Interim Influenza Vaccine Safety Update: Live Attenuated Influenza Vaccine and Inactivated Influenza Vaccine in Persons <18 Years of Age, US, 2013-14

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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

Outline

- Vaccine Adverse Event Reporting System (VAERS) surveillance data
- Vaccine Safety Datalink (VSD) Rapid Cycle Analysis
- Clinical Immunization Safety Assessment (CISA) study plans
- Summary and next steps

VAERS Surveillance for the 2013-2014 Influenza Season

(July 1-Dec 31)

Newly licensed influenza vaccines, US, 2013-14*

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

*Reference: CDC. MMWR 2013;62(7);21 23

Methods

- VAERS US reports received after LAIV or IIV
  - Reports received: July 1, 2013 – January 31, 2014
  - Vaccination date: July 1, 2013 – December 31, 2013
- LAIV4 in 2013-14 vs. LAIV3 in 2012-13
- IIV4 vs. IIV3 in 2013-14
- Signs, symptoms, and diagnosis coded using Medical Dictionary for Regulatory Activities (MedDRA)
- Conducted Empirical Bayesian data mining* (FDA)
  - To detect disproportional reporting in the VAERS database

*Banks D, et al. Comparing data mining methods on the VAERS database. Pharmacoepidemiology and drug safety 2005;14:601-9.

Vaccine Adverse Event Reporting System (VAERS) (co-managed by CDC and FDA)*

Strengths

- National data; accepts reports from anyone
- Rapid signal detection; rare adverse events (AE)
- Collects information about vaccine, characteristics of vaccinee, adverse event†
- Data available to public

Limitations

- Reporting bias
- Inconsistent data quality and completeness
- Generally cannot assess if vaccine caused an AE
- Lack of unvaccinated comparison group
- Pregnancy status not included on VAERS form

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

†Some reports have no adverse event

US reports to VAERS following Live Attenuated Influenza Vaccines (LAIV), ages 2-17 years

	LAIV4 2013-14* Total N = 276 N (%)	LAIV3 2012-13* Total N = 244 N (%)
Serious reports†	25 (9)	23 (9)
Male	128 (46)	115 (47)
Median age (yrs)	7	7
Median onset interval (days) [range]	1 [0-99]	0 [0.5-44]
LAIV given alone	163 (59)	127 (52)

*Reports received: Jul 1 Jan 31, vaccinated: Jul 1 Dec 31; LAIV4: quadrivalent live attenuated influenza vaccine; LAIV3: trivalent live attenuated influenza vaccine

†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 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=600.80)

US reports to VAERS following Live Attenuated Influenza Vaccines (LAIV), ages 2-17 years

Adverse Events[Ψ]	LAIV4 2013-14* Total N = 276 N (%)	LAIV3 2012-13* Total N = 244 N (%)
Asthma	13 (5)	16 (7)
Anaphylaxis[†]	0	3 (1)
Seizures[†]	6 (2)	8 (3)
Guillain-Barré syndrome	1 (0.4)	2 (0.8)

- ~12.5 million LAIV4 doses distributed in 2013-14; ~13 million LAIV3 doses distributed in 2012-13 for all ages[‡]
- No disproportional reporting in data mining for 'Guillain-Barré syndrome', 'seizures', 'febrile seizures' or 'anaphylaxis' for 2013-14 season as of 1/31/14[¶]

[Ψ]Based on Medical Dictionary for Regulatory Activities (MedDRA) codes
*Reports received: Jul 1 Jan 31, vaccinated: Jul 1 Dec 31; LAIV4: quadrivalent live attenuated influenza vaccine; LAIV3: trivalent live attenuated influenza vaccine
[†]Onset interval 0 1 day post vaccination
[‡]Data provided by manufacturer (personal communication)
[¶]Data mining data provided by FDA

Top 12 MedDRA† terms following Live Attenuated Influenza Vaccines (LAIV) given alone, ages 2-17 years

LAIV4* 2013-14	Total N = 163 N (%)	LAIV3* 2012-13	Total N = 127 N (%)
Pyrexia	41 (25)	Pyrexia	37 (29)
Cough	27 (17)	Cough	21 (17)
Urticaria	25 (15)	Vomiting	21 (17)
Vomiting	20 (12)	Urticaria	14 (11)
Headache	17 (10)	Diarrhea	9 (7)
Nausea	14 (9)	Wheezing	8 (6)
No adverse event	11 (7)	Abdominal pain upper	7 (6)
Dizziness	10 (6)	Dizziness	7 (6)
Expired drug administered	10 (6)	Fatigue	7 (6)
Rhinorrhea	10 (6)	Headache	7 (6)
Wheezing	10 (6)	Pain	7 (6)
Dyspnea	9 (6)	Swelling face	7 (6)

†Medical Dictionary for Regulatory Activities
*Reports received: Jul 1 Jan 31, vaccinated: Jul 1 Dec 31

US reports to VAERS following Inactivated Influenza Vaccines (IIV), ages 6 months-17 years

	IIV4 2013-14* Total N = 121 N (%)	IIV3 2013-14* Total N = 715 N (%)
Serious reports†	12 (10)	51 (7)
Male	61 (50)	379 (53)
Median age (yrs)	5	5
Median onset interval (days) [range]	0 [0-16]	1 [0-103]
IIV given alone	68 (56)	380 (53)

*Reports received: Jul 1 Jan 31, vaccinated: Jul 1 Dec 31; IIV4: quadrivalent inactivated influenza vaccine; IIV3: trivalent inactivated influenza vaccine

†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 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=600.80)

US reports to VAERS following Inactivated Influenza Vaccines (IIV), ages 6 months-17 years

Adverse Events[Ψ]	IIV4 2013-14 * Total N = 121 N (%)	IIV3 2013-14* Total N = 715 N (%)
Anaphylaxis[†]	1 (0.8)	1 (0.1)
Seizures[†]	6 (5)	46 (6)
Guillain-Barré syndrome	0	5 (0.7)

- ~12.9 million IIV4 and ~122.6 million IIV3 doses distributed in 2013-14 for all ages[‡]
- No disproportional reporting in data mining for 'Guillain-Barré syndrome', 'seizures', 'febrile seizures' or 'anaphylaxis' for 2013-14 season as of 1/31/14[¶]

[Ψ]Based on Medical Dictionary for Regulatory Activities (MedDRA) codes
*Reports received: Jul 1 Jan 31, vaccinated: Jul 1 Dec 31; IIV4: quadrivalent inactivated influenza vaccine; IIV3: trivalent inactivated influenza vaccine
[†]Onset interval 0 1 day post vaccination
[‡] Data provided by manufacturers
[¶] Data mining data provided by FDA

Top 12 MedDRA† terms following Inactivated Influenza Vaccines (IIV) given alone, ages 6 months-17 years

IIV4* 2013-14	Total N = 68 N (%)	IIV3* 2013-14	Total N= 380 N (%)
Injection site erythema	16 (24)	Injection site erythema	58 (15)
Injection site warmth	10 (15)	Injection site swelling	56 (15)
Pyrexia	9 (13)	Pyrexia	55 (15)
Injection site swelling	8 (12)	Erythema	39 (10)
Urticaria	8 (12)	Injection site warmth	37 (10)
Erythema	7 (10)	Urticaria	34 (9)
Vomiting	7 (10)	Rash	31 (8)
Local swelling	6 (9)	Pruritus	24 (6)
Rash	5 (7)	Injection site pain	23 (6)
Rash erythematous	5 (6)	Syncope	23 (6)
Injection site induration	4 (6)	Dizziness	21 (6)
Injection site pain	4 (6)	Pain	20 (5)

†Medical Dictionary for Regulatory Activities
*Reports received: Jul 1 Jan 31, vaccinated: Jul 1 Dec 31

Vaccine Safety Datalink (VSD) Surveillance for the 2013-14 Influenza Season

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

Pre-specified outcomes*	LAIV	IIV
	Age group	
Anaphylaxis	2-49 yrs	≥6 mos
Acute disseminated encephalitis	2-49 yrs	≥6 mos
Encephalitis	2-49 yrs	≥6 mos
Transverse myelitis	2-49 yrs	≥6 mos
Guillain-Barré syndrome	2-49 yrs	≥6 mos
Bell's palsy	2-49 yrs[Ψ]	≥6 mos[†]
Seizures	24-59 mos	6-59 mos[††]

*Using ICD 9 codes
[Ψ]Strata: 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) Rapid Cycle Analysis for 2013-14 influenza season

- LAIV4 dose 1: 194,080 doses
- IIV3 dose 1: 3,153,747 doses†
- Limited uptake of IIV4 (19,182 dose 1 doses), cell culture-based IIV3 and recombinant IIV3
- No signals in Rapid Cycle Analysis during the 2013-14 influenza season for any pre-specified outcomes

*Doses administered through January 16, 2014

†High Dose IIV and Intradermal IIV not included in the IIV3 total; includes cell culture based IIV3 and recombinant IIV3

Clinical Immunization Safety Assessment (CISA) Project Study

CISA Project Study: Fever rates in children ages 24 to 59 months after Live Attenuated Influenza Vaccine (LAIV) or Inactivated Influenza Vaccines (IIV) using text messaging for US influenza vaccines*

- Columbia University and CDC are conducting an observational study of influenza vaccine safety during 2012-13 and 2013-14
- Primary Aim
  - To assess the rates of fever in 24-59 month old children receiving LAIV compared to those receiving IIV in the 0-10 days after vaccination
- Design
  - Children receive LAIV or IIV per usual care, with or without other childhood vaccines
  - Temperatures monitored daily via text messaging
- Timeline
  - Preliminary data expected by June 2014

*Study registered at ClinicalTrials.gov NCT01764269

Summary and next steps

- No new safety concerns detected for LAIV4, IIV4 or IIV3 during the 2013-14 influenza season in persons <18 years of age
  - VAERS and VSD surveillance data studied
- Comparable safety profile of LAIV4 vs. LAIV3 and IIV4 vs. IIV3 in persons <18 years of age
- Influenza vaccine safety monitoring in VAERS, VSD, and CISA continuing

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Thank You

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