Vaccine Safety

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Disclosure

- I have no financial interests to disclose.
- I will not be presenting on investigational products.

Learning Objectives

- Describe how vaccine safety is monitored in the United States
- Review the safety of HPV vaccines
- Identify resources for addressing parents’ concerns about vaccines and vaccine safety
HOW VACCINE SAFETY IS MONITORED

Vaccines

- Biological products that – by eliciting a specific immune response to specific disease-causing agents – use the body’s own immune response to provide protection
- Provide enormous individual and community benefits
- Because they are preventive measures that are given to healthy individuals including young children, must be as safe as possible

Vaccine Safety

- When the vaccine is under development, studies are done to find out if it is safe and effective
- FDA review: if safe and effective, vaccine can be licensed
  - Other issues (manufacturing etc.) also considered by FDA
- Ongoing monitoring by both CDC and FDA and by the manufacturer after licensure
  - Post-licensure studies by the manufacturer
  - Vaccine Adverse Event Reporting System (VAERS)
  - Active surveillance and special studies by CDC and FDA
- If vaccine safety issues are identified, actions are taken
Not Everything Bad that Happens after Vaccination is *Caused* by the Vaccine

- Most of the conditions that people are concerned that vaccines may cause occur unrelated to vaccination
  - Guillain-Barré syndrome occurs unrelated to immunization with about 1 case per year in 100,000 people

- Except for the disease the vaccine prevents, all of the other health outcomes – including deaths – that would have happened anyway keep happening after vaccination

Vaccine Adverse Event Reporting System (VAERS)

- National spontaneous reporting system for adverse events after US-licensed vaccines
  - In recent years, received around 30,000 U.S. reports annually
  - Accepts reports from healthcare providers, manufacturers and the public
  - Signs/symptoms of adverse event coded and entered into database
  - Signal detection and hypothesis generation
- Jointly administered by CDC and FDA
- Authorized by National Childhood Vaccine Injury Act of 1986

How Do We Decide if an Adverse Event is Caused by a Vaccine?

- Live virus vaccine strains can be isolated or detected and distinguished by molecular techniques from “wild type” strains
  - Oral poliovirus associated with vaccine-associated polio
  - Zoster caused by wild- or vaccine-type varicella virus

- We compare the frequency of an adverse event in a time interval after vaccination with the frequency of the adverse event in a time interval that is *not* after vaccination
VAERS: Serious Reports of Syncope Following HPV4 – June 1, 2006 – September 15, 2011

- Total number of serious reports: 202
- Injuries resulting from syncopal event:
  - Fractures (nose, skull, maxillary)
  - Dental injuries
  - Contusions
  - Concussions
  - Intracranial hemorrhages (subdural hematoma, subarachnoid hemorrhage)
- No reports of death resulting from injury following a vasovagal syncopal event

Presented by Julianne Gee, ACIP, October 2011.

*Unverified reports coded as syncope or syncope vasovagal.

How Do We Decide What We Are Going to Worry About?

- Consistent pattern of clinical findings
- Biologic plausibility
- Consistency of findings in other studies
- Clustering of cases in time after vaccination, especially in a “biologically plausible” interval
- Observed cases > expected cases
  - Calculations require knowing what the incidence of the condition is, and how many doses of vaccine have been given

VAERS Verified Reports of Death following HPV4 June 1, 2006 – September 15, 2011

- 34 deaths reported
- Reported causes of death after clinical review with median onset interval:
  - Neurological: 7 (seizures [5]; ALS [2]) – 53 days (13-745)
  - Cardiac: 7 (tachyarrhythmia [3]; myocardiitis [3]; congenital) – 9 days (2-25)
  - Pulmonary embolism: 4 – 14.5 days (13-181)
  - Infectious: 5 (Group A strep [2]; N meningitidis, MRSA, HIV-CNS vasculitis) – 29 days (4-117)
  - Other non-infectious: 4 (suicide; type 1 DM DKA; drug overdose; dermatomyositis)
  - Undetermined cause of death: 7 – 17 days (2-121)
- No pattern in verified death events

Presented by Julianne Gee, ACIP, October 2011.
VAERS Verified Reports of Death following HPV4 in Males – June 1, 2006 – September 15, 2011

- 2 deaths in males
- **Myocarditis**
  - Age: 10 yrs
  - Days from vaccination to death: 9 days
  - Received other vaccines on same day
    - Meningococcal, Hepatitis A, Tdap, HPV4 (Dose 1)
  - No past medical history
- **Obstructive congenital subaortic membrane**
  - Age: 15 yrs
  - Days from vaccination to death: 25 days
  - Received only HPV4, Dose 1
  - Past medical history: asthma; cardiac disorder

Presented by Julianne Gee, ACIP, October 2011

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**Vaccine Safety Datalink**

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

**Vaccine Safety Datalink Sites: 2015**

- Group Health Cooperative
- Northwest Kaiser Permanente
- No. CA Kaiser Permanente
- So. CA Kaiser Permanente
- Kaiser Permanente Oregon
- Marshfield Clinic
- Harvard Pilgrim
- Health Partners
- SHQ
- CDC
VSD Methodologies for Vaccine Safety Surveillance and Research Studies

- Near real-time surveillance (Rapid Cycle Analysis [RCA]) and traditional epidemiologic studies
- Different study designs:
  - Cohort studies
  - Case-control studies
  - Self-controlled designs
- Observe adverse events in a “risk window” following vaccination

SAFETY OF HPV VACCINES

HPV vaccines

- 4vHPV (GARDASIL®)
  - Licensed in 2006
  - 79 million doses distributed\(^1,2\)
- 2vHPV (CERVARIX®)
  - Licensed in 2009
  - 832,000 doses distributed\(^1,3\)
- 9vHPV (GARDASIL® 9)
  - Licensed in 2014
  - 2 million doses distributed\(^1,2\)

1. Doses distributed in the US through June 2015
2. Kuter B, personal communication, 2 October 2015
3. Tofa A, personal communication, 14 October 2015
Postlicensure 4vHPV Vaccine Safety Publications:

**General Safety**
- VAERS postlicensure safety summary (2009)¹
  - Proportion of reports for venous thromboembolism (VTE) and syncope after 4vHPV were higher than expected
  - Updated reviews in 2013 and 2014—no new concerns identified²,³
- VSD conducted near-real time monitoring following 600,558 4vHPV doses (2011)⁴
  - No associations with Guillain-Barré Syndrome, stroke, appendicitis, seizures, syncope, allergic reactions, and anaphylaxis
  - Non-significant elevated risk (RR=1.98)⁵ for VTE in females 9-17 years
- General safety assessment from two large US health plans with 189,629 female vaccinees (2012)⁶
  - 4vHPV associated with syncope on the day of vaccination and skin infections in the two weeks following vaccination

¹ Slade et al, Post-licensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA 2009
⁴ Gee et al, Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the VSD. Vaccine 2011
⁵ Relative risk calculated using Poisson based maximized sequential probability ratio test (maxSRPT)

Postlicensure 4vHPV Vaccine Safety Publications:

**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 years³
- FDA Sentinel System found no increased risk for VTE following 4vHPV among 650,000 females aged 9-26 years⁴

² Scheller et al, Quadrivalent human papillomavirus vaccine and the risk of venous thromboembolism. JAMA 2014.

Postlicensure 4vHPV Vaccine Safety Surveillance:

**Guillain-Barré Syndrome (GBS)**
- Vaccine Safety Datalink (VSD) did not observe an increased risk of GBS following 4vHPV among females aged 9-26 years*¹
  - 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 CDC unpublished data
Postlicensure 4vHPV 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 (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) 14-26 year olds (France)\(^3\)
  - Multiple sclerosis and demyelinating diseases among 789,082 vaccinated females aged 10-44 years (Denmark and Sweden)\(^4\)

4. Scheller NM et al, Quadrivalent HPV vaccination and the risk of multiple sclerosis and other demyelinating diseases of the central nervous system. JAMA 2015.

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\(^2\)


Safety of Inadvertent 2vHPV Vaccination in Pregnancy

- Pre-licensure clinical trials showed possible increased risk of spontaneous abortion (SAB) in pregnant women 15-25 years vaccinated around last menstrual period (LMP)\(^1,2\)
- Post-licensure study found no evidence of an increased risk of SAB and other adverse pregnancy outcomes in women inadvertently vaccinated around LMP\(^3\)

2011 Institute of Medicine (IOM) Report on Adverse Effects of Vaccines

- **Syncope**
  - IOM concluded that, "the injection of a vaccine was a contributing cause of syncope."

- **Anaphylaxis**
  - IOM concluded that, "the evidence favors acceptance of a causal relationship between HPV vaccine and anaphylaxis."

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**Recent Concerns in HPV Vaccine Safety**

- **Primary Ovarian Insufficiency (POI)**
  - Case reports in the media led to public concern
  - No safety findings in VAERS

- **Complex Regional Pain Syndrome (CRPS)**
  - Case reports in Japan of pain following HPV vaccination led to suspension of their HPV vaccine recommendation
  - Review and adjudication of case reports found no evidence for causal association observed between 2vHPV and CRPS
  - VAERS data suggest that with over 80M doses of 4vHPV distributed in US through September 2015, CRPS is rare

- **Postural Orthostatic Tachycardia Syndrome (POTS)**
  - No evidence to support a causal link between HPV vaccine and POTS
    - European Medicines Agency detailed review
    - No safety findings in VAERS

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**CDC’s Immunization Safety Office: Current HPV Vaccine Safety-Related Activities**

- **Vaccine Adverse Event Reporting System (VAERS)**
  - Ongoing monitoring of US reports
  - Clinical review of deaths (and other pre-specified adverse outcomes as needed)
  - FDA collaborates with CDC on HPV 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)

- Postural Orthostatic Tachycardia Syndrome (POTS) Technical Review
  - Will be done in response to spontaneous reports and public concern about POTS as a possible AE following HPV vaccination

CDC’s Immunization Safety Office: Current HPV Vaccine Safety-Related Activities

- Vaccine Safety Datalink (VSD) studies
  - Addressing 4vHPV vaccine safety following inadvertent exposure during pregnancy
  - Addressing HPV vaccine safety concerns from case reports and/or media
    - Autoimmune disease risk (long-term) following 4vHPV
    - Primary ovarian insufficiency following 4vHPV
    - Mortality following 4vHPV and other adolescent vaccines
  - No increased risk of death during 30 days after immunization

9vHPV Vaccine Safety

- 6 prelicensure studies
  - Generally well tolerated in >15,000 subjects
    - Adverse event profile similar to that of 4vHPV
    - More injection site-related swelling and erythema with 9vHPV
    - Among inadvertent pregnancies during clinical studies
      - The proportion of adverse outcomes observed was consistent with pregnancy outcomes observed in the general population
      - In post-hoc analysis, pregnancies within 30 days of 9vHPV 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: 10.4-31%

References:
Gardasil 9® (9vHPV) reports in VAERS: 06/01/2016

<table>
<thead>
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<th>Category</th>
<th>Total Reports*</th>
<th>Male</th>
<th>Female</th>
<th>Unknown</th>
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<td>Total</td>
<td>1,652</td>
<td>396</td>
<td>577</td>
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<td>Serious</td>
<td>36</td>
<td>2</td>
<td>0</td>
<td>34</td>
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<td>Deaths</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
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<td>Age Range (years)</td>
<td>0 - 72 [median]</td>
<td>0 - 72 [median]</td>
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<tr>
<td>Onset Interval (days)</td>
<td>0 - 966 [median]</td>
<td>0 - 966 [median]</td>
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</table>

Common MedDRA# terms:
- No adverse event‡
- Incorrect product storage
- Dizziness
- Syncope
- Headache
- Nausea

No new data mining findings for 9vHPV

*US primary reports (foreign reports excluded)
†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, ‡Medical Dictionary for Regulatory Activities, #Vaccination errors without adverse event

Conclusion

- Large body of published and preliminary data from many sources demonstrate 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

Vaccine Safety

COMMUNICATING WITH PARENTS
What Determines Credibility?
Low Concern Settings

- Competence/Expertise: 80-85%
- All other factors: 15-20%

Randall Hyer, NIC, 2005

What Determines Credibility?
High Concern Settings

- Competence/Expertise: 15-20%
- Listening/Caring/Empathy: 50%
- Honesty/Transparency: 15-20%
- All other factors: 15-20%

Randall Hyer, NIC, 2005

Talking with Parents about Vaccines for Infants

This resource provides communication strategies for successful vaccine conversations with parents and caregivers.

http://www.cdc.gov/vaccines/hcp/conversations/conv-materials.html
If You Choose Not to Vaccinate Your Child, Understand the Risks and Responsibilities

This resource outlines possible risks for parents who choose to delay or decline a vaccine, offers steps for parents to take to protect their child, family and others.

http://www.cdc.gov/vaccines/hcp/conversations/conv-materials.html

Provider Resources for Vaccine Conversations with Parents

Understanding Vaccines and Vaccine Safety
http://www.cdc.gov/vaccines/hcp/conversations/provider-resources-safety-sheets.html

Diseases and the Vaccines that Prevent Them for Parents of Infants and Young Children (Birth through Age 6)
https://www.cdc.gov/vaccines/hcp/conversations/prevent-diseases/provider-resources-factsheets-infants.html

Diseases and the Vaccines that Prevent Them for Parents of Preteens and Teens (7 through 18 years old)
http://www.cdc.gov/vaccines/hcp/conversations/prevent-diseases/provider-resources-factsheets-teens.html

Reasons for Not Vaccinating Adolescents with HPV Vaccine, Unvaccinated Adolescents* Aged 13-17 Years, NIS-Teen, United States, 2014

<table>
<thead>
<tr>
<th>Reason</th>
<th>Parents of Girls (%) (95% CI)</th>
<th>Parents of Boys (%) (95% CI)</th>
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<tr>
<td>Not needed/necessary</td>
<td>18.3 (15.8-21.1)</td>
<td>18.9 (16.8-21.1)</td>
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<td>Safety concerns/side effects</td>
<td>16.2 (13.6-19.2)</td>
<td>18.0 (16.0-20.3)</td>
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<td>Lack of knowledge</td>
<td>12.9 (10.9-14.7)</td>
<td>13.7 (11.8-15.8)</td>
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<tr>
<td>Not recommended</td>
<td>9.9 (7.9-12.1)</td>
<td>9.8 (7.2-12.2)</td>
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<tr>
<td>Not sexually active</td>
<td>8.8 (7.0-11.4)</td>
<td>7.3 (5.6-9.4)</td>
</tr>
</tbody>
</table>

* Adolescents were unvaccinated with even HPV vaccine does, whose parents reported that they were not likely to seek HPV vaccination for their adolescent in the next 12 months.
FILLING IN KNOWLEDGE GAPS

SMEI and “Vaccine Encephalopathy”

- Epileptic encephalopathies, without other specific cause identified, with first seizure onset within 72 hours of vaccination
- Cases ascertained by child neurologists in Australia and New Zealand 2002-2003

Diagnoses:
- SMEI – 8 patients
- SMEB – 4 patients
- Lennox-Gastaut syndrome – 2 patients

Molecular analysis:
- Heterozygous mutations of SCN1A in 11 of 14 cases
Filling in Knowledge Gaps

- Concerns about whole cell pertussis vaccine (DTP) and encephalopathy
- Dravet syndrome
  - Severe disease with hard-to-control seizures, progressive course, poor prognosis
  - Many cases are associated with de novo mutations in a specific gene
- A recent study suggests that many cases of encephalopathy after DTP are Dravet syndrome

Berkovic, Lancet Neurology 2006

Medical Mysteries: It wasn’t the vaccine — so why did baby have seizures?


Vaccine Safety: A Shared Responsibility

- Manufacturers: Prelicensure and postlicensure studies, good manufacturing practices
- Government agencies: Licensing, oversight of manufacturing, vaccine recommendations, surveillance, public health response, research
- Academic researchers: Clinical observations, research, clinical guidelines
- Immunization providers: Safe storage & handling, safe immunization practices, communicating risks and benefits, reporting of adverse events
- Parents: Ask questions and get the information you need
Thank you!

www.cdc.gov/vaccines
www.cdc.gov/hpv
www.cdc.gov/vaccinesafety