Quadrivalent Human Papillomavirus Vaccine (HPV4): United States Post-licensure Safety Update

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Outline

- Background: vaccine licensure, recommendations and pre-licensure safety summary
- Summary of data from Vaccine Adverse Event Reporting System (VAERS) including data on serious adverse events (SAE)
- Summary of Vaccine Safety Datalink (VSD) uptake data and study plan
- Media and consumer group interest

Vaccine composition

- The L1 major capsid protein of HPV is the antigen used for HPV vaccination. Using recombinant DNA technology, the L1 protein is expressed in *Saccharomyces cerevisiae* (yeast), and the proteins self-assemble into noninfectious VLPs
- Each 0.5-mL dose contains 20 µg HPV 6 L1 protein, 40 µg HPV 11 L1 protein, 40 µg HPV 16 L1 protein, and 20 µg HPV 18 L1 protein
- VLPs are adsorbed on an aluminum-containing adjuvant; each 0.5-mL dose contains 225 µg amorphous aluminum hydroxyphosphate sulfate. The formulation also includes sodium chloride, L-histidine, polysorbate 80, sodium borate, and water for injection
- HPV4 contains no thiomersal or antibiotics

Vaccine licensure and recommendations

- On June 8, 2006, HPV4 (Types 6, 11, 16, 18) (Gardasil™) was licensed in the United States by the Food and Drug Administration (FDA) for use in females ages 9-26 years
- On June 29, 2006 the vaccine was recommended by the Advisory Committee on Immunization Practices (ACIP) for routine use in females aged 11-12
- Catch-up vaccination is recommended for females aged 13--26 years who have not been previously vaccinated. The recommended schedule is a three dose series

Pre-licensure trial safety data

- Safety data on HPV4 vaccine are available from seven clinical trials and include 11,778 persons aged 9--26 years who received quadrivalent vaccine and 9,686 who received placebo

- Detailed data were collected using report cards for 14 days following each injection of study vaccine on a subset of participants aged 9--23 years. The population with detailed safety data included 5,088 females who received HPV4 and 3,790 who received placebo

Pre-licensure safety summary

- In five trials the most common adverse reactions observed for HPV4 versus placebo were pain at the injection site, swelling and erythema
- The most common systemic adverse events were fever and nausea, but the differences between vaccinees and placebo recipients were not statistically significant

Pre-licensure safety summary: SAE

- SAE occurred in <0.1% of persons studied
- The most frequently reported SAE for HPV compared to placebo on days 1-15 post-vaccination, **regardless of causality** were headache (0.03% for HPV4 and 0.02% for placebo), gastroenteritis (0.03 vs. 0.01), appendicitis (0.02 vs. 0.01), and pelvic inflammatory disease (0.02 vs. 0.01)
- One case of bronchospasm and 2 cases of asthma were also reported as SAE
- There were 17 death reports. Ten of the 17 received Gardasil™. The cause of death was motor vehicle accident in four of these cases; other causes of death included two reports of sepsis, one overdose/suicide, one report of pancreatic cancer, one death due to an arrhythmia and one fatal thromboembolic event

Thrombosis in pre-licensure data

- There was one fatal case of deep venous thrombosis (DVT) in each of the study groups (vaccine or placebo) in the clinical trials. Both of these subjects were on OCP
- Among non-fatal thrombosis cases, there was one additional case of severe thrombophlebitis in a 19 year old subject at 4 days after dose 2 of Gardasil. The subject was also on OCP, was treated and recovered. This event was attributed to the OCP by the investigator. She subsequently received Dose 3 of the vaccine. In addition, there was also one placebo recipient who had a non-severe DVT
- In the period after 7 months following vaccination, there were 2 additional cases of DVT in the Gardasil group and 4 in the placebo group

Objectives

- Describe post-licensure safety surveillance for HPV4 using data from the U.S. Vaccine Adverse Event Reporting System (VAERS) and Vaccine Safety Datalink (VSD)

- Commonly reported VAE (safety profile)
- SAE of interest
- Population subgroups of interest
  - Pre-adolescents, “off label” use

Methods

- Domestic reports to VAERS received through May 8, 2007 reviewed
- Serious reports according to U.S. regulatory and international criteria
  - Hospitalization, death, “life-threatening” or “disabling” illness, other medically important conditions
- Dose distribution data obtained from vaccine manufacturer
- Preliminary VSD data reviewed

Methods: VAERS

- National post-licensure safety surveillance system jointly operated by CDC and FDA
- Spontaneous reporting system in existence since 1990; reports submitted by clinicians, manufacturers, patients/parents, others
- Medical Dictionary for Regulatory Activities (MedDRA) used for coding since January 2007
- Subject to well described limitations of passive surveillance including underreporting, stimulated reporting due to media attention and other factors, and lack of availability of denominator data

HPV4 events reported to VAERS as of May 8, 2007

- 1763 total reports
- Demographics:
  - 96% females (n=1700) (Males = 11, Unknown gender = 52)

  - Persons < 9 years old: 1% (n=13)
  - 9-11 years: 3% (n=57)
  - 12-18 years: 39% (n=694)
  - 19-26 years: 27%(n=474)
  - Persons >26 years: 4%(n=63)
  - Unknown age: 26% (n=462)

- Vaccine(s)
  - 87% HPV4 alone (n=1539)
  - 3% with Menactra® meningococcal conjugate vaccine (n=44)

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HPV4 events reported to VAERS by dose number

Dose	n	%
1	857	49
2	235	13
3	20	1
Unknown	651	37

HPV4 events reported to VAERS: Overview

- Source of reports:
  - 73% (n=1291) vaccine manufacturer
  - 15% (n=272) provider
- Adverse event symptom onset interval:
  - 39% (n=685) occurred same day of vaccination
  - median onset interval two days after vaccination
- Recovery:
  - 46% (n=811) reported recovered at time of report submission
  - 31% (n=542) reported unknown recovery status

HPV4 events reported to VAERS: Most frequently reported symptoms

MedDRA Term	n	%
Dizziness	221	13
Syncope	176	10
Injection site pain	170	10
Nausea	160	9
Pain	122	7
Rash	122	7
Pyrexia	117	6
Urticaria	111	6
Headache	104	6
Loss of consciousness	102	5

- As coded using the MedDRA preferred terms (PT)
- More than one code may be assigned to a single event

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HPV4 events reported to VAERS: Serious adverse events*

- 94 serious reports (5% of total reports)
  - HPV4 given alone in 82% of reports (n=77)
  - Onset interval:
    - 42% (n=39) occurred same day of vaccination
    - Median onset interval one day after vaccination

*Defined by Code of Federal Regulations as involving hospitalization, death, disability, life threatening illness, or certain other medically important conditions

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HPV4 events reported to VAERS: Most common symptoms among SAE

MedDRA Term	n	%
Vomiting	13	14
Syncope	11	12
Pyrexia	10	11
Nausea	10	11
Headache	9	10

- As coded using the MedDRA PT.
- More than one code may be assigned to a single event.

Deaths following HPV4

- CASE #1: 12 year old vaccinated with first dose of HPV4, 2nd doses of varicella and Hepatitis A vaccine March 1; died March 7 after presenting with ventricular tachycardia. Autopsy showed myocarditis. Presented to ED earlier same day with gastroenteriitis; had respiratory illness~2 weeks prior to death. Past medical history of mitral and aortic valve regurgitation and insufficiency

- CASE #2: 19 year old vaccinated with first dose of HPV4 March 12. Patient died March 26 from emboli; autopsy found large clots in right and left atria and dilated right ventricle. Cause of death (COD) listed as sudden cardiac death and pulmonary embolism (PE). Patient was taking oral contraceptives (OCP) but did not smoke. Patient was exercising on field when she collapsed and began convulsing

Deaths following HPV4

- CASE #3: minimal information received from a third party. History indicates that the vaccinee was taking OCP and that death from “blood clot” occurred 3 hours post vaccination

- CASE #4: 14 year old received Tdap and HPV4 on January 2, 2007, then received HPV4 dose #2 on March 2, 2007. Developed fever, sore throat and cough around March 4; diagnosed with influenza on March 5. Symptoms worsened and she was hospitalized on March 6 with initial diagnoses of pneumonia and ARDS; placed on ECMO. Past medical history includes hernia repair, migraines; started Topamax® for migraines February 19, 2007. **Labs: nasopharyngeal isolation of influenza B virus.** MRSA cultured from multiple sites including blood and endotracheal aspirate. Died on March 16; COD listed as multiorgan system failure due to influenza B viral sepsis with secondary staphylococcal infection.

HPV4 events reported to VAERS: Guillain-Barrė Syndrome (GBS) reports

- 13 total reports; 2 have extremely limited information
- 11 reports among 13-16 year olds (one 50 y/o, one age unknown)
- Co-administered vaccines:
  - MCV4 6 (3 with onset in 1st post-vaccine week, 2 in 2nd week)
  - None 4 (2 with onset in 1st post-vaccine week, 1 in 2nd week)
  - Other vaccine given within 30 days 1
  - Unknown 2
- Onset intervals
  - 0-3 days: 4
  - 4-7 days: 1
  - 8-14 days: 4
  - > 30 days: 2 (33, 42 days)
  - Unknown: 2
- Classification according to Brighton Collaboration case definition:
  - 5 cases meet level I, II, or III of Brighton criteria
  - Classification pending or insufficient information: 8
- **Confirmed cases involving HPV vaccine alone with onset within 42 days following vaccination: 2 (6 and 8 day onset intervals)**

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SAE involving syncope

- 11 reports; 5 involved co-administration of at least one other vaccine
- Onset intervals following vaccination:
  - "immediate": 2
  - < 5 minutes: 1
  - 10 minutes: 2
  - Other intervals unspecified
- Most commonly associated symptoms headache, fall, vomiting, dizziness, nausea
  - 1 report of prior post vaccination syncope

- 7 hospitalizations; diagnoses include vasovagal syncope, dehydration
  - 2 hospitalizations for febrile illnesses apparently unrelated to vaccination

- **Head trauma following syncope: 1 seizure, 1 subarachnoid hemorrhage, 1 parieto-frontal subdural hematoma**

HPV4 events reported to VAERS: Thrombosis and embolism

Non-fatal reports

- **Case 1**:
  - Female of unknown age vaccinated with HPV4 on unknown date
  - Patient subsequently developed blood clots in her legs
  - Non-serious report; further information has been requested

- **Case 2:**
  - 21 year old female who was vaccinated with HPV4 on 9 January 07
  - Traveled from 3-10 March on 2 flights of 3 hours each
  - 6 March: calf pain that traveled to the thigh
  - 19 March: seen in ER for severe pain in lower back
    - Discovered two large clots found in lung (PE)
  - Started taking OCP for the first time in February 2007
  - Genetic testing revealed multiple common risk factors for thromboembolism (e.g. prothrombin gene mutation)
  - Patient recovered

Background Rates of Venous Thromboembolism (VTE) Among Women

- Rate among OC users for ages 14-29 years:
  21-31 per 100,000 woman years
  (Farmer et al. Lancet 1997)

- Rate among OC users for all ages approximately 41/100,000 woman years (Farmer et al. Lancet 1997)

- Among ages 20-29 years without OC use or smoking:
  3.3-4.0/100,000 woman years
  (Farley et al . J Epi and Comm Health 1998)

- Among ages 20-29 years of unknown risk status 35-50/100,000 (Silverstein. Arch Int Med 1998)

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HPV4 events reported to VAERS: Summary in 9-11 year olds

- 57 reports
- 33% (n=19) occurred on day of vaccination; median onset interval 3 days after vaccination
- Most common coding terms rash, dizziness, pruritus, pyrexia, erythema
- 2 serious reports:
  - Stevens-Johnson syndrome (SJS)
    - 5th hand report involving 11-12 year old who developed SJS “1 month” after 1st dose; no information on concomitant medications
  - Other serious report involved rash, nausea

HPV4 events reported to VAERS: "Off label" use

- < 9 years old:
  - Among 13 total reports, 10 reports involving children < 2 years of age
  - No serious reports
- > 26 years old:
  - Among 63 total reports:
    - 44 involved persons under 40
    - 15 reports of administration errors
    - 3 serious reports
- Reports in males:
  - Among 11 reports, at least 4 reported as vaccine administration errors
  - No serious reports

Dose distribution and reporting rates

- Approximately 5 million doses distributed in U.S. through March 2007
  - Age specific dose distribution data is not available
- Overall VAE reporting rate 33/100,000 doses
- SAE reporting rate 1.8/100,000 doses

VSD update

- At 6 VSD sites 68,266 doses used between 6 August 2006 and 13 May 2007
- Age distribution among vaccinees:
  - 9-17 years 74.5%
  - 18-26 years 24.6%
- Safety outcomes being monitored include GBS, seizure, syncope, anaphylaxis, appendicitis, stroke, thrombosis, and pulmonary embolism

Vaccine Injury Compensation Program

- Individuals thought to be injured by the human papillomavirus (HPV) vaccine may be eligible for compensation from the National Vaccine Injury Compensation Program (VICP) as of 1 February, 2007

- No claims alleging injuries involving HPV4 filed as of 7 June, 2007

Broader context

- Coverage, post-licensure effectiveness, phase IV trial data, VSD safety data not yet available
  - May lead to initial focus on VAERS data that is available more rapidly
  - VAERS data is publicly available and may be analyzed and disseminated by any person(s) who wish to
- Safety concerns regarding HPV4 are occurring in the context of broader concerns about vaccination policy, funding, and access
- This comes at a time when post licensure product safety surveillance in the U.S. is increasingly being scrutinized by policy makers and the media

Media coverage

- Featured articles in Time, Wall Street Journal, Associated Press, Nature Medicine
- Press releases from National Vaccine Information Center, Judicial Watch
- CDC/FDA response includes interviews with subject matter experts, preparation of Q and A on vaccine safety and efficacy
  - http://www.cdc.gov/nip/vaccine/hpv/default.htm
- Proposed state-based vaccination mandates of most interest, in additions to efficacy and safety concerns

Issues raised in media interviews or voiced by consumer advocacy groups

- Syncope
- Relative lack of safety data in 9-11 year olds
- Safety of simultaneous vaccination
- GBS
- Study plans in VSD
- Deaths
- Birth defects and miscarriages
- Plans for monitoring vaccine effectiveness and HPV disease burden
- Lack of long-term safety data
- Studies conducted by for-profit companies
- Cervical cancer is rare and/or on the decline
- Pap smears prevent cervical cancer; patients now won't get them
- Lack of public input
- Parents should have the right to opt out
- An "experiment" on people of color or the poor
- Inappropriate marketing/lobbying by sponsor

Summary and conclusions

- Post licensure safety reporting has been vigorous to date, as is expected for a new vaccine that is attracting professional and media attention
  - Overall dose-adjusted adverse event reporting rate for Gardasil is approximately three times what is seen on average for VAERS
- SAE reported rarely and no concerning pattern among serious events
  - Proportion of serious reports below overall average for VAERS of 10-15%
- Within a non-representative sample of managed care organizations, most vaccine uptake is occurring among adolescents and pre-adolescents rather than young adults
  - Coverage data not yet available

Summary and conclusions

- Many events reported have high baseline rates in absence of vaccination (e.g. syncope)
- As during trials, SAE of embolism and thrombosis attributable to OCP use have been detected
- Interpretation of some SAE confounded by concomitant vaccination and/or medication use, and by missing or incomplete data
  - Reported deaths do not appear to be causally related to vaccination

Next Steps

- CDC and FDA collaborating on one year post licensure safety surveillance summary
  - Syncope in adolescents across vaccine types to be reviewed as well
- Global Advisory Committee on Vaccine Safety (GACVS) of the World Health Organization (WHO) summarizing available data on safety of HPV vaccines
- Ongoing coordinated response to media inquiries

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