Human Papillomavirus (HPV) Vaccine Safety Update

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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

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Outline

- Background
- Review of HPV vaccine safety publications*
- Current HPV vaccine safety-related activities at CDC
- Plans for 9vHPV vaccine safety monitoring

* Predominately quadrivalent human papillomavirus vaccine (4vHPV)

HPV vaccines

- 4vHPV (GARDASIL®)
  - Licensed in 2006
  - 80 million doses distributed[1,2]
- 2vHPV (CERVARIX®)
  - Licensed in 2009
  - 839,600 doses distributed[1,3]
- 9vHPV (GARDASIL®9)
  - Licensed in 2014
  - 5 million doses distributed[1,2]

1. Doses distributed in the US through September 2015
2. Kuter B, personal communication, 20 October 2015
3. Tofa A, personal communication, 14 October 2015

CDC Immunization Safety Office Post-licensure Vaccine Safety Monitoring Infrastructure

System	Collaboration	Description
Vaccine Adverse Event Reporting System (VAERS)	CDC and FDA	Frontline spontaneous reporting system to detect potential vaccine safety issues
Vaccine Safety Datalink (VSD)	CDC and 9 Integrated Health Care Systems	Large linked database system used for active surveillance and research ~9.4 million members (~3% of US pop.) -Conducts monitoring & evaluation -Can calculate rates & risk estimates
Clinical Immunization Safety Assessment (CISA) Project	CDC and 7 Academic Centers	Expert collaboration that conducts individual clinical vaccine safety assessments and clinical research

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 identified[2,3]
- 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[5] (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)[6]
  - 4vHPV associated with syncope on the day of vaccination and skin infections in the two weeks following vaccination

[1] Slade et al, Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA 2009
[2] Stokley et al, Human Papillomavirus vaccination coverage among adolescent girls, 2007-12, and postlicensure vaccine safety monitoring 2006-2013 – United States. MMWR 2013
[3] Stokley et al, Human Papillomavirus vaccination coverage among adolescents 2007-13 and postlicensure vaccine safety monitoring 2006-2014 – United States. MMWR 2014
[4] Gee et al, Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. Vaccine 2011
[5] Relative risk calculated using Poisson based maximized sequential probability ratio test (maxSRPT)
[6] Klein et al, Safety of quadrivalent human papillomavirus vaccine administered routinely to females, Arch Ped Adolesc Med 2012

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 using self-controlled case series method found no increased risk of VTE following 4vHPV among persons aged 9-26 years[3]

[1] Arnheim-Dahlstrom et al, Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. BMJ 2013.

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

[3] Naleway et al, Absence of venous thromboembolism risk following quadrivalent human papillomavirus vaccination, Vaccine Safety Datalink, 2008-2011. Vaccine (in press).

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*
  - 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

*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 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]

[1]Chao 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 after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. BMJ 2013.

[3]Grimaldi-Bensouda et al, Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects. J Intern Med 2013.

[4]Scheller 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]

[1] Garland et al. Pregnancy and infant outcomes in the clinical trials of a human papillomavirus type 6/11/16/18 vaccine: a combined analysis of five randomized controlled trials. Obstetrics & Gynecology 2009.

[2] Goss et al. Final report on exposure during pregnancy from a pregnancy registry for quadrivalent human papillomavirus vaccine. Vaccine 2015.

Safety of Inadvertent 2vHPV Vaccination in Pregnancy

- Pre-licensure 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]
  - Observational cohort of 207 vaccinated and 632 non-vaccinated pregnant women aged 15-25 years (United Kingdom)

[1] Descamps et al. Safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine for cervical cancer prevention: A pooled analysis of 11 clinical trials. Human Vaccines 2009.

[2] Wacholder et al. Risk of miscarriage with bivalent vaccine against human papillomavirus (HPV) types 16 and 18: pooled analysis of two randomised controlled trials. BMJ 2010.

[3] Baril et al. Risk of spontaneous abortion and other pregnancy outcomes in 15-25 year old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom. Vaccine 2015.

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*."

Adverse Effects of Vaccines: Evidence and Causality, Institute of Medicine, Aug 2011
http://www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx

Recent Concerns in HPV Vaccine Safety

- Primary Ovarian Insufficiency (POI)
  - Case reports in the media led to public concern
  - No safety findings in VAERS[1]
- 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[2]
  - No safety findings in VAERS
- Postural Orthostatic Tachycardia Syndrome (POTS)
  - Concerns in Europe led to European Medicines Agency (EMA) review of POTS (and CRPS) following vaccination[3]
  - Review ongoing, and the EMA has not recommended any change in vaccination

[1]http://www.cdc.gov/vaccinesafety/vaccines/hpv/hpv-safety-faqs.html

[2]Huygen et al. Investigating Reports of Complex Regional Pain Syndrome: An Analysis of HPV-16/18-Adjuvanted Vaccine Post-Licensure Data. EBioMedicine 2015.

[3]http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2015/07/WC500189481.pdf

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 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[1]
      - No increased risk of death during 30 days after immunization

[1]McCarthy et al. Abstract presented at Vaccine Research Conference, 2015.

9vHPV Vaccine Safety

- 7 prelicensure studies[1,2]
- 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[3] 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% [4,5]

[1] http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf
[2] https://clinicaltrials.gov/ct2/show/NCT01651949?term=v503&rank=3
[3] 9vHPV is FDA Category B for pregnancy
[4] Gray RH, Wu LY. Subfertility and risk of spontaneous abortion. Am J Public Health 2000.
[5] Wilcox A et al. Incidence of early loss of pregnancy. NEJM 1988

9vHPV Safety Monitoring and Evaluation: CDC

- Vaccine Adverse Event Reporting System (VAERS)
  - Monitoring of US reports
  - Clinical review of pre-specified adverse outcomes as needed
  - FDA collaborates with CDC on 9vHPV monitoring

Gardasil 9®(9vHPV)[1] reports in VAERS as of 10/02/2015

Gardasil 9®	N
Total reports[2]	193
Male	79
Female	68
Not provided	46
Age range, years [median]	5 - 72 [14]
Onset interval, days [median]	0 – 20 [0]
Serious reports[3]	8
Deaths	0
Most common MedDRA[4] terms • No adverse event[5] • Dizziness • Syncope	 52 27 25

- No new data mining findings for 9vHPV

[1] 5 million doses of Gardasil 9 distributed in US through Sept 2015 [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. Includes reports of dizziness, syncope, seizure, fever, chest pain, abdominal pain and arthralgia.

[4] Medical Dictionary for Regulatory Activities [5] Vaccination errors without adverse event

9vHPV Safety Monitoring and Evaluation: CDC

- Vaccine Safety Datalink (VSD)
  - 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 9vHPV administration
    - Label indicates possible increase relative to 4vHPV[1]

[1] http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf

9vHPV Safety Monitoring and Evaluation

- Postmarketing commitments by manufacturer[1]
  - 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 occuring 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

[2]http://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 and preliminary 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

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