End-of-season update: 2013-2014 Influenza Vaccine Safety Monitoring

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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
  - General update
  - Pregnancy outcomes
  - Allergy/anaphylaxis in egg allergic patients
- Vaccine Safety Datalink (VSD) surveillance
- Summary

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

Strengths

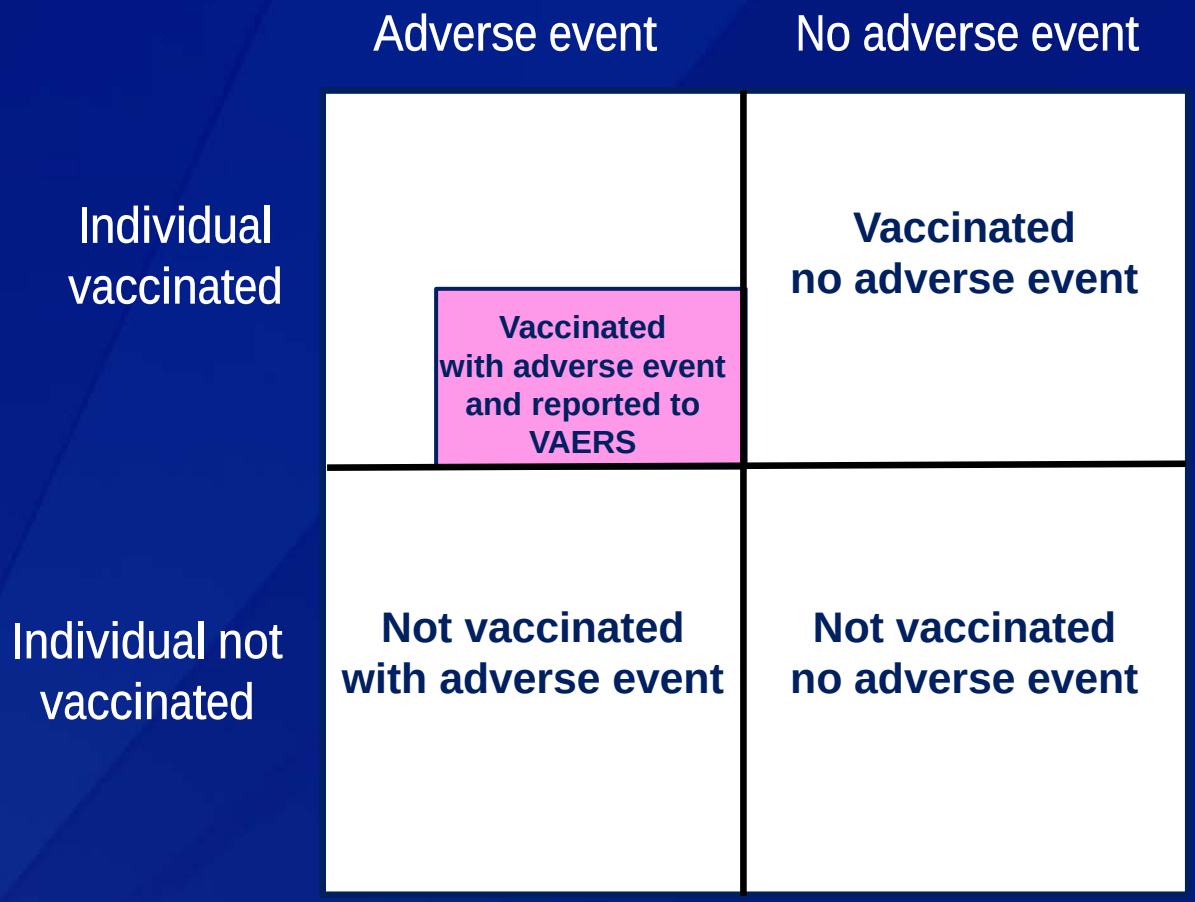
- Rapid signal detection
- Can detect rare adverse events
- Generates hypothesis
- Encourages reports from healthcare providers and accepts reports from patients and others
- Data available to the public

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

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

VAERS surveillance for the 2013-2014 influenza season

Methods

- US reports after IIV and LAIV, received by VAERS and vaccinated 7/1/2013 – 5/2/2014
- Signs and symptoms, or diagnoses coded with Medical Dictionary for Regulatory Activities (MedDRA) terms
- Medical record review for:
  - All serious* reports after newly licensed influenza vaccines** and Fluzone Intradermal®
  - Pregnancy reports for spontaneous abortion, stillbirth, congenital anomalies, serious reports
  - All reports of anaphylaxis with history of egg allergy
- Empirical Bayesian data mining by FDA‡
  - To detect disproportional reporting in the VAERS database

*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

**IIV4: quadrivalent inactivated influenza vaccine; LAIV4: quadrivalent live attenuated influenza vaccine; RIV3: recombinant trivalent inactivated influenza vaccine; ccIIV3: cell culture-based trivalent inactivated influenza vaccine

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

US reports to VAERS following inactivated influenza vaccines (IIV), 7/1/2013 – 5/2/2014

	IIV3 2012-2013 N (%)	IIV3 2013-2014 N (%)	IIV4 2013-2014 N (%)
Total reports*	7,568	7,370	493
Serious reports†	478 (6.3)	444 (6.0)	43 (8.7)
Non-serious reports	7,090 (93.7)	6,926 (94.0)	450 (91.3)
Guillain-Barré syndrome (GBS)‡	84 (1.1)	73 (1.0)	5 (1.0)
Anaphylaxis‡	37 (0.5)	30 (0.4)	6 (1.2)

- No data mining findings for GBS and anaphylaxis

*US primary reports (foreign reports excluded), all 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

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

US reports to VAERS following live attenuated influenza vaccine (LAIV), 7/1/2013 – 5/2/2014

	LAIV3 2012-2013 N (%)	LAIV4 2013-2014 N (%)
Total reports*	486	657
Serious reports†	42 (8.6)	37 (5.6)
Non-serious reports	444 (91.4)	620 (94.4)
Guillain-Barré syndrome (GBS)‡	2 (0.4)	2 (0.3)
Anaphylaxis‡	6 (1.2)	1 (0.2)

- No data mining findings for GBS and anaphylaxis

*US primary reports (foreign reports excluded), all live attenuated 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

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

Fluzone Intradermal (IIV3-ID) reports in VAERS 7/1/2013 – 5/2/2014

Fluzone Intradermal	N (%)
Total reports*	243
Serious reports†	8 (3)
Male	48 (20)
Age range#, years [median]	1 – 92 [44]
Onset interval, days [median]	0 – 170 [1]
Common MedDRA‡ terms	
• Injection site erythema	62 (26)
• Injection site swelling	55 (23)
• Injection site pain	40 (16)
• Erythema	39 (16)
• Injection site pruritus	34 (14)

- No new data mining findings for IIV3-ID

*US primary reports (foreign reports excluded), all intradermal 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: 21 (9%) ; 9 <18 yrs, 12 >64 yrs

‡Medical Dictionary for Regulatory Activities

Flucelvax® reports in VAERS 7/1/2013 – 5/2/2014

Flucelvax®	N (%)
Total reports*	167
Serious reports†	5 (3)
Male	76 (46)
Age range#, years [median]	7 – 81 [36]
Onset interval, days [median]	0 – 115 [0]
Common MedDRA‡ terms	
• Drug administered to patient of inappropriate age	49 (31)
• Pain in extremity	18 (11)
• Injection site pain	13 (8)
• Rash	13 (8)
• Nausea	11 (7)

*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: 62 (37%) <18 yrs

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

FluBlok ® reports in VAERS 7/1/2013 – 5/2/2014

Flublok ®	N (%)
Total reports*	20
Serious reports†	0
Female	20
Age range#, years [median]	36 – 65 [47]
Onset interval, days [median]	0 – 2 [0]
Common MedDRA‡ terms	
• Pruritus	6 (35)
• Dyspnoea	3 (18)
• Headache	3 (18)
• Erythema	3 (18)
• Rash	3 (18)

*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 (20%) >49 yrs

‡Medical Dictionary for Regulatory Activities

Pregnancy reports in VAERS following influenza vaccination, 7/1/2013-5/2/2014

	N (%)
Total reports after IIV3 or IIV4[†]	61
Median age, range, yrs	30 (14-40)
Median gestational age at vaccination (N=25), wks	18 (2-34)
Trimester of vaccination	26
• 1st	9
• 2nd	9
• 3rd	8
Pregnancy-specific outcomes	
• Spontaneous abortion	5
• Stillbirth	1
• Fetal death	1
• Pre-term delivery	1
• Cleft lip & palate	1
• Trisomy 18	1
• Increased fetal movement	1
Non-pregnancy specific reports	31
No adverse event	19
Total reports after LAIV4 (no adverse event, N=22)	23
• Serious report of pulmonary hypertension in infant	1

[†]Three patients required hospitalization for hypersensitivity pneumonitis, preterm delivery, Guillain-Barré Syndrome

One anaphylaxis report in VAERS following influenza vaccination in egg-allergic persons* 7/1/2013 – 5/2/2014

- 4-yr-old male developed diffuse hives, watery eyes, sneezing and vomiting within 15 min after IIV3
- Past medical history
  - Perioral rash after ingestion of meringue icing
  - Increased salivation, abdominal pain and weakness after ingestion of gummy candies and marshmallows
- Positive skin prick test for commercial egg extract and gelatin
- Positive serum test for egg white and bovine gelatin

*Albin S et al. A patient with gelatin allergy and anaphylaxis to the influenza vaccine. Annals of Allergy, Asthma and Immunology 111:A53-A54 abstr. P104, No. 51, Nov 2013 (Conclusion: anaphylaxis likely secondary to gelatin)

Vaccine Safety Datalink (VSD) surveillance for 2013-2014 influenza season

Vaccine Safety Datalink (VSD) Rapid Cycle Analysis for 2013-14 influenza season

Pre-specified outcomes*	IIV	LAIV
Anaphylaxis	≥6 months	2-49 years
Acute disseminated encephalomyelitis	≥6 months	2-49 years
Encephalitis	≥6 months	2-49 years
Transverse myelitis	≥6 months	2-49 years
Guillain-Barré syndrome	≥6 months	2-49 years
Bell's palsy	≥6 months†	2-49 yearsΨ
Seizures	6-59 months††	24-59 months

- 2013-14 influenza vaccine RCA used automated data from ~ 9.3 million patient records

*Using ICD-9 codes
ΨStrata: 2-5 yrs, 6-49 yrs
†Strata: 6 mos-17 yrs, 18-49 yrs, ≥50 yrs
††Strata: 6-23 mos, 24-59 mos

Vaccine Safety Datalink (VSD) surveillance for 2013-2014 influenza season*

- IIV3 (dose 1): 3,811,478 doses administered†
- LAIV4 (dose 1): 218,875 doses administered
- Very limited uptake of IIV4, cell culture-based IIV3 and recombinant IIV3
- No signals in VSD Rapid Cycle Analysis during the 2013-2014 influenza season for any pre-specified outcomes

*Doses administered through April 11, 2014

†High-Dose IIV (13,000 doses) and Intradermal IIV (3,416 doses) not included in the IIV3 total; includes cell culture-based IIV3 and recombinant IIV3

Summary

- No new safety concerns detected for IIV or LAIV during the 2013-2014 influenza season
- Surveillance for the 2014-2015 influenza season will include enhanced safety monitoring for:
  - Quadrivalent IIV and LAIV vaccines
  - Cell culture-based IIV
  - Recombinant IIV
  - Pregnancy reports
  - Reports of anaphylaxis in persons with history of egg allergy after IIV and LAIV
  - Reports with history of asthma/wheezing after LAIV4

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Thank You

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