesc Med 2012
4vHPV General Safety Studies

• VSD conducted near-real time monitoring following 600,558 4vHPV doses (2011)\(^1\)
  • No associations with Guillain-Barré Syndrome (GBS), stroke, appendicitis, seizures, syncope, allergic reactions, and anaphylaxis
  • Non-significant elevated risk (RR=1.98) for VTE in females 9-17 years
  • Continued surveillance in the VSD for GBS, did not observe an increased risk of GBS following 4vHPV among females aged 9-26 years\(^2\)
    • Surveillance period: August 2006-February 2012
    • 1,490,428 4vHPV doses administered
    • After medical record review, 0 incident cases of GBS within 42 days following 4vHPV

\(^1\)Gee et al, Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. Vaccine 2011
\(^2\)Sukumaran L. HPV vaccine safety update; ACIP presentation. October 2015
4vHPV and Venous Thromboembolism (VTE)

- Two national register-based cohort studies found no elevated risk for VTE following 4vHPV
  - 296,826 vaccinated females 10-17 years (Denmark and Sweden)\(^1\)
  - 500,345 vaccinated females 10-44 years (Denmark)\(^2\)
- VSD study found no increased risk of VTE following 4vHPV among 650,737 vaccinated persons aged 9-26 years\(^3\)
- PRISM study found no increased risk for VTE following 4vHPV among 650,000 females aged 9-26 years\(^4\)

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\(^2\) Scheller et al, Quadrivalent human papillomavirus vaccine and the risk of venous thromboembolism. JAMA 2014.
4vHPV and Autoimmune/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 (US)\(^1\)
  
  • 23 autoimmune, 5 neurologic conditions and VTE among 296,826 vaccinated females aged 10-17 years (Denmark and Sweden)\(^2\)
  
  • 6 autoimmune conditions among 1,365 (269 cases, 1,096 controls) 14-26 year olds (France)\(^3\)
  
  • Multiple sclerosis and demyelinating diseases among 789,082 vaccinated females aged 10-44 years (Denmark and Sweden)\(^4\)

---


\(^4\) Scheller et al, Quadrivalent HPV vaccination and the risk of multiple sclerosis and other demyelinating diseases of the central nervous system. JAMA 2015.
Mortality Following 4vHPV

• VAERS review of confirmed death reports found no pattern with respect to:
  • Time after vaccination, vaccine dose number, combination of vaccines administered or diagnoses at death¹

• VSD study concluded that the risk of death was not increased during 30 days following 4vHPV vaccination²

• Manufacturer 4vHPV post-marketing commitment did not find any deaths to have a causal relationship with vaccination³

¹ [Link](http://www.cdc.gov/vaccinesafety/vaccines/hpv/hpv-safety-faqs.html)
³ Klein et al, Safety of quadrivalent human papillomavirus vaccine administered routinely to females, Arch Ped Adolesc Med 2012
Safety of Inadvertent 4vHPV Vaccination in Pregnancy

- No increased risk of fetal loss, spontaneous abortion (SAB), congenital anomalies in phase III trials\(^1\)
  - 1,796 4vHPV vaccine and 1,824 placebo recipients inadvertently vaccinated in pregnancy

- 4vHPV pregnancy registry identified no concerns\(^2\)
  - 1,752 prospective pregnancy reports, rates of SAB and major birth defects similar to population rates\(^2\)

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2011 Institute of Medicine (IOM): Syncope & Anaphylaxis

• IOM reviewed possible associations between 8 vaccines and adverse health events. Key findings:
  – Evidence “favors acceptance” of a causal relationship between HPV vaccine and anaphylaxis (rare)
  – Evidence “convincingly supports” a causal relationship between the injection of a vaccine and syncope

• Inadequate evidence was found for causal relationships between HPV vaccination and 12 other specific health events studied

Adverse Effects of Vaccines: Evidence and Causality, Institute of Medicine, Aug 2011
Two sisters, 20 and 19, are suing the makers of the HPV vaccine, claiming the drug caused them to lose their fertility.

Dozens of teenage girls from Japan injured by HPV vaccine file suit against government, drug makers; complaints of constant full-body pain.

by Admin on in Health
Current Safety Issues with HPV Vaccine

- Primary ovarian insufficiency (POI):
  - No safety findings in VAERS¹

- Complex regional pain syndrome (CRPS):
  - VAERS data suggest that with over 80 million doses of 4vHPV distributed in US through Sept 2015, CRPS following 4vHPV is rare²

- Postural Orthostatic Tachycardia Syndrome (POTS):
  - No evidence to support a causal link between HPV vaccine and POTS
    - European Medicine’s Agency detailed review³
    - No safety findings in VAERS¹

¹ http://www.cdc.gov/vaccinesafety/vaccines/hpv/hpv-safety-faqs.html
Ongoing and Planned
US HPV Vaccine Safety Activities
CDC’s Immunization Safety Office: Current HPV Vaccine Safety-Related Activities

• Vaccine Adverse Event Reporting System (VAERS)
  • Ongoing monitoring of US reports following all HPV vaccines
    • Cases of POTS reported to VAERS following HPV vaccination, June 1, 2006 – September 1, 2015
    • HPV VAERS reports from 2009-2015
  • Clinical review of deaths (and other pre-specified adverse outcomes)
  • FDA collaborates with CDC on monitoring
CDC’s Immunization Safety Office: Current HPV Vaccine Safety-Related Activities

- Clinical Immunization Safety Assessment (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: Current HPV Vaccine Safety-Related Activities

- Vaccine Safety Datalink (VSD) studies
  - 4vHPV:
    - Safety following inadvertent exposure during pregnancy
    - Autoimmune disease risk (long-term) following 4vHPV
    - Primary ovarian insufficiency following 4vHPV
  - 9vHPV:
    - Near real-time monitoring for several pre-specified outcomes through Rapid Cycle Analysis
      - Anaphylaxis, allergic reactions, appendicitis, GBS, seizure, stroke, syncope, VTE, pancreatitis, injection site reaction
    - Epidemiologic study evaluating spontaneous abortion following inadvertent 4vHPV and 9vHPV administration
FDA: 9vHPV Safety Monitoring and Evaluation

• Postmarketing commitments by manufacturer¹
  • Completion of two 10-year study extensions evaluating long-term safety, immunogenicity, and 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 of exposures occurring within 30 days prior to the last menstrual period or any time during pregnancy

• PRISM pharmacovigilance plan²
  • General safety study
  • Pregnancy outcomes study

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

• Large body of published data from many sources demonstrates the safety of HPV vaccines

• Safety monitoring and evaluation will continue for all HPV vaccines with enhanced monitoring for 9vHPV during the initial uptake phase
HPV Vaccine Information and Resources

- HPV and HPV Vaccine:  [www.cdc.gov/hpv](http://www.cdc.gov/hpv)
- HPV vaccine safety frequently asked questions:
- Vaccine safety:
  - [https://vaers.hhs.gov/](https://vaers.hhs.gov/)
Thank You

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: 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.