

Influenza Vaccine Safety Monitoring Update

**Advisory Committee on Immunization Practices
October 28, 2010**

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2010-11 influenza season

- ❑ Seasonal influenza vaccine for 2010-11
 - A/California/7/2009 (H1N1)-like virus strain
 - A/Perth/16/2009 (H3N2)-like virus strain
 - B/Brisbane/60/2008-like virus strain
- ❑ Universal recommendation for influenza vaccine for all people ages 6 months and older
- ❑ High dose inactivated influenza vaccine approved for people ages 65 years and older
- ❑ As of Oct 15, 2010, ~139 million doses of influenza vaccine have been distributed in U.S.

2009 H1N1 influenza vaccine safety: Vaccine Adverse Event Reporting System (VAERS) general assessment

- **“Adverse events following influenza A (H1N1) 2009 monovalent vaccines reported to the Vaccine Adverse Event Reporting System, United States, October 1, 2009–January 31,2010” ***
 - **VAERS received ~10,000 reports after 2009 H1N1 vaccine for persons vaccinated during first 4 months of the vaccination program (93% non-serious)**
 - **Reporting rate was higher after 2009 H1N1 vaccines than 2009-10 seasonal influenza vaccines; may be due to stimulated reporting**
 - **Death, Guillain–Barré syndrome and anaphylaxis reports after 2009-H1N1 vaccination were rare (each not higher than 2 per million doses administered)**
 - **Adverse event reporting profile after 2009-H1N1 vaccines was consistent with that of seasonal influenza vaccines**

Vaccine Safety Risk Assessment Work Group summary of 2009 H1N1 vaccine safety

- National Vaccine Advisory Committee Report on 2009 H1N1 Vaccine Safety Risk Assessment (June 2010) – previously presented at June 2010 ACIP meeting
 - Weak signal for Guillain–Barré syndrome in Emerging Infections Program data
 - Weak signal for Bell’s Palsy in VSD* and the Indian Health Service (IHS) database; *signal in VSD has since ruled out
 - Weak signal for TP/ITP in the Defense Medical Surveillance System, Veterans Affairs database and IHS database
- Further work is ongoing and the final end-of-season analysis for 2009-10 will be presented to the NVAC’s Vaccine Safety Risk Assessment Work Group in November 2010

Source: http://www.hhs.gov/nvpo/nvac/reports/vsrawg_repot_may2010.html

Vaccine safety monitoring for the 2010-11 influenza season

- **CDC Monitoring systems**
 - Vaccine Adverse Event Reporting System (VAERS)
 - Vaccine Safety Datalink (VSD)
 - Real Time Immunization Monitoring System (RTIMS)
 - Clinical Immunization Safety Assessment (CISA) Network
 - Vaccine Analytic Unit (VAU)

- **High priority conditions/areas & enhanced monitoring**
 - Guillain–Barré syndrome
 - Seizures (especially in children aged <9 years old)
 - Narcolepsy
 - Events associated with high dose influenza vaccine

Vaccine safety monitoring for the 2010-11 influenza season

- ❑ VAERS surveillance period for influenza vaccine began September 2010
- ❑ VSD rapid cycle analysis underway for influenza vaccine safety monitoring

As of Oct 10, 2010:

- 424,322 TIV doses in VSD
- 45,843 LAIV doses in VSD

Narcolepsy/cataplexy: European situation

- ❑ Events in Europe have raised concerns about a possible link between Pandemrix™ and narcolepsy
 - Pandemrix™ is a monovalent 2009 H1N1 influenza vaccine containing AS03 adjuvant used widely in Europe during 2009-10 (no adjuvated influenza vaccines used in the U.S.)
- ❑ European Medicines Agency reviewed available data and concluded the available evidence was insufficient confirm a link and suggested further studies were necessary
- ❑ ECDC is funding VAESCO network to conduct further research to examine the possible link between Pandemrix™ and narcolepsy
- ❑ VAESCO network, coordinated by Brighton Collaboration, is finalizing case definition for narcolepsy along with partner researchers
- ❑ 2010-11 seasonal influenza vaccines in Europe are unadjuvanted

Narcolepsy/cataplexy: U.S. situation

- ❑ Comprehensive influenza vaccine safety monitoring in VAERS during the 2009-10 influenza vaccination season yielded no signals for narcolepsy/cataplexy
- ❑ Enhanced monitoring was put in place in VAERS and VSD for the 2010-11 influenza season
- ❑ As of Oct 22, 2010 NO REPORTS of narcolepsy/cataplexy after 2010-11 seasonal influenza vaccines have been submitted to VAERS

Update on febrile seizures

- ❑ Febrile seizures have not been associated with influenza vaccines in previous seasons
- ❑ No special concerns for the 2010-11 influenza season with the exception of CSL vaccine in children aged <9 years
- ❑ CDC implemented enhanced monitoring for seizure following receipt of 2010-11 seasonal influenza vaccine in VAERS and VSD

Update on VAERS reports of febrile seizures 2010-11 influenza season, Jul 1–Oct 15, 2010

2,421 total AE
reports following
influenza vaccine



25 reports of
possible seizure
in children <9 y/o



13 confirmed febrile
seizures (all <5 y/o,
none with CSL vaccine)
2 indeterminate and 2
pending further review

Automated data review and clinical review of cases do not indicate a signal in VAERS for febrile seizures following receipt of influenza vaccine in children aged <9 years

Update on VSD monitoring for febrile seizures for the 2010-11 influenza season

As of Oct 11, 2010:

- 16,513 doses of TIV have been administered to children <5 years of age
 - 0 cases of seizures have been observed within 0-1 days of vaccine administration

High dose Fluzone prelicensure data

Table 3: Frequency of Solicited Injection Site and Systemic Adverse Events within 7 Days Post-Vaccination

	Fluzone High-Dose (N^a= 2573) Percent	Fluzone (N^a= 1260) Percent
Injection site reactions		
Pain	35.6	24.3
Erythema	14.9	10.8
Swelling	8.9	5.8
Systemic adverse events		
Myalgia	21.4	18.3
Malaise	18.0	14.0
Headache	16.8	14.4
Fever	3.6	2.3

^aN is the number of subjects in the Safety Analysis Set.

<http://www.fda.gov/downloads/biologicsbloodvaccines/.../ucm195479.pdf>

High dose Fluzone

- ❑ **As of October 15, 2010, VAERS received 258 reports after high dose Fluzone**
 - 94% were coded as non-serious
- ❑ **Adverse events reported in VAERS after high dose influenza vaccine were consistent with those that are clinically expected adverse events, e.g., fever and headaches**
- ❑ **As of Oct 11, 2010, 700 high dose Fluzone doses have been administered in the VSD system**
 - 0 anaphylaxis cases have been observed

Acknowledgments

- ❑ **CDC Immunization Safety Office**
 - **Surveillance and Public Health Response Team**
 - **Research and Prevention Team**



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Thank you

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Extra slides

VAERS

U.S. frontline early warning system to detect potential vaccine safety concerns

Strengths

- Rapid signal detection
- Can detect rare adverse events
- Generates hypothesis for further study
- Encourages reports from healthcare providers and accepts reports from others
- Data available to the public

Limitations

- Reporting bias (e.g., underreporting, stimulated reporting)
- Inconsistent data quality and completeness
- Not designed to assess if vaccine caused an AE
- Lack of unvaccinated comparison group

VAERS: 3 methods for analyses

Method	Information provided
Automated data analysis (information provided on VAERS form)	<ul style="list-style-type: none">• Look at numbers and characteristics of reports• Compare with seasonal influenza vaccines (from past years) and 2009 H1N1 vaccine• Calculate VAERS reporting rates per doses distributed or doses administered if available
Clinical review of VAERS reports and medical records	<ul style="list-style-type: none">• Detect unusual clinical patterns or new types of adverse events• Describe information about cases with adverse events of interests (e.g., GBS)• Provide more accurate information to calculate reporting rates than the automated data (e.g., GBS reporting rate)
Data mining (information on the VAERS form)	<ul style="list-style-type: none">• Assess for patterns of disproportionate reporting for adverse events in VAERS for H1N1 vaccines compared with other vaccines (FDA lead)

2009 H1N1 influenza vaccine safety: Vaccine Adverse Event Reporting System (VAERS) pregnant women

- ❑ **Pregnant women were a priority group for 2009 H1N1 vaccine**
 - **Expected to find reports of spontaneous abortion (SAB) and stillbirths by chance**
- ❑ **During Oct 1, 2009 – Jun 30, 2010, 3% of 11,230 reports after 2009 H1N1 vaccine submitted to VAERS involved pregnant women who reported an adverse event**
 - **344 reports (330 inactivated, 13 live vaccine, 1 unknown type)**
 - **SAB (N=149; ~43% of all pregnancy reports)**
 - **Stillbirths (N=21; ~6% of all pregnancy reports)**
- ❑ **Review of VAERS reports in pregnant women who received H1N1 vaccines revealed no unexpected patterns or unusual events**
- ❑ **VAERS reporting rates of stillbirths and spontaneous abortions after 2009 H1N1 vaccine were well below background rates**

***Moro PL, unpublished CDC data**

Vaccine Safety Datalink (VSD)

- ❑ A collaborative project among CDC and 8 managed care organizations (MCOs)
- ❑ Data on ~ 9 million persons (~ 3% of U.S. population with a birth cohort of 95,000)
- ❑ Pilot project with 3 additional new sites for flu studies
- ❑ Monitors/analyzes data on pre-specified conditions
- ❑ Allows for planned immunization safety studies as well as timely investigations arising from
 - Hypothesis from medical literature and pre-licensure
 - Reports to VAERS
 - Changes in immunization schedules, intro of new vaccines

Narcolepsy/cataplexy

□ Challenges

- No universally accepted standard case definition(s) for narcolepsy/cataplexy
- Background rate of is really unknown
- Rare diagnosis that often takes a long period of time (months to years) to be definitively be diagnosed – often initially misdiagnosed as seizure d/o, depression, psychiatric d/o
- ICD-9 coding in administrative databases may be of variable quality and chart review and direct follow-up may be necessary to confirm
- Frequency of diagnosis likely related to presence of sleep expert and sleep center in a geographic area

ACIP recommendation on CSL Afluria

- ❑ **Afluria should not be used in children aged 6 months through 8 years**
- ❑ **Other age-appropriate, licensed seasonal influenza vaccine formulations should be used for prevention of influenza in children aged 6 months through 8 year.**
- ❑ **If no other age-appropriate, licensed seasonal influenza vaccine is available for a child aged 5 years through 8 years old who has a medical condition that increases their risk for influenza complications, Afluria may be given, and providers should discuss the benefits and risks of influenza vaccination with the parents or caregivers before administering Afluria**

Update on CSL seasonal 2010 TIV

- ❑ **CSL's FLUVAX and FLUVAX JUNIOR (2010 TIV used in Australia and New Zealand)**
 - **Associated with higher rates of fever and febrile seizures in children ages 6 mo–4 years**
 - **Increased reports of fever in children ages 5–8 years**
- ❑ **No increased risk of fever and febrile seizures with other licensed TIV vaccines used in Australia and New Zealand**
- ❑ **Australian Therapeutic Goods Administration report “Overview of vaccine regulation and safety monitoring and investigation into adverse events following 2010 seasonal influenza vaccination in young children” available at <http://www.tga.gov.au/alerts/medicines/vaccine-overview.htm>**

Febrile seizures: VSD planned

- ❑ Monitor for seizures in children (including children aged <5 years) after receipt of influenza vaccines
- ❑ If signals then chart review possible seizure cases to verify diagnosis and type of seizure (febrile vs. other)
- ❑ Add as additional sub analysis seizures on day 0 and day 1 compared to expected based upon previous influenza seasons
- ❑ Look at the feasibility of conducting a self-controlled case series study of day 0 and day 1 outcomes compared to predetermined time window
- ❑ If necessary, have the capabilities of looking at specific manufacturers

High dose Fluzone

- ❑ **As of 10/15/2010, VAERS has received 258 reports after high dose influenza vaccine (15 serious)**
- ❑ **Serious reports**
 - **Anaphylaxis (2) [1 additional case coded as non-serious]**
 - **Allergic reaction (3)**
 - **Death (1)**
 - **Idiopathic pericarditis, gastroenteritis (2), chronic renal insufficiency, acute renal failure, atypical chest pain, syncope, fever of unknown origin, rhabdomyolysis**

2010-11 influenza vaccine safety: Vaccine Adverse Event Reporting System (VAERS) Summary from July 1, 2010 through October 15, 2010

- **VAERS received 2,421 reports after 2010-11 influenza vaccine (95% non-serious*)**
- **Proportion serious* adverse event reports similar after trivalent 2010-11 and 2009-10 influenza vaccines**
 - **4.5% serious (2010-11) vs. 4.6% serious (2009-10)**
- **Adverse event reporting profile after 2010-11 seasonal influenza vaccine was consistent with that of past seasonal influenza vaccines and clinical trials**
- **No safety concerns identified in VAERS during first few weeks of the 2010-11 influenza season; too early in the season to draw conclusions about VAERS data**

*Report coded as serious when the following outcomes occurred: death, hospitalization, prolongation of hospitalization, life-threatening illness, persistent or significant disability, congenital anomaly; other reports coded as non-serious