End-of-season update: 2014-2015 Influenza Vaccine Safety Monitoring

Advisory Committee on Immunization Practices
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Disclaimer

The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of CDC.

Agenda

- Vaccine Adverse Event Reporting System (VAERS) surveillance
- Vaccine Safety Datalink (VSD) Rapid Cycle Analysis
- Update on a VSD study looking at trivalent inactivated influenza vaccine and spontaneous abortion:
  - "Evaluating the risk of spontaneous abortion following administration of influenza vaccines containing H1N1pdm09 and H3N2 viral antigens"

US influenza vaccine abbreviations*

Vaccine	Abbreviation
Trivalent inactivated influenza vaccine	IIV3
Quadrivalent inactivated influenza vaccine	IIV4
Quadrivalent live attenuated influenza vaccine	LAIV4
High-dose trivalent inactivated influenza vaccine	IIV3-HD
Intradermal trivalent inactivated influenza vaccines	IIV3-ID
Cell culture-based trivalent inactivated influenza vaccine	ccIIV3
Recombinant trivalent inactivated influenza vaccine	RIV3

*** IIV is commonly used when generally discussing inactivated influenza vaccines and LAIV when generally discussing live attenuated influenza vaccines**

VAERS surveillance for the 2014-2015 influenza season

VAERS: Spontaneous Reporting System Co-administered by CDC and FDA

Strengths

- Rapid signal detection
- Can detect rare adverse events
- Generates hypothesis
- Encourages reports from healthcare providers and accepts reports from patients and 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 adverse event (AE)
- Lack of unvaccinated comparison group

VAERS website: http://vaers.hhs.gov

VAERS surveillance: methods

- US influenza vaccine reports received through May 22, 2015 (vaccinated July 1, 2014-May 1, 2015)
- Signs, symptoms and diagnoses coded using Medical Dictionary for Regulatory Activities (MedDRA) terms
- VAERS report and medical record review (if available) conducted for:
  - All serious* reports after IIV4, LAIV4, ccIIV3, RIV3
  - All anaphylaxis reports in persons with a history of egg allergy
  - Pregnancy reports for spontaneous abortion, stillbirth, congenital anomalies, serious reports
- Empirical Bayesian data mining conducted by FDA†

*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

†Banks et al. Comparing data mining methods on the VAERS database. Pharmacoepidemiol Drug Saf. 2005;14:601–609

US reports to VAERS following IIV3, IIV4, LAIV4 and IIV3-HD: 2014-15

	IIV3 N (%)	IIV4 N (%)	LAIV4 N (%)	IIV3-HD N (%)
Total reports*	5,207	1,269	571	1,479
Serious reports†	299 (5.7)	79 (6.2)	32 (5.6)	78 (5.3)
Non-serious reports	4,908 (94.3)	1,190 (93.8)	539 (94.4)	1,401 (94.7)
Guillain-Barré syndrome (GBS)‡	44 (0.9)	11 (0.9)	3 (0.5)	4 (0.3)
Anaphylaxis‡	11 (0.2)	8 (0.6)	2 (0.4)	4 (0.3)

- No confirmed anaphylaxis reports with history of documented egg allergy
- No data mining findings for GBS or anaphylaxis

*US primary reports (foreign reports excluded), all ages

†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

‡Based on MedDRA (Medical Dictionary for Regulatory Activities) terms; onset interval 0-1 days post vaccination for anaphylaxis

US reports to VAERS following ccIIV3, RIV3 and IIV3-ID: 2014-15

	ccIIV3 N (%)	RIV3 N (%)	IIV3-ID N(%)
Total reports*	227	18	81
Serious reports†	10 (4.4)	1 (5.6)	1 (1.2)
Non-serious reports	217 (95.6)	17 (94.4)	80 (98.8)
Guillain-Barré syndrome (GBS)‡	5 (2.2)	0	0
Anaphylaxis‡	1 (0.4)	1 (5.6)	0

- No confirmed anaphylaxis reports with history of documented egg allergy
- No data mining findings for GBS and anaphylaxis

*US primary reports (foreign reports excluded), all ages

†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

‡Based on MedDRA (Medical Dictionary for Regulatory Activities) terms; onset interval 0-1 days post vaccination for anaphylaxis

Pregnancy reports in VAERS following influenza vaccination, 2014-15

	N (%)
Total reports after IIV3 or IIV4	85
Median age, range, yrs	32 (17-48)
Median gestational age at vaccination (N=39), wks	16 (2-37)
Trimester of vaccination • 1st • 2nd • 3rd	40 16 (40) 17 (43) 7 (18)
Non-pregnancy specific adverse event reports	23 (27)*
No adverse event reported	54 (64)
Pregnancy-specific outcomes • Spontaneous abortion • Stillbirth • Vaginal bleeding	8 (9) 6 1 1
	N (%)
Total reports after LAIV4 • No adverse event reported • Spontaneous abortion	18 17 1

* Includes injection site reactions/pain in extremity/joint pain (9), systemic reactions (6), neurological conditions (4), non-anaphylaxis allergic reactions (2), and one each of tachycardia and dyspnea

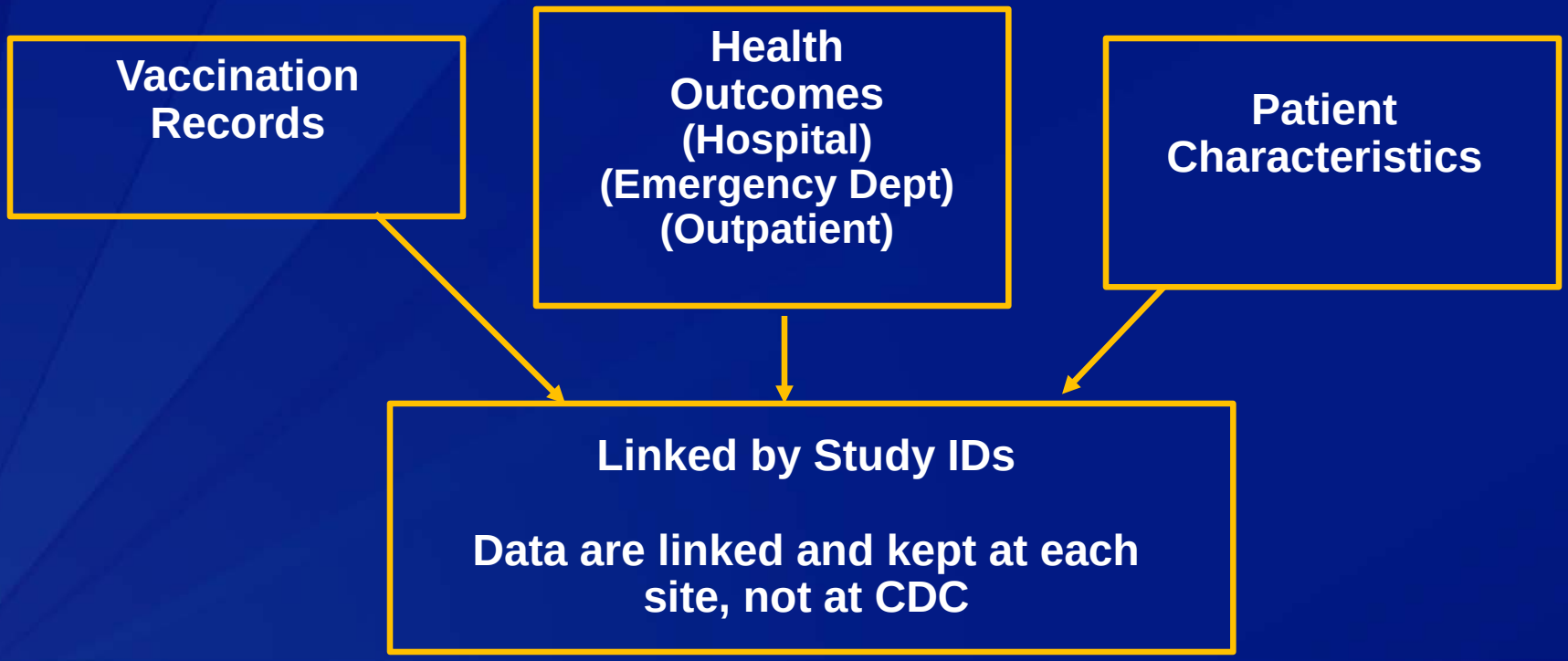
Summary of VAERS surveillance for 2014-15 and plans for the 2015-16 influenza season

- No new safety concerns detected for IIVs, LAIV4, ccIIV3 or RIV3 during the 2014-15 influenza season
- Surveillance for the 2015-16 influenza season will include enhanced safety monitoring (i.e., clinical review of reports and medical records for selected reports) for:
  - Quadrivalent vaccines (IIV4 and LAIV4)
  - ccIIV and RIV3
  - Pregnancy reports
  - Reports in persons with history of egg allergy

Vaccine Safety Datalink Rapid Cycle Analysis for the 2014-2015 influenza season

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



Vaccine Safety Datalink (VSD)

Strengths

- All medical encounters are available
- Vaccine registry data
- Can calculate rates
- Can assess risk of an AE
- Can review medical records
- Tested algorithm to identify pregnancies
- Annual birth cohort = 100k

Limitations

- Sample size may be inadequate for very rare events
- Vaccines administered outside of medical home may not be captured
- Medically unattended health events not captured
- Potential for lack of socioeconomic diversity
- Data lags

Rapid Cycle Analysis in the Vaccine Safety Datalink (2014-15 influenza season outcomes)

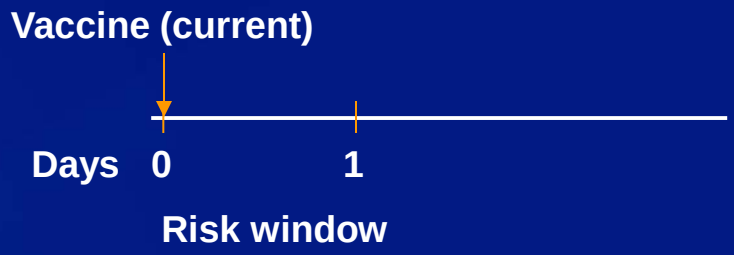
Pre-specified outcome	Age group	Risk window (days)	Control window* (days)
Anaphylaxis	≥6 mos	0-2	7-9
Bell's palsy	≥6 mos to <18 yrs 18-49 yrs ≥50 yrs	1-42	-56 to -15
Encephalitis	≥6 mos	1-21	-56 to -15
Guillain-Barré syndrome	≥6 mos	1-42	43-260
Seizures	6-23 mos 24-59 mos	0-1 for IIV 0-14 for LAIV	14-20 for IIV 15-29 for LAIV
Transverse myelitis	≥6 mos	1-21	-56 to -15

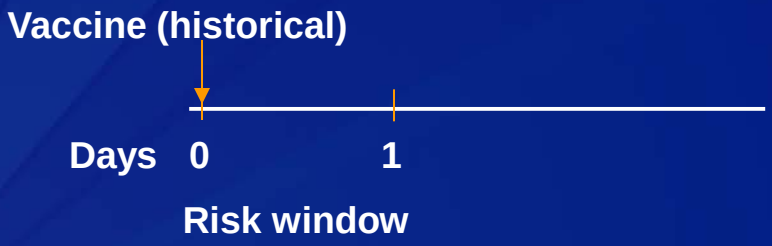
*For self-control design

Rapid Cycle Analysis in the Vaccine Safety Datalink

Self controlled design*

Current vs. historical†





* Each patient serves as his/her own control, looking at events in risk window and events in comparison window

† Looking at events in risk window in patients in current season versus patients during historical comparison period

Rapid Cycle Analysis in the Vaccine Safety Datalink (2014-15 influenza season)

Dose 1 doses administered* in all ages

Age	IIV3	IIV4	LAIV4	IIV3-HD
All ages	3,429,406	251,271	307,967	103,121

Subset of dose 1 doses administered in children 6-23 months

Age	IIV3	IIV4
6-23 mo	73,732	86,752

*Doses administered through March 27, 2015; limited uptake of RIV3 (1,593) and intradermal IIV3 (5,167)

Rapid Cycle Analysis signal detection and evaluation: Bell's palsy and encephalitis

- Current vs. historical design signaled for Bell's palsy in patients 50+ years old following IIV4 in October 2014 (automated ICD-9 code-based analysis)
  - After chart review of cases it was determined to be a false signal*
- Current vs. historical and self-controlled risk interval designs both signaled for encephalitis following IIV3 in December 2014 (automated ICD-9 code-based analysis)
  - No significant clustering found within 1-21 day risk window
  - After chart review of cases it was determined to be a false signal

* Not incident case, onset of symptoms not in risk window, etc.

Rapid Cycle Analysis signal detection: Seizures

- Self-controlled risk interval design "signaled"* for seizures† in children 6-23 months old following IIV3 in December 2014
  - 73,732 total IIV3 dose 1 doses administered
  - Events in days 0-1 risk window: 5
  - Events in days 14-20 comparison window: 1
  - Relative risk: 17.5 (statistically significant)
- Self-controlled risk interval design had non-statistically significant elevated relative risk for seizures in children 6-23 months old following IIV4
  - 86,752 total IIV4 dose 1 doses administered
  - Events in days 0-1 risk window: 8
  - Events in days 14-20 comparison window: 8
  - Relative risk: 3.5 (not statistically significant, but approaching the critical value of the log likelihood ratio)

* Although the log likelihood ratio exceeded the critical value, this is not considered a true safety signal or a new safety problem since it has been observed in several previous influenza seasons (http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2014-06/Vaccine-Safety-02-Duffy.pdf).

† Positive predictive value of seizure ICD-9 code being a febrile seizure in this age group is >80%

Rapid Cycle Analysis signal* evaluation: Seizures

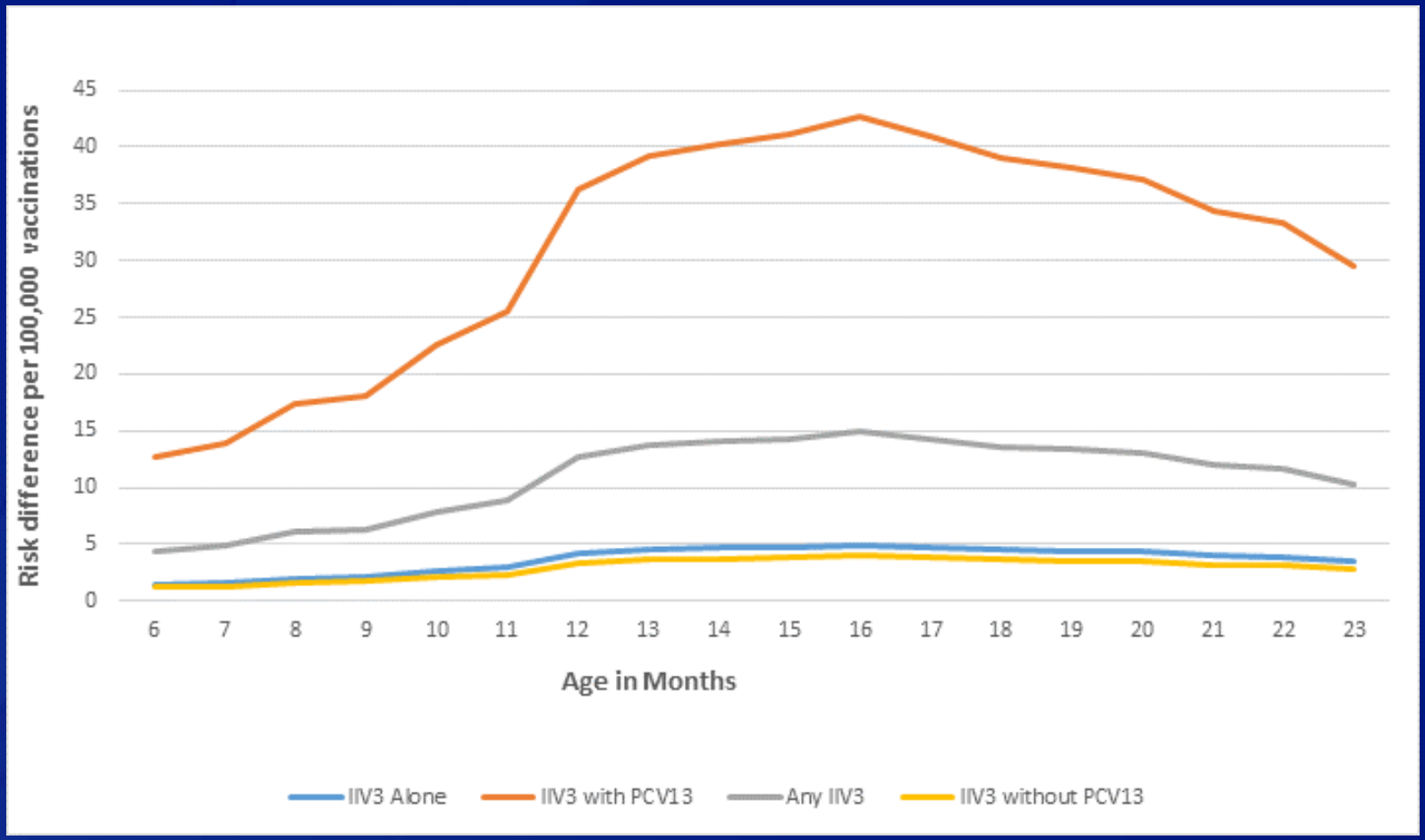
- Combined IIV3 data for 2014-15 and 2013-14† influenza seasons (same vaccine formulation) for 6-23 months old
- 244,394 total IIV3 doses administered for 6-23 months old

Vaccines/vaccine combinations	Relative risk‡ (95% CI)
IIV3 +/- other vaccines (i.e., +/- PCV13)	2.5 (1.3-4.8)¶
IIV3 + PCV13 +/- other vaccines	5.3 (1.9-14.7)¶
IIV3 +/- other vaccines, but not PCV13	1.4 (0.5-3.6)
IIV3 given alone without other vaccines	1.5 (0.4-5.8)

* Although the log likelihood ratio exceeded the critical value, this is not considered a true safety signal or a new safety problem since it has been observed in several previous influenza seasons (http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2014-06/Vaccine-Safety-02-Duffy.pdf);
† No Rapid Cycle Analysis signals for seizures in children during the 2013-14 influenza season for IIV3; ‡ Self-control design; ¶ Statistically significant

Rapid Cycle Analysis signal evaluation: Seizures

- Combined IIV3 data for 2014-15 and 2013-14† influenza seasons (same vaccine formulation) for 6-23 months old
- 244,394 total IIV3 doses administered for 6-23 months old



* Automated data based on ICD-9 codes, not chart confirmed seizures

Summary of Rapid Cycle Analysis in the Vaccine Safety Datalink (2014-15 influenza season)

- Detected signals for Bell's palsy and encephalitis
  - Both ruled out for true signals after chart review of cases
- Detected statistically significant elevated relative risk for seizures in children 6-23 months-old following IIV3* and non-statistically significant elevated relative risk following IIV4
  - Further assessment indicated risk was highest when IIV3 or IIV4 was administered together with PCV13, and was highest in children 12-23 months-old as has been seen in previous seasons for IIV3

* Although the log likelihood ratio exceeded the critical value, this is not considered a true safety signal or a new safety problem since it has been observed in several previous influenza seasons (http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2014-06/Vaccine-Safety-02-Duffy.pdf)

Update on the Vaccine Safety Datalink (VSD) study:

Donahue* et al. "Evaluating the risk of spontaneous abortion following administration of influenza vaccines containing H1N1pdm09 and H3N2 viral antigens"

*Marshfield Clinic Research Foundation

Background

- ACIP recommends seasonal influenza vaccination for women in all stages of pregnancy (since 2004)
- Available data indicate IIV is safe during pregnancy
- However, limited data exists on IIV safety in first trimester of pregnancy
- Uptake of influenza vaccine in pregnancy increased during the 2009-10 pandemic influenza season and in subsequent influenza seasons*

* http://www.cdc.gov/flu/pdf/partners/flu-pregnancy-infographic.pdf (primary sources: www.cdc.gov/mmwr/preview/mmwrhtml/mm6337a3.htm, 2007-2010 BRFSS, 2010-2014 Internet Panel Survey)

Background

- **Spontaneous abortion (SAB) is a relatively common outcome of pregnancy**
  - **SAB is the spontaneous loss of a fetus before the 20th week of pregnancy (pregnancy losses after the 20th week are called stillbirths)**
  - **SAB occurs in 15-20% of women who know they are pregnant**
  - **Most SABs occur during the first 7 weeks of pregnancy**
  - **Risk factors for SAB include advanced maternal age, smoking, obesity, autoimmune disease, prior SAB**

Background

- A previous case-control study in the Vaccine Safety Datalink (VSD) in 2005-06 and 2006-07 did not find an association with SAB and IIV3*
- A recent meta-analysis did not find an association between SAB and monovalent pH1N1 vaccination†
  - Results of these studies were not available when the current VSD IIV3-SAB study was initiated
  - Largest study in meta-analysis involved adjuvanted vaccines
- Other studies of seasonal IIV3 in pregnancy and SAB have been reassuring‡

* Irving et al. Obstet Gynecol. 2013 Jan;121(1):159-65

† Bratton et al. Clin Infect Dis. 2015 Mar 1;60(5):e11-9

‡ McMillan et al. Vaccine. 2015 Apr 27;33(18):2108-17; Chambers et al. Vaccine. 2013 Oct 17;31(44):5026-32; Moro et al. Am J Obstet Gynecol. 2011 Feb;204(2):146.e1-7; Moro et al. Am J Obstet Gynecol. 2011 Nov;205(5):473.e1-9.

Study purpose

- **Using similar methods to the previous VSD study (2005-07 data), conduct a study to assess if IIV3 containing the influenza A (H1N1) pandemic antigen was associated with SAB during the combined 2010-11 and 2011-12 influenza seasons**
  - **Primary objective to estimate the association of SAB with IIV3 in a 28-day risk window**
  - **IIV3 formulation was the same during both seasons and contained the influenza A (H1N1) pandemic antigen***

* **Formulation for 2010-11 and 2011-12 influenza seasons:**
  - **A/California/7/09 (H1N1)-like virus (pandemic (H1N1) 2009 influenza virus)**
  - **A/Perth /16/2009 (H3N2)-like virus**
  - **B/Brisbane/60/2008-like virus**

Methods

- Matched case-control design (1:1 matching ratio)
  - Cases: women with SAB from 5 to <20 weeks gestational age
  - Controls: women with live births or stillbirths (≥20 weeks gestational age)
  - SAB identified using ICD-9 codes, confirmed through medical record abstraction, adjudicated to confirm SAB and SAB date
  - Date of SAB was reference date for each case-control pair
  - Cases and controls matched on age group (<30, 30+), VSD site, last menstrual period (LMP)

- Eligibility criteria
  - Women 18 to 44 years old
  - Enrolled ≥ 1 year prior to LMP
  - LMP documented in record
  - Confirmed intrauterine pregnancy by ultrasound

Methods (cont.)

- **Vaccine exposure**
  - **Receipt of IIV3 documented in medical record**
  - **Risk window: 28 days before reference date**
    - **Also examined 29-56 and >56 days before reference date**

- **Conditional logistic regression, included covariates:**
  - **Maternal age**
  - **Smoking during pregnancy**
  - **History of type 1 or 2 diabetes mellitus**
  - **Concomitant IIV3 and Tdap vaccination**
  - **Pre-pregnancy body mass index**
  - **Previous healthcare utilization**

Preliminary results

Final combined analysis

- 485 matched pairs in final analysis
- Adjusted odds ratio (aOR) 2.0 (95% CI 1.1-3.6) for IIV3 receipt in 1-28 days before SAB compared to unvaccinated women
- No association in other risk windows

Post-hoc analysis (1-28 day risk window)

- Season-specific analyses
  - 2010-2011: aOR 3.7 (95% CI 1.4-9.4)
  - 2011-2012: aOR 1.4 (95% CI 0.6-3.3)

Same IIV3 formulation in both seasons

Association between SAB and IIV3 in 1-28 day risk window is restricted to women who received pH1N1-containing vaccine in the previous season (preliminary results)

2010-11, 2011-12 combined data

pH1N1-containing vaccine in previous season*	pH1N1-containing vaccine in current season*, 1-28 days before reference date	Cases/ controls	Adjusted OR (95% CI)
Yes	Yes	14/4	7.7 (2.2-27.3)†
No	Yes	21/19	1.3 (0.7-2.7)

Effect modification (p=0.02)

- * Previous season was:
  - 2009-10 (monovalent pH1N1 vaccine) if current season was 2010-11
  - 2010-11 (pH1N1-containing IIV3) if current season was 2011-12
- Effect modification due to prior season vaccination with a pH1N1-containing vaccine observed in each season
- No association in other risk windows regardless of prior exposure to a pH1N1-containing vaccine

† Statistically significant

Limitations

- Findings of effects of prior H1N1 vaccination were post-hoc secondary analyses
- Study not powered for the secondary analyses and although some relative risks were high, the confidence intervals were very wide
- This is an observational study subject to possible biases and confounding
  - Possible that vaccinated women who had SABs more likely to come to medical attention
  - Not able to include possible risks from influenza infection
  - Other unmeasured confounding

Summary of VSD IIV3-SAB study

- Results suggest an increased risk of SAB in some pregnant women in the 1-28 days after receiving IIV3 during the combined 2010-11 and 2011-12 seasons
- Risk was not increased in risk intervals more than 28 days after vaccination
- Increased risk observed in 2010-11, but not in 2011-12, when disregarding prior season vaccination with a pH1N1-containing vaccine
- In both seasons, increased risk was seen in women who had also received a pH1N1-containing vaccine the previous season, but not in women who did not receive a pH1N1-containing vaccine the previous seasons

Summary of VSD IIV3-SAB study (cont.)

- Findings are preliminary and inconsistent with prior research on IIV safety in pregnancy
  - Prior VSD study (2005-2007 seasons) did not find increased risk of SAB associated with IIV3
  - Meta-analysis of studies of monovalent pH1N1 vaccine did not find an increased risk of SAB
    - Prior studies, however, did not evaluate effect of prior vaccination
- CDC plans to follow-up this finding for SAB following IIV3 with additional research in the VSD
  - Replicate the study in more recent influenza seasons
  - Assess the effect of prior vaccination with pH1N1-containing vaccines as a primary objective
  - Attempt to evaluate risk of SAB from influenza infection

[1] Irving et al. Trivalent inactivated influenza vaccine and spontaneous abortion.Obstet Gynecol. 2013 Jan;121(1):159-65

[2] Bratton et al. Maternal influenza immunization and birth outcomes of stillbirth and spontaneous abortion: a systematic review and meta-analysis. Clin Infect Dis. 2015 Mar 1;60(5):e11-9.

Summary of influenza vaccine safety

2014-15 influenza season

- No new safety concerns detected in VAERS surveillance
- Elevated relative risk detected in VSD Rapid Cycle Analysis for seizures following IIV3 and IIV4 in children aged 6-23 months
  - Highest risk when IIV co-administered with PCV13
  - Similar to findings from previous influenza seasons for IIV3

VSD case-control study of SAB following IIV3

- Preliminary results of 2010-11 and 2011-12 seasons' data show an increased risk of SAB following IIV3 among pregnant women in the 1-28 day risk window who had received a pH1N1-containing vaccine the prior influenza season
  - Findings are inconsistent with prior studies looking at IIV3 and SAB and follow-up studies are planned

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Thank You

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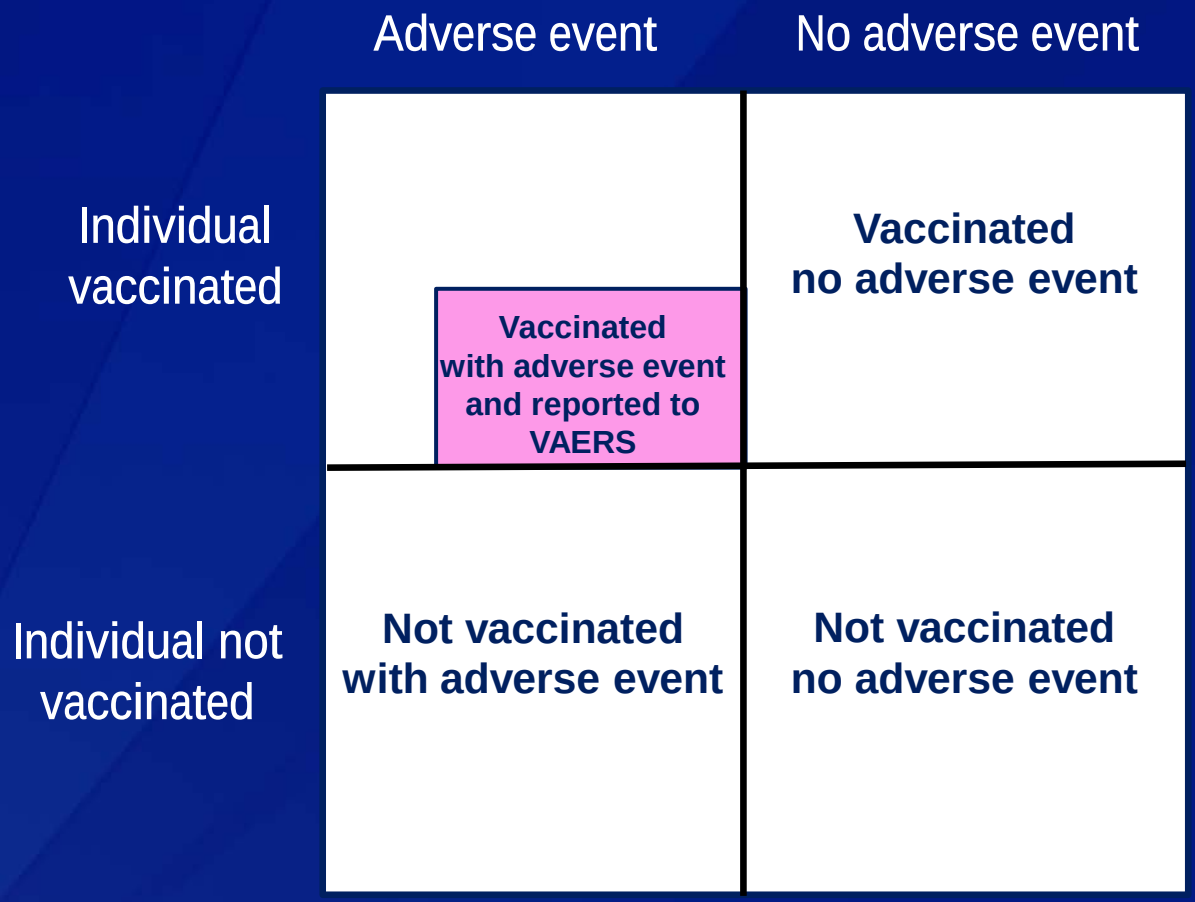
E-mail: cdcinfo@cdc.gov Web: www.cdc.gov

Extra Slides

Limitations of VAERS data



- **VAERS only contains partial data in pink cell (incomplete population data)**
  - **Not able to calculate rates of occurrence of adverse events**
  - **Not able to determine increased risk**
  - **Not able to calculate vaccination coverage**

Newly licensed US influenza vaccines

Vaccine	Abbreviation	Brand name (Manufacturer)	Year licensed	Recommended age group
Quadrivalent inactivated influenza vaccine	IIV4	Fluarix® Quadrivalent (GlaxoSmithKline)	2012	≥3 yrs
		Fluzone® Quadrivalent (Sanofi Pasteur)	2012	≥6 mos
		Flulaval® Quadrivalent (GlaxoSmithKline)	2013	≥3 yrs
Cell culture-based trivalent inactivated influenza vaccine	ccIIV3	Flucelvax® (Novartis)	2012	≥18 yrs
Recombinant trivalent inactivated influenza vaccine	RIV3	FluBlok® (Protein Sciences)	2013	18-49 yrs
Quadrivalent live attenuated influenza vaccine	LAIV4	FluMist® Quadrivalent (MedImmune)	2013	2-49 yrs

Fluzone High-Dose® (IIV3-HD) reports in VAERS 2014-2015

Fluzone High-Dose®	N (%)
Total reports*	1,479
Serious reports†	78 (5)
Male	399 (27)
Age range, years [median]	7 – 99 [71]
Onset interval, days [median]	0 – 162 [0]
Common MedDRA‡ terms	
• Chills	253 (17)
• Pyrexia	251 (17)
• Pain	224 (15)
• Injection site erythema	221 (15)
• Pain in extremity	219 (15)

- No new data mining findings for IIV3-HD

*US primary reports (foreign reports excluded), all high-dose inactivated influenza vaccine, all ages

†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

#Out of recommended age: 45 reports <65 yrs

‡Medical Dictionary for Regulatory Activities

Flucelvax® reports in VAERS 2014-2015

Flucelvax®	N (%)
Total reports*	227
Serious reports†	10 (4)
Male	58 (26)
Age range#, years [median]	0 – 85 [44]
Onset interval, days [median]	0 – 33 [0]
Common MedDRA‡ terms	
• No adverse event	47 (21)
• Drug administered to patient of inappropriate age	34 (15)
• Pruritis	23 (10)
• Pyrexia	23 (10)
• Pain	22 (10)

*US primary reports (foreign reports excluded), all cell culture-based trivalent inactivated influenza vaccine, all ages

†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

#Out of recommended age: 45 reports <18 yrs

‡Medical Dictionary for Regulatory Activities; term 'No adverse event' in 30 (19%) reports

FluBlok® reports in VAERS 2014-2015

FluBlok®	N (%)
Total reports*	18
Serious reports†	1 (6)
Female	18
Age range#, years [median]	30 – 59 [41]
Onset interval, days [median]	0 – 6 [0]
Common MedDRA‡ terms	
• Hypersensitivity	5 (28)
• Throat tightness	5 (28)
• Dysphonia	4 (22)
• Rash	4 (22)
• Urticaria	4 (22)

*US primary reports (foreign reports excluded), all recombinant trivalent inactivated influenza vaccine, all ages

†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

#Out of recommended age: 4 reports >50 yrs

‡Medical Dictionary for Regulatory Activities