End-of-season update: 2012-2013 Influenza Vaccine Safety Monitoring

Advisory Committee on Immunization Practices
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Outline

- Vaccine Adverse Event Reporting System (VAERS) influenza vaccine surveillance*
  - General VAERS influenza vaccine update
  - High-dose trivalent inactivated influenza vaccine (TIV-HD)
  - Intradermal TIV (TIV-ID)
  - Pregnancy outcomes
  - Anaphylaxis following influenza vaccination in suspected egg allergic patients
- Vaccine Safety Datalink (VSD) influenza vaccine surveillance†
- Summary and next steps

* 2012-13 influenza season through 5/3/13
† 2012-13 influenza season through 3/14/13

VAERS surveillance for the 2012-2013 influenza season

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 trivalent inactivated influenza vaccines (TIV)

	2011-12 N (%)	2012-13 N (%)
Total reports (US primary reports)	6,588	7,121
Serious reports*	495 (7.5)	457 (6.4)
Non-serious reports	6,093 (92.5)	6,664 (93.6)
Guillain-Barré syndrome†	100 (1.5)	72 (1.0)
Anaphylaxis† (onset interval 0-1 days post-vaccination)	26 (0.4)	31 (0.4)

- Approximately 121.9 million TIV doses distributed in 2012-13‡
- No disproportional reporting in data mining for 'Guillain-Barré syndrome', 'febrile seizures' or 'anaphylaxis' for 2012-13¶

* 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 Medical Dictionary for Regulatory Activities (MedDRA) codes; ‡ Determined by subtracting expected LAIV doses for the 2012-13 influenza season from total influenza vaccine doses distributed in 2012-13 (available at http://www.cdc.gov/flu/professionals/vaccination/vaccinesupply.htm); ¶ Data mining data provided by FDA

US reports to VAERS following live attenuated influenza vaccine (LAIV)

	2011-12 N (%)	2012-13 N (%)
Total reports (US primary reports)	498	494
Serious reports*	26 (5.2)	41 (8.3)
Non-serious reports	472 (94.8)	453 (91.7)
Guillain-Barré syndrome†	3 (0.6)	2 (0.4)
Anaphylaxis† (onset interval 0-1 days post-vaccination)	1 (0.2)	5 (1.0)

- Approximately 13 million LAIV doses expected for 2012-13‡
- No disproportional reporting in data mining for 'Guillain-Barré syndrome' or 'anaphylaxis' for 2012-13¶

* 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 Medical Dictionary for Regulatory Activities (MedDRA) codes;
‡ http://www.medimmune.com/media/press-releases/2012/08/02/flumist-sup-sup-(influenza-vaccine-live-intranasal)-begins-shipping-for-2012-2013-influenza-season; ¶ Data mining data provided by FDA

Fluzone® High-Dose (TIV-HD) reports in VAERS

	2010-11 N (%)*	2011-12 N (%)	2012-13 N (%)
Total number	642	605	730
Serious	58 (9.0)	69 (11.4)	64 (8.8)
Female	412 (64.2)	407 (67.3)	511 (70.0)
Median age (range)	71 (1-95)	71 (24-98)	71 (2-98)
TIV-HD alone	587 (91.4)	540 (89.3)	590 (80.8)

- Common signs/symptoms following TIV-HD include:
  - Pyrexia
  - Chills
  - Nausea
  - Vomiting
  - Headache
  - Injection site reactions

* Adapted from Moro et al. Postlicensure safety surveillance for high-dose trivalent inactivated influenza vaccine in the Vaccine Adverse Event Reporting System, 1 July 2010-31 December 2010. Clin Infect Dis. 2012;54:1608-14.

Fluzone® High-Dose (TIV-HD) reports in VAERS, 2012-13 influenza season

- Disproportional reporting in data mining* identified for:
  - 'Vomiting' (persisted since 2010-11; not a new safety concern)
  - 'Drug administered to patient of inappropriate age'

- Most reports of vomiting are non-serious and self-limiting
  - Vomiting frequently accompanied by:

Nausea	51%†
Chills	41%
Diarrhea	36%
Pyrexia	30%

* Data mining data provided by FDA

† For example, in 51% of TIV-HD VAERS reports where vomiting was coded, nausea was also a coded outcome

Fluzone® Intradermal (TIV-ID) reports in VAERS

	2011-12 N (%)	2012-13 N (%)
Total no.	86	391
Serious	1 (1.2)	9 (2.3)
Female	61 (70.9)	295 (75.4)
Median age (range)	44 (12-69)	43 (4-88)
TIV-ID alone	81 (94.2)	353 (90.3)

- Common signs/symptoms following TIV-ID are those of mild and self-limited injection site reactions

Fluzone® Intradermal (TIV-ID) reports in VAERS, 2012-13 influenza season

- Disproportional reporting in data mining* identified for:
  - 'Injection site nodule'
  - 'Injection site pruritus'
  - 'Drug administered to patient of inappropriate age'
- Local reactions are in the package label and expected
- Findings for injection site nodule and injection site pruritus do not represent new safety concerns

* Data mining data provided by FDA

Summary of VAERS reports for TIV administered during pregnancy, 2012-13 influenza season

- 43 total TIV pregnancy reports
  - 14 spontaneous abortion reports (32.6%)
  - 1 placenta previa
  - 1 excessive bleeding during labor
  - 27 non-pregnancy specific reports or no reported AE
- No reports of major birth defects
- Approximately 2 million pregnant women received influenza vaccine during the 2012-13 season*
- Review of VAERS reports identified no unusual patterns

* Based on preliminary vaccination coverage estimates from the Pregnant Women Internet Panel Survey, April 2013; courtesy Immunization Services Division/CDC

Influenza vaccine administration in patients with history of egg allergy

- Recommendation for egg allergic patients updated 2011-12*
  - Persons with a history of egg allergy who have experienced only hives should receive TIV with some additional safety measures
  - Persons with more severe reactions to egg should be referred to a physician with allergy expertise for further risk assessment
- CDC ~~has~~ conducted enhanced monitoring for allergy and anaphylaxis in VAERS since 2011-12
  - Search for 'anaphylaxis' code combined with text search for "egg"
  - Manual review of reports and medical records
  - VAERS reports of possible anaphylaxis in suspected egg allergic patients reviewed through CDC's Clinical Immunization Safety Assessment (CISA) Project†

* http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6033a3.htm

† http://www.cdc.gov/vaccinesafety/activities/cisa.html

CISA assessment of VAERS anaphylaxis reports after influenza vaccine in individuals with suspected egg allergy, 7/1/2010-5/3/2013

- CDC search identified 4 reports
- CISA Project reviewed the 4 cases (3 TIV and 1 LAIV)
  - 3 cases did not meet the criteria of (1) existing egg allergy, (2) diagnosis of anaphylaxis, (3) anaphylaxis consistent with reaction to egg protein in the vaccine
  - 1 case met the criteria (vaccinated in 2012-13)
    - 12 month old male with history of atopic dermatitis and egg allergy (prick test positive for ovalbumin) developed generalized urticaria, dyspnea, cough, wheezing and angioedema of the uvula following TIV; child had never ingested egg in the past
    - Case met Brighton Level 1 criteria*

* Rüggeberg et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25(31):5675-84.

Vaccine Safety Datalink (VSD) surveillance for 2012-13 influenza season

Vaccine Safety Datalink (VSD)

- Data on over 9 million persons per year (~3% of US pop)
- Links vaccination data to health outcome (outpatient, emergency dept., inpatient) and demographic data

Strengths

- All medical encounters are available
- Vaccine registry data
- Can calculate rates
- 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
- Potential for lack of socioeconomic diversity
- Data lags

Vaccine Safety Datalink (VSD) surveillance for 2012-13 influenza season

- Near real-time monitoring (Rapid Cycle Analysis) pre-specified outcomes* for TIV and LAIV
  - Guillain-Barré syndrome
  - Seizures
  - Encephalitis, myelitis and encephalomyelitis
  - Anaphylaxis
- 2012-13 influenza vaccine Rapid Cycle Analysis used automated data from ~9.2 million health plan members

* Using ICD-9 codes

Vaccine Safety Datalink (VSD) surveillance for 2012-13 influenza season*

- TIV dose 1: 3,672,076 doses
  - TIV-HD: 31,257 doses†
  - TIV-ID: 4,713 doses†
- LAIV dose 1: 264,262 doses
- No signals in Rapid Cycle Analysis during the 2012-13 influenza season for any pre-specified outcomes

* Doses administered through March 14, 2013

† TIV-HD and TIV-ID included in TIV total but dropped from final analysis for Rapid Cycle Analysis

Summary

- No new safety concerns detected for TIV or LAIV during the 2012-13 influenza season
- Review of pregnancy reports in VAERS identified no unusual patterns
- Review of VAERS reports for the past 3 influenza seasons identified 1 case of anaphylaxis in an egg allergic individual following TIV that was consistent with a reaction to egg protein in the vaccine

Next steps

- Enhanced VAERS surveillance for 2013-14 to include physician review of reports for:
  - Pregnancy
  - Anaphylaxis in egg allergic individuals
  - New vaccines:
    - Quadrivalent (IIV4 and LAIV4)
    - Cell culture-based
    - Recombinant
- Vaccine Safety Datalink (VSD) near real-time monitoring (Rapid Cycle Analysis) for 2013-14
  - Surveillance of new vaccines will depend on number of doses observed in VSD

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Thank You

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Extra slides

Immunization Safety Office's post-licensure vaccine safety monitoring infrastructures

System	Collaboration	Description
Vaccine Adverse Event Reporting System (VAERS)	CDC and FDA	US frontline spontaneous reporting system to detect potential vaccine safety problems
Vaccine Safety Datalink (VSD)	CDC and Healthcare Plans	Large linked database system used for active surveillance and research
Clinical Immunization Safety Assessment (CISA) Project	CDC and Academic Centers	Expert collaboration which conducts individual clinical vaccine safety assessments and clinical research

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Median age (range)	71 (1-95)	71 (24-98)	71 (2-98)
TIV-HD alone	587 (91.4)	540 (89.3)	590 (80.8)
Most common coded outcomes (based on MedDRA codes, excluding abnormal lab results)	Pyrexia 170 (26.5)	Chills 147 (24.3)	Pyrexia 127 (17.4)
	Chills 169 (26.3)	Pyrexia 128 (21.2)	Chills 123 (16.8)
	Nausea 119 (18.5)	Pain 102 (16.9)	Inj. site erythema 97 (13.3)
	Pain 106 (16.5)	Headache 87 (14.4)	Pain in extremity 94 (12.9)
	Vomiting 105 (16.4)	Vomiting 76 (12.6)	Pain 92 (12.6)
	Headache 101 (15.7)	Dyspnea 68 (11.2)	Nausea 86 (11.8)

* Adapted from Moro et al. Postlicensure safety surveillance for high-dose trivalent inactivated influenza vaccine in the Vaccine Adverse Event Reporting System, 1 July 2010-31 December 2010. Clin Infect Dis. 2012;54:1608-14.

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Female	61 (70.9)	295 (75.4)
Median age (range)	44 (12-69)	43 (4-88)
TIV-ID alone	81 (94.2)	353 (90.3)
Most common coded outcomes **(based on MedDRA codes, excluding abnormal lab results)**	Injection site erythema 24 (22.2)	Injection site erythema 93 (25.0)
	Erythema 17 (15.7)	Erythema 69 (18.5)
	Injection site swelling 17 (15.7)	Pain 54 (14.5)
	Pain 15 (13.9)	Injection site pruritus 53 (14.2)
	Injection site pain 14 (13.0)	Injection site pain 52 (14.0)
	Pruritus 14 (13.0)	Pruritus 50 (13.4)