End-of-season update: 2018-2019 influenza vaccine safety monitoring

June 2019 Advisory Committee on Immunization Practices (ACIP) meeting

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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 and FDA
- The use of product trade names is for identification purposes only

Overview

- Background
- Safety monitoring update
  from the **Vaccine Adverse Event Reporting System** (VAERS)
- Rapid Cycle Analysis (RCA)
  from the **Vaccine Safety Datalink** (VSD)
- FDA assessment of Guillain-Barré syndrome following influenza vaccine
  from **Medicare data**
- Clinical research studies in progress
  from the **Clinical Immunization Safety Assessment (CISA)** Project

Vaccine safety monitoring and research terms

Term	Explanation
Adverse event	An adverse medical or health event following vaccination (a temporally associated event), which may or may not be related to vaccination (i.e., coincidental).
Adverse reaction	An adverse health event following vaccination where substantial evidence exists to suggest the event is causally related to vaccination.
MedDRA	A clinically-validated international medical terminology used by regulatory authorities to describe health outcomes and events.
ICD-10 and 9	A system used by physicians and other healthcare providers to classify and code diagnoses, symptoms and procedures associated with healthcare.
Automated analysis	Analysis on administrative or claims data or non-chart/health record confirmed data.
Chart confirmed/ medical record confirmed case	A case where review of medical charts and records by physicians or medical personnel confirms the diagnosis as valid and with accurate onset relative to timing of vaccination.
Incident case	A new case occurring for the first time ever or during a specified time period.
Prevalent or non-incident case	A case that has been diagnosed in the past prior to vaccination or prior the study period that has become part of the patient's past medical history and therefore is not new.
Biologically plausible risk interval	The time interval following vaccination where it is biologically plausible, based on the best available science, that an observed adverse event could be related to vaccination.
Statistical signal	A finding from an analysis where a calculated value (i.e., the test statistic) exceeds a specified statistical threshold; a statistical signal does not necessarily represent a vaccine safety problem and requires further assessment before conclusions can be drawn.

Influenza vaccine abbreviations[1]

Abbreviation	Vaccine
IIV3, IIV4	Trivalent and quadrivalent inactivated influenza vaccine
IIV3-HD	High-dose trivalent inactivated influenza vaccine (approved for use in individuals 65+ years old)
ccIIV4	Cell culture-based quadrivalent inactivated influenza vaccine
RIV4	Recombinant quadrivalent influenza vaccine
aIIV3	Adjuvanted trivalent inactivated influenza vaccine (approved for use in individuals 65+ years old)
LAIV4	Quadrivalent live attenuated influenza vaccine

[1]IIV is commonly used when discussing inactivated influenza vaccines as a general category

Safety monitoring update

from the **Vaccine Adverse Event Reporting System (VAERS)**

Vaccine Adverse Event Reporting System

Co-managed by CDC and FDA

http://vaers.hhs.gov

Vaccine Adverse Event Reporting System (VAERS)

Strengths

- National data
- Accepts reports from anyone
- Rapidly detects safety signals
- Can detect rare adverse events
- Data available to public

Limitations

- Reporting bias
- Inconsistent data quality and completeness
- Lack of unvaccinated comparison group
- Generally cannot assess causality

- VAERS accepts all reports from all reporters without making judgments on causality, irrespective of clinical seriousness
- As a hypothesis generating system, VAERS identifies potential vaccine safety concerns that can be studied in more robust data systems

VAERS monitoring: methods

- U.S. influenza vaccine reports from July 2018-April 2019 (as of May 10, 2019)
- Signs, symptoms, and diagnoses coded using Medical Dictionary for Regulatory Activities (MedDRA) terms
- Clinical review of reports (includes medical records when available):
  - All serious[1] reports
  - Pregnancy reports for spontaneous abortion, stillbirth, congenital anomalies
  - Anaphylaxis reports in persons with a history of egg allergy
- Empirical Bayesian data mining to detect disproportional reporting for vaccine-adverse event pairings

[1]Based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, permanent disability, congenital anomaly or birth defect (FDA routinely reviews all serious reports)

Reports by vaccine type, 2018-2019 influenza season

	IIV3 N (%)	IIV4 N (%)	IIV3-HD N (%)
Total reports[1]	150	4,890	2,169
Non-serious reports	141 (94%)	4,621 (94%)	2,076 (96%)
Serious reports[2]	9 (6%)	269 (6%)	93 (4%)
Guillain-Barré syndrome (GBS)	2 (1.3%)	33 (0.7%)	13 (0.6%)
Anaphylaxis[3]	0 (0%)	24[4] (0.5%)	2[4] (0.1%)
Febrile convulsion[5]	1 (0.7%)	25 (0.5%)	---

- No data mining signals for Guillain-Barré syndrome, anaphylaxis, or febrile convulsion in association with IIV3, IIV4 or IIV3-HD

[1]U.S. primary reports (foreign reports excluded), all ages; [2]Based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, permanent disability, congenital anomaly or birth defect; [3]Onset interval 0-1 days post vaccination for anaphylaxis; [4] No anaphylaxis reports in persons with a history of egg allergy; [5]Limited to reports in children aged 6-59 months old

Reports by vaccine type, 2018-2019 influenza season

	ccIIV4 N (%)	aIIV3 N (%)	RIV4 N (%)	LAIV4 (N%)
Total reports[1]	1,040	708	276	23
Non-serious reports	1,007 (97%)	692 (98%)	268 (97%)	22 (96%)
Serious reports[2]	33 (3%)	16 (2%)	8 (3%)	1 (4%)
Guillain-Barré syndrome (GBS)	16 (1.5%)	1 (0.1%)	4 (1.4%)	0 (0%)
Anaphylaxis[3]	3[4] (0.3%)	1[4] (0.1%)	1[4] (0.4%)	0 (0%)
Febrile convulsion[5]	0 (0%)	---	---	0 (0%)

- No data mining signals for Guillain-Barré syndrome, anaphylaxis, or febrile convulsion in association with ccIIV4, aIIV3, RIV4, or LAIV4

[1]U.S. primary reports (foreign reports excluded), all ages; [2]Based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, permanent disability, congenital anomaly or birth defect; [3]Onset interval 0-1 days post vaccination for anaphylaxis; [4] One ccIIV4 anaphylaxis report in a person with a history of egg allergy. No anaphylaxis reports in persons with a history of egg allergy for aIIV3, RIV4, or LAIV; [5]Limited to reports in children aged 6-59 months old

Reports involving vaccination during pregnancy, 2018-2019

Total reports (IIV4=55, ccIIV4=67, IIV3=4, RIV4=6, unknown type/brand=9)	**141[1]**
Median maternal age (range) at vaccination	32 years (16-43)
Median gestational age (range) at vaccination, n=117 with GA reported	21 weeks (1-41)
Trimester of vaccination, n=117 reports with trimester documented • 1st trimester • 2nd trimester • 3rd trimester	 36 (31%) 44 (38%) 37 (32%)
Pregnancy-specific adverse event reports Spontaneous abortion (13), preterm delivery (9), premature labor (6), stillbirth (2), pre-eclampsia (2), oligohydramnios (2), placenta previa (2), dysmature placenta (2), premature rupture of membranes (1), gestational hypertension (1), gestational diabetes (1), placentae abruption (1), vaginal discharge (1), nausea (1)	44 (31%)
Non-pregnancy specific adverse event reports	43 (30%)
Infant or fetal adverse event[2]	18 (13%)
No adverse event documented in report	38 (27%)

[1]141 reports described 143 adverse events (two reports described adverse events in mother and infant); [2]Low birth weight (5), large for gestational age (2), meconium in amniotic fluid (2), nuchal chord (1), hypospadias and chyothorax (1), dystocia of shoulder (1), intrauterine growth retardation (1), jaundice (1), tricuspid regurgitation and pulmonary insufficiency (1), upper respiratory tract infection, (1), cystic fibrosis carrier (1), asymmetrical growth (1)

Summary of VAERS monitoring

- No new safety concerns detected for IIV3, IIV4, LAIV4, IIV3-HD, ccIIV4, aIIV3, or RIV4 during the 2018-2019 influenza season
- Surveillance for the 2019-2020 influenza season will include enhanced safety monitoring[1] for:
  - aIIV3 (FLUAD®)
  - RIV4 (Flublok® Quadrivalent)
  - Pregnancy reports
  - Anaphylaxis reports in persons with history of egg allergy

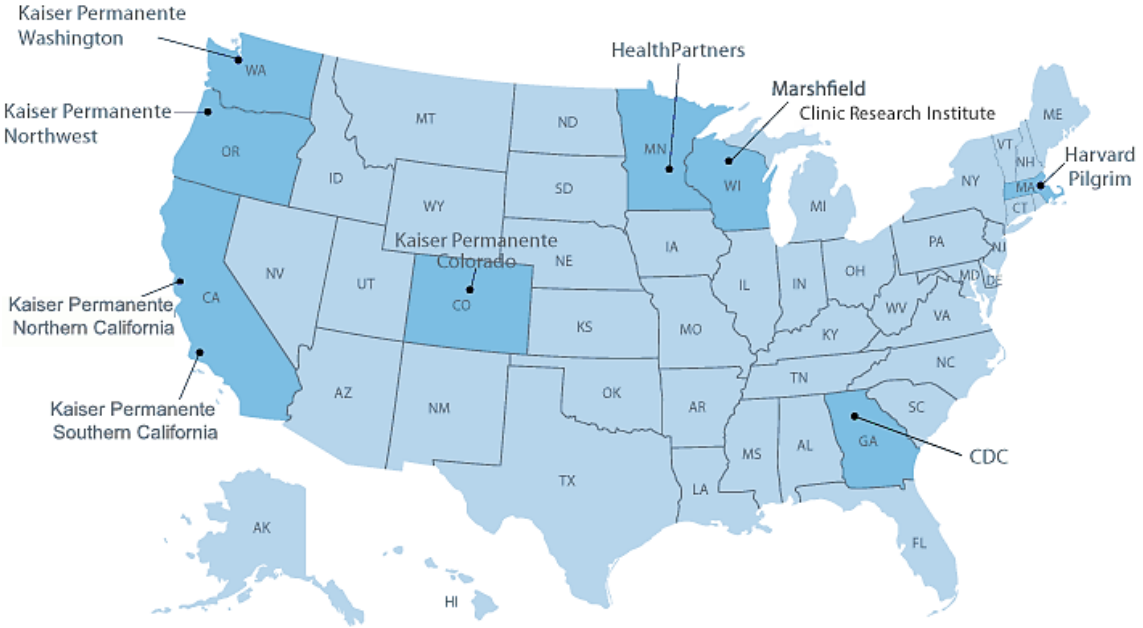
[1]Includes clinical review of all reports and available medical records for the specific vaccines and outcomes and conditions specified

Rapid Cycle Analysis (RCA)

from the **Vaccine Safety Datalink (VSD)**

VSD

Vaccine Safety Datalink

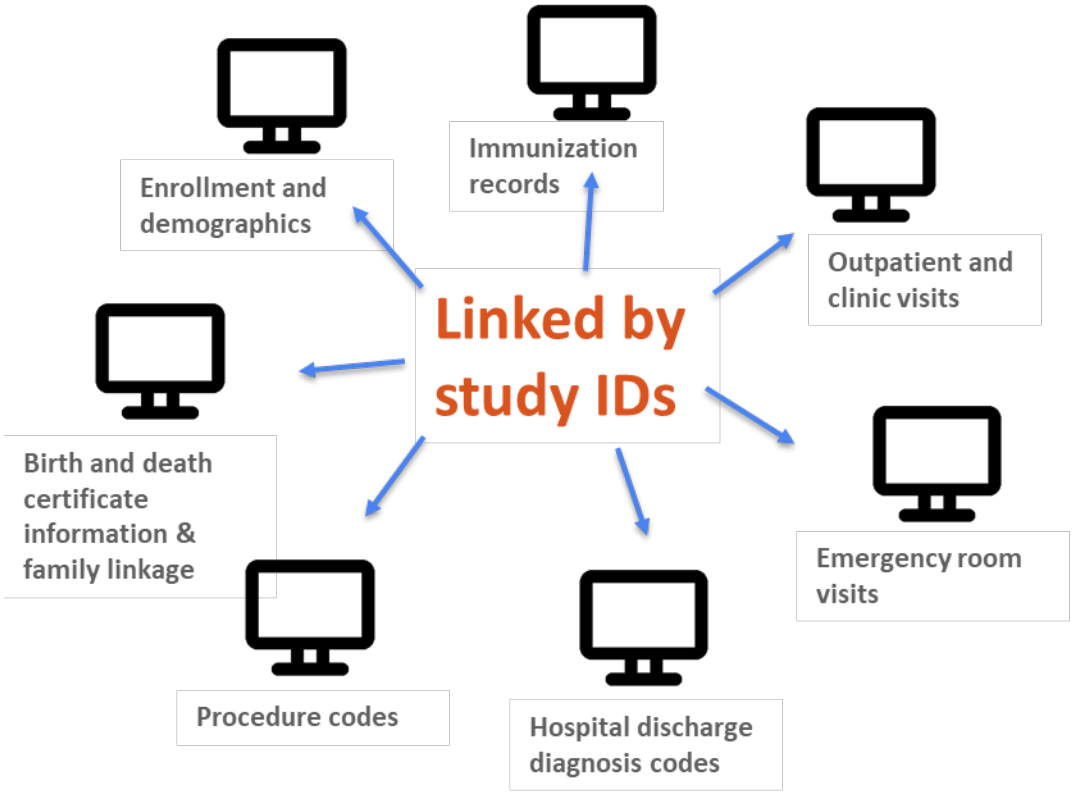


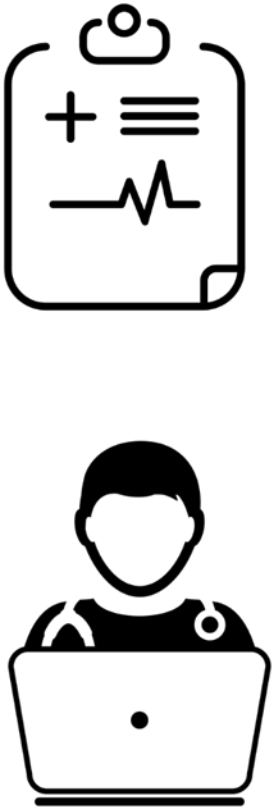
8 participating integrated healthcare organizations

Vaccine Safety Datalink (VSD)

- Established in 1990
- Collaboration between CDC and several integrated healthcare organizations
- Medical care and demographic data on over 12.1 million persons per year (~3.7% of U.S. population)
- Links vaccination data to health outcome data
- Used for surveillance and research

VSD electronic files + chart review

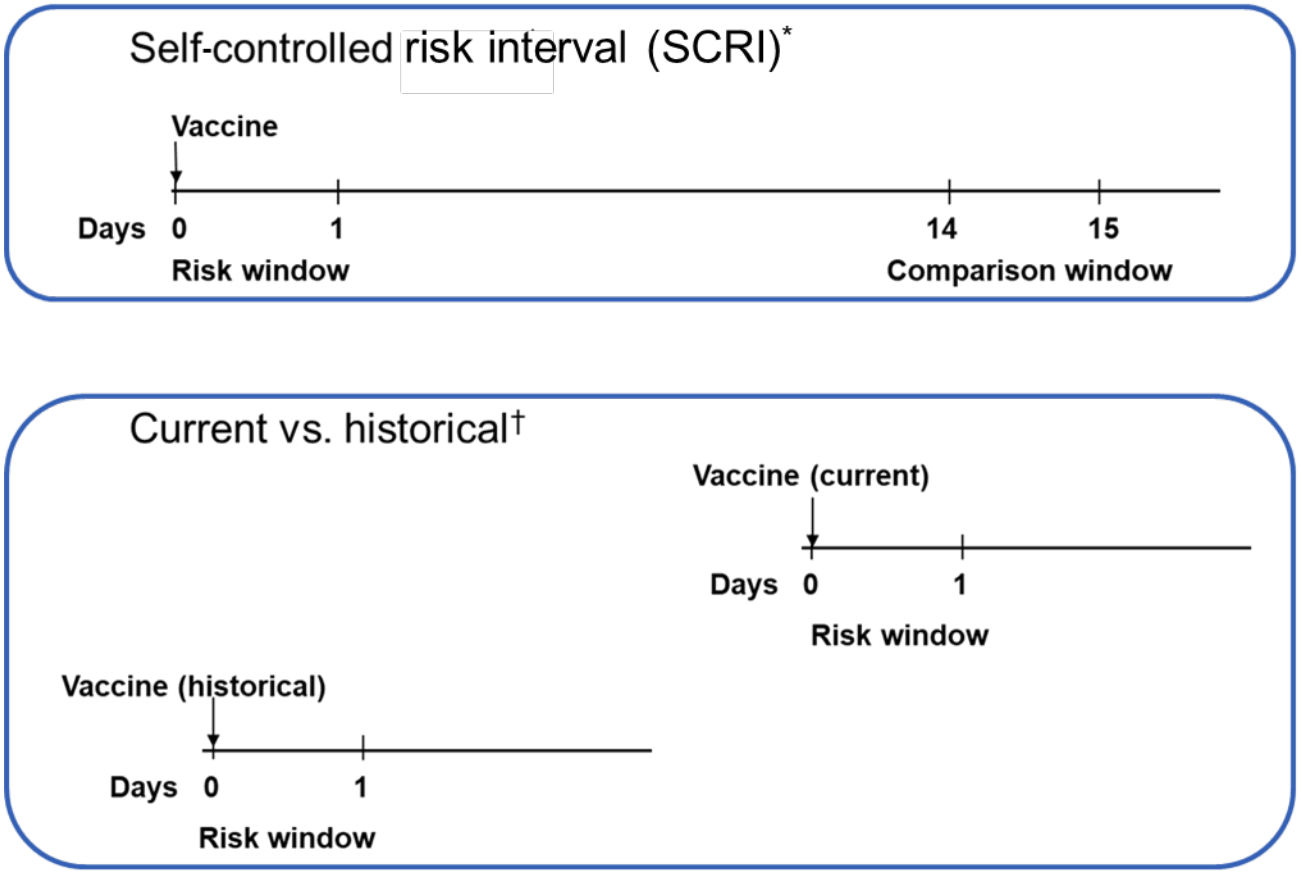




Images created by Wilson Joseph, Megan Mitchell, Ananth, and Iga from the noun project

Influenza vaccine Rapid Cycle Analysis (RCA) in the VSD

- Weekly near real-time sequential monitoring to detect statistical signals for pre-specified outcomes
- Includes methods to adjust for sequential testing
- Focused on standard dose IIV4 and IIV3 High-Dose
- Uptake of other influenza vaccine products is still relatively low in VSD



*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 (RCA) in VSD

A powerful and sophisticated tool

- Near real-time vaccine-safety monitoring (using sequential monitoring techniques)
- Employs an automated analysis that uses ICD-coded diagnoses from administrative data
- A surveillance activity (signal detection and signal refinement), which is not the same as an epidemiologic study (signal evaluation, causality assessment)
- Requires careful thought and customization in the design, set-up, interpretation

Designed to detect statistical signals (values above specified statistical thresholds)

- When a statistical signal occurs, CDC conducts a series of evaluations using traditional epidemiologic methods
- Chart-confirmation of diagnoses to confirm or exclude cases as true incident cases is a key part of statistical signal assessment

Not all statistical signals represent a true increase in risk for an adverse event

RCA outcomes for the 2018-2019 influenza season

Pre-specified outcome	Age group	Risk window (days)	Comparison window[1] (days)
Acute disseminated encephalomyelitis (ADEM)	≥6 mo	1-21	-56 to -15
Anaphylaxis	≥6 mo	0-2	7-9
Bell's palsy	≥6 mo to <18 yr 18-49 yr ≥50 yr	1-42	-56 to -15
Encephalitis	≥6 mo	1-21	-56 to -15
Guillain-Barré syndrome (GBS)	≥6 mo	1-42	43-84
Seizures	6-23 mo 24-59 mo	0-1	14-20
Transverse myelitis	≥6 mo	1-21	-56 to -15

[1]For self-controlled risk interval design

Influenza vaccine dose 1 doses administered in 2018-2019

Vaccine	Dose 1 doses administered[1] all ages
IIV4	3,898,542 (71%)
IIV3 High-Dose	645,362 (12%)
ccIIV4	510,010 (9%)
aIIV3	27,177 (0.5%)
RIV4	374,996 (7%)
Total	**5,456,087**

[1]Doses administered through April 3, 2019; percentages subject to rounding errors

Influenza vaccine RCA – summary of statistical signals

Pre-specified outcomes	Risk interval	Age group	Current vs. historical design			Self-controlled risk interval design		
			IIV4	ccIIV4	IIV3-HD	IIV4	ccIIV4	IIV3-HD
ADEM	1-21	≥6 mo						
Anaphylaxis	0-2	≥6 mo	Yes ✓ 10/21/18	Yes (≥4 yr) ✓ 11/11/18			Yes (≥4 yr) ✓ 12/9/18	
Bell's Palsy	1-42	<18 yr					Yes (4-17 yr) ✓ 12/9/18	
		18-49 yr						
		≥50 yr						
Encephalitis	1-21	≥6 mo						
GBS	1-42	≥6 mo						Yes (65+) ✓ 12/9/18
Seizures	0-1	6-23 mo				Yes ✓ 11/25/18		
		24-59 mo	Yes ✓ 12/9/18			Yes ✓ 11/4/18		
Transverse myelitis	1-21	≥6 mo						

[1]Doses administered through April 3, 2019; percentages subject to rounding errors

Anaphylaxis

Statistical signal week of Oct 21, 2018 for anaphylaxis following IIV4 in current vs. historical analysis

Risk interval	Age group	Vaccine doses	Observed # events	Expected # events	RR	Log likelihood ratio (LLR)	Critical value of LLR
0-2 days	≥6 months	1,880,068	9	3.119	2.88	3.66	3.0

- For end-of-season analysis, chart reviewed 18 potential cases (9 additional cases)
  - 11 had symptom onset prior to vaccination (i.e., other exposures and vaccinated in ED)
  - 6 had onset post vaccination but with other exposures to explain anaphylaxis: foods (3), medications (2), exercise induced (1)
  - 1 case determined to be potentially vaccine related: patient received IIV4 and recombinant zoster vaccine simultaneously
- Signal assessment: after chart review, observed rate of 0.26 cases/1 million vaccinated, which is below published VSD rate of 1.6 cases/1 million vaccinated

Statistical signal week of Nov 11, 2018 for anaphylaxis following ccIIV4 in current vs. historical analysis*

Risk interval	Age group	Vaccine doses	Observed # events	Expected # events	RR	Log likelihood ratio (LLR)	Critical value of LLR
0-2 days	≥4 years	342,965	4	0.526	7.61	4.64	3.06

- For end-of-season analysis, chart reviewed 7 potential cases (3 additional cases)
- Signal assessment: after adjudication, 0 cases were determined to be related to vaccine
  - Most had symptoms prior to vaccination and other exposures included codeine, naproxen, milk, and gentamicin

*Self-controlled risk interval analysis (that signaled Dec 9, 2019) included the same exposed cases as in the current vs. historical analysis

Bell’s palsy

Statistical signal week of Dec 9, 2018 for Bell's palsy following ccIIV4 in self-controlled risk interval analysis

Risk interval	Age group	Vaccine doses	Events in risk window (1 to 42d)	Events in comparison window (-56 to -15d)	RR	Log likelihood ratio (LLR)	Critical value of LLR
1-42 days	4-17 yr	45,453	4	1	4	4.3944	3.4657

Assessment of statistical signal for Bell's palsy following ccIIV4

- Chart confirmed self-controlled risk interval (SCRI) analysis:
  - Risk window cases chart review (n=4)
    - 1 case had an initial diagnosis of Bell's palsy, later determined that symptoms were related to acute otitis media (on day 4 after vaccination)
    - 3 cases determined to be Bell's palsy with symptom onset in risk window
  - Comparison window case chart review (n=1)
    - 1 case determined to be Bell's palsy with symptom onset 55 days prior to vaccination
  - Final chart reviewed SCRI signal assessment: 3 cases in risk window, 1 case in comparison window, RR=3.0 (95% CI: 0.31-28.8)
- Current vs. historical analysis using automated data: 4 observed cases, 1.51 expected cases, RR=2.65, LLR=1.41, critical value of LLR=3.99

Seizures

Statistical signal week of Nov 25, 2018 for seizures following IIV4 in self-controlled risk interval analysis

Children aged 6-23 months old

Risk interval	Age group	vaccine doses	Events in risk window (0-1d)	Events in comparison window (14-20d)	RR	Log likelihood ratio (LLR)	Critical value of LLR
0-1 days	6-23 months	93,892	10	11	3.18	3.273	3.0082

Statistical signal for seizures following IIV4

Children aged 24-59 months old

Self-controlled risk interval analysis: statistical signal week of Nov 4, 2018

Risk interval	Age group	vaccine doses	Events in risk window (0-1d)	Events in comparison window (14-20d)	RR	Log likelihood ratio (LLR)	Critical value of LLR
0-1 days	24-59 months	106,853	8	4	6.125	4.3235	3.0082

Current vs. historical analysis: statistical signal week of Dec 9, 2018

Risk interval	Age group	vaccine doses	Obs. # events	Exp. # events	RR	Log likelihood ratio (LLR)	Critical value of LLR
0-1 days	24-59 months	151,826	11	4.80	2.29	2.91	2.87

Seizures: final self-controlled risk interval (SCRI) analysis using chart confirmed cases of febrile seizure

Age group	Events in risk window (0-1 days)	Events in comparison window (14-20 days)	Incidence rate ratio IRR (95% CI)	Attributable risk per 100,000 doses administered
6-23 months	11	16	2.41 (1.12-5.18)	4.24
24-59 months	5	5	3.50 (1.01-12.09)	1.80
Vaccines (in 6-59 mo)				
IIV4 alone	6	9	2.33 (0.83-6.56)	1.60
IIV4 w/any other vax	10	12	2.92 (1.26-6.75)	4.84
IIV4 w/PCV13	5	7	2.50 (0.79-7.88)	4.73

Guillain-Barré Syndrome (GBS)

Statistical signal week of Dec 9, 2018 for Guillain-Barré Syndrome following IIV3 high-dose in SCRI analysis

Self-controlled risk interval analysis: statistical signal week of Dec 9, 2018

Risk interval	Age group	Vaccine doses	Events in risk window (1-42d)	Events in comparison window (43-84d)	RR*	Log likelihood ratio (LLR)	Critical value of LLR
1-42 days	≥65 years	614,200	5	0	11	3.4657	3.3914

Last self-controlled risk interval analysis: Apr 3, 2019

Risk interval	Age group	Vaccine doses	Events in risk window (1-42d)	Events in comparison window (43-84d)	RR	Log likelihood ratio (LLR)	Critical value of LLR
1-42 days	≥65 years	645,362	8	1	8	---	---

*When denominator is 0, 0.5 is added to both numerator and denominator to estimate relative risk

Assessment of statistical signal for Guillain-Barré Syndrome (GBS) following IIV3 high-dose

- Chart reviews and adjudication
  - Risk window (n=8): 1 GBS case classified as Brighton Collaboration Level 2
    - Other 7 GBS cases ruled out as prevalent/non-incident cases, alternate diagnoses, symptom onset prior to or on day of vaccination, lack of clinical evidence
  - Comparison window (n=1): 1 GBS case classified as Brighton Collaboration Level 1
  - After case adjudication (above), RR=1.0 comparing 1 case in the risk window to 1 case in the comparison window
- No statistical signal has been observed by Apr 3, 2019 for the corresponding current vs. historical analysis
  - RR=1.60, LLR=0.76, critical value of LLR=3.03

FDA assessment of Guillain-Barré syndrome following influenza vaccine

from **Medicare data**

FDA/CDC/CMS analysis of Guillain-Barré syndrome risk following influenza vaccine

Slides courtesy Rich Forshee, PhD

FDA/CDC/CMS Analysis of GBS Risk: Methods

- FDA conducted a self-controlled risk interval (SCRI) analysis with an 8-21 day risk interval for the association between influenza vaccines and GBS
- Data source was Medicare claims for recipients 65+y
- This was an early vaccination cutoff analysis that included beneficiaries vaccinated between August 11, 2018 and November 9, 2018
- Included more than 12 million beneficiaries in total; more than 7 million who received IIV3-HD
- An end-of-season analysis is planned

FDA/CDC/CMS Analysis of GBS Risk: Results

- Highest point estimate was for IIV3-HD
  - 16 cases in 8-21 day risk interval; 26 cases in 43-84 day control interval
  - Odds ratio = 1.85 (95% CI 0.99, 3.44; p-value = 0.054)
  - Attributable risk = 0.98 per million vaccinations
  - Magnitude of the odds ratio is similar to what has been observed in previous seasons
  - Attributable risk is consistent with the labeled risk of GBS

Summary

Summary of VSD RCA monitoring for influenza vaccine, 2018-2019[1]

- Following signal assessment and end-of-season analysis:
  - Statistical signals for anaphylaxis following IIV4 and ccIIV4 ruled out
  - Finding of an elevated risk for Bell's palsy following ccIIV4 in 4-17 year olds (RR=3.0, 95% CI 0.31-28.8) was based on a small number of cases and doses; CDC will continue to monitor and explore options for additional analyses
    - 2001-2006 case-centered analysis with IIV3 did not find an association[2]
  - Statistical signal for GBS following IIV3-HD (65+ years old) ruled out
  - Preliminary FDA analysis of GBS following IIV3-HD in CMS data indicate that the risk, if any, is no greater than in some previous seasons and consistent w/labeled risk of GBS

[1]Including FDA analysis of GBS and IIV3-HD; [2]Rowhani-Rahbar et al. Immunization and Bell's palsy in children: a case-centered analysis. Am J Epidemiol. 2012;175(9):878-85.

Summary of VSD RCA monitoring for influenza vaccine, 2018-2019 (cont.)

- Final self-controlled risk interval (SCRI) analysis of confirmed febrile seizure cases showed:
  - An elevated IRR in children aged 6-23 and 24-59 months
  - Risk was similar in those who received IIV4 alone and those who received IIV4 simultaneously with other vaccines, including PCV13
    - In some previous seasons risk was greater with simultaneous PCV13
  - Attributable risk was less than that observed in some previous influenza seasons and less than the febrile seizure risk associated with MMR or PCV

Clinical Research Studies in Progress

from the **Clinical Immunization Safety Assessment (CISA) Project**

Vaccine safety monitoring

CISA

Clinical Immunization Safety Assessment

7 participating medical research centers*

*Boston Medical Center, MA; Cincinnati Children's Hospital Medical Center, OH; Columbia University, NY; Duke University, NC; Johns Hopkins University, MD; Kaiser Permanente Northern California, CA; Vanderbilt University TN

vaccine safety experts

- assist U.S. healthcare providers with complex vaccine safety questions about their patients CISAeval@cdc.gov†
- conduct clinical research

†More information about clinical consults available at http://www.cdc.gov/vaccinesafety/Activities/CISA.html

Current CISA influenza vaccine studies

Title (ClinicalTrials.gov number)	Enrollment completed (influenza season)	CISA Study Sites
Safety and immunogenicity of simultaneous Tdap and IIV in pregnant women (NCT02783170)	Yes* (2016-17 & 2017-18)	Duke University (lead), Cincinnati Children's Hospital Medical Center
Safety of LAIV4 in children with asthma (NCT03600428 and NCT02967393)	No	Vanderbilt University (lead), Cincinnati Children's Hospital Medical Center, Duke University
Adjuvanted versus high-dose IIV in older adults (NCT03183908)	Yes (2017-18 & 2018-19)	Duke University (lead), Boston Medical Center, Cincinnati Children's Hospital Medical Center‡
Fever after simultaneous versus sequential vaccination in young children (NCT03165981)	Yes* (2017-18)	Duke University, Kaiser Permanente Northern California
Safety of quadrivalent recombinant influenza vaccine (RIV4) (Flublok® Quadrivalent) vs IIV4 (Flublok®) in pregnant women (NCT03969641)	No	Duke University (lead), Cincinnati Children's Hospital Medical Center, Boston Medical Center

*Results posted on ClinicalTrials.gov ‡Cincinnati Children's Hospital Medical Center site is supported via a sub-contract with Boston Medical Centers for this study

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Thank you

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