Influenza vaccine safety monitoring: Findings from the 2018-2019 season

September 2019 National Vaccine Advisory Committee (NVAC) meeting

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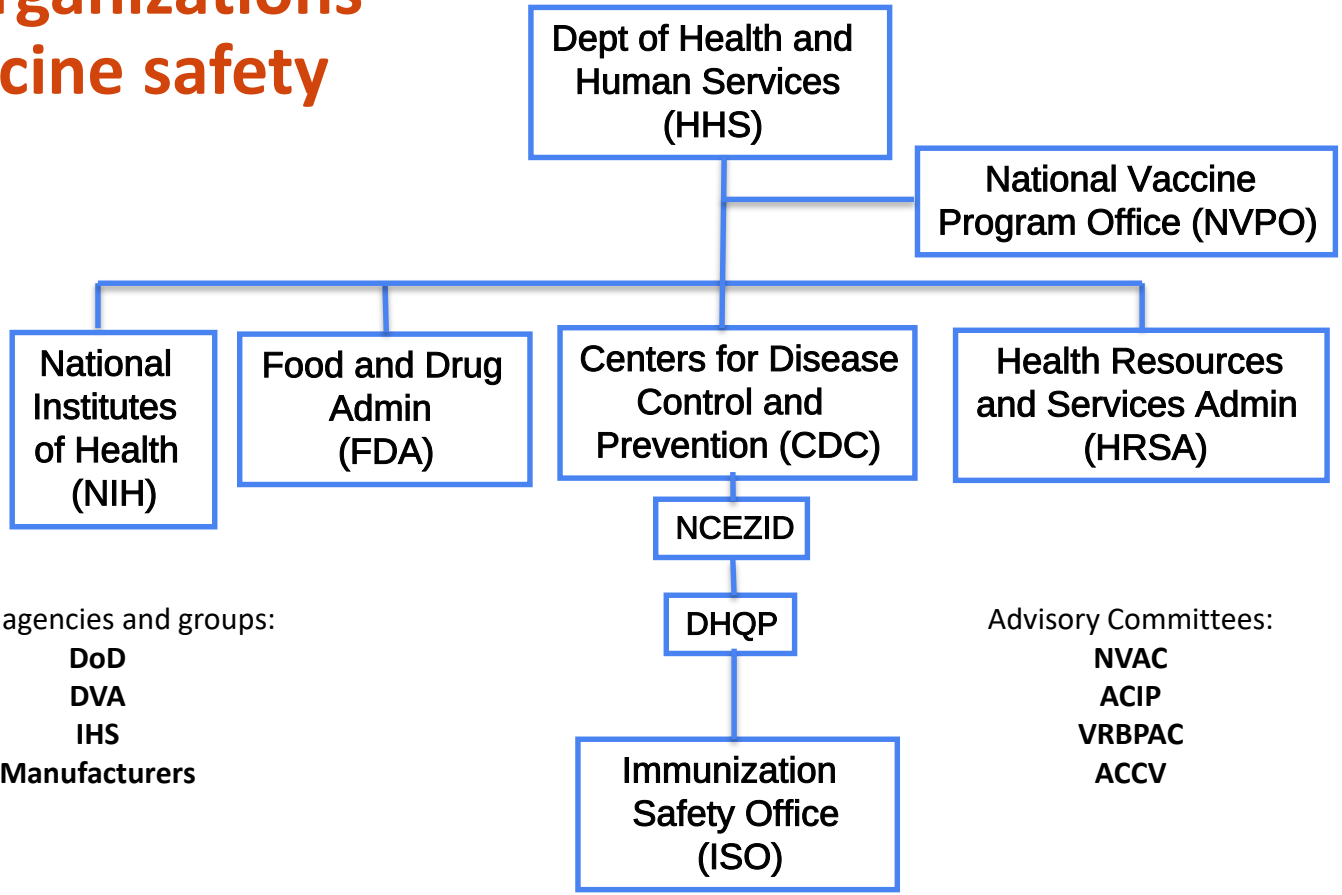
Overview

- 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

Primary HHS organizations engaged in vaccine safety activities



US Post-licensure Vaccine Safety System

System	Collaboration	Description
Vaccine Adverse Event Reporting System (VAERS)	CDC and FDA	Frontline spontaneous reporting system to detect potential vaccine safety signals
Vaccine Safety Datalink (VSD)	CDC and 8 Integrated Health Care Systems	Large linked database system used for active surveillance and research >10 million members
Clinical Immunization Safety Assessment (CISA) Project	CDC and 7 Academic Centers	Expert collaboration that conducts individual clinical vaccine safety assessments and clinical research
Post-Licensure Rapid Immunization Safety Monitoring Program (SENTINEL/PRISM)	FDA and partner organizations	Large distributed database system used for active surveillance and research ~170 million individuals

There are four components to the US Vaccine Safety Monitoring Infrastructure

The Vaccine Adverse Event Reporting System, or VAERS, is the frontline spontaneous reporting system to detect potential vaccine safety issues;

The Vaccine Safety Datalink, or VSD, is a large linked database system used for active surveillance and research;

The Clinical Immunization Safety Assessment Project, or CISA, is an expert collaboration that conducts individual clinical vaccine safety assessments and clinical research

And Post Licensure Immunization Safety Monitoring Program, or PRISM, which is a FDA program that monitors and evaluates the safety of vaccines on a very large population

Safety monitoring update

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

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)

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

VAERS reports, 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

VAERS reports, 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

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, including vaccinations during pregnancy (data not shown)
- Surveillance for the 2019-2020 influenza season is underway

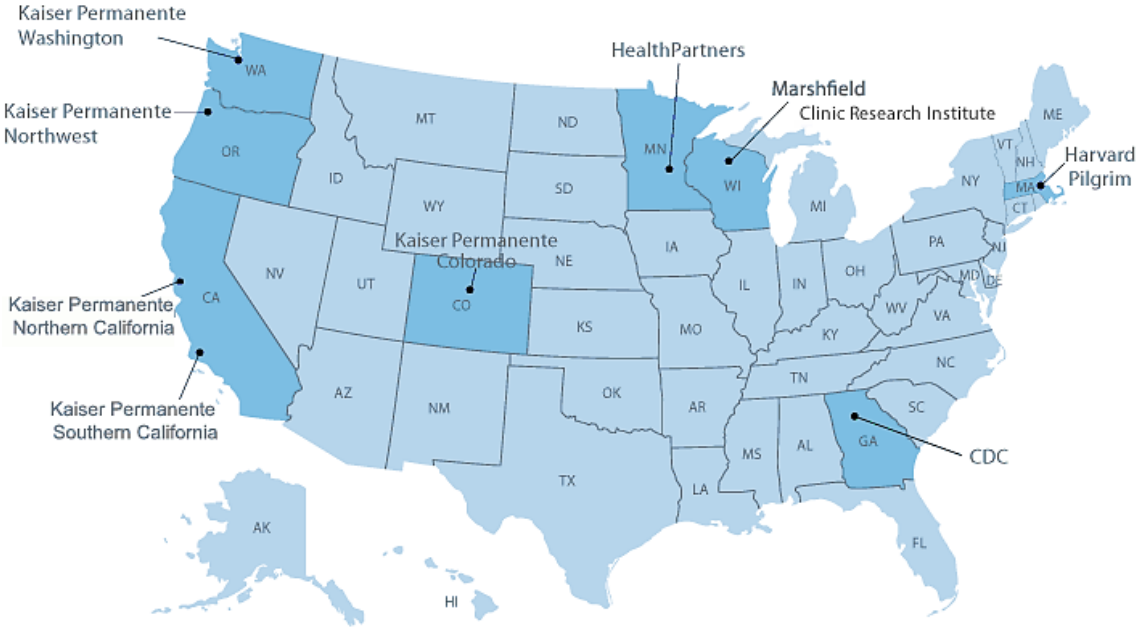
[1]Includes clinical review of all reports and available medical records for the specific vaccines and outcomes and conditions specified

Rapid Cycle Analysis (RCA)

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

VSD

Vaccine Safety Datalink

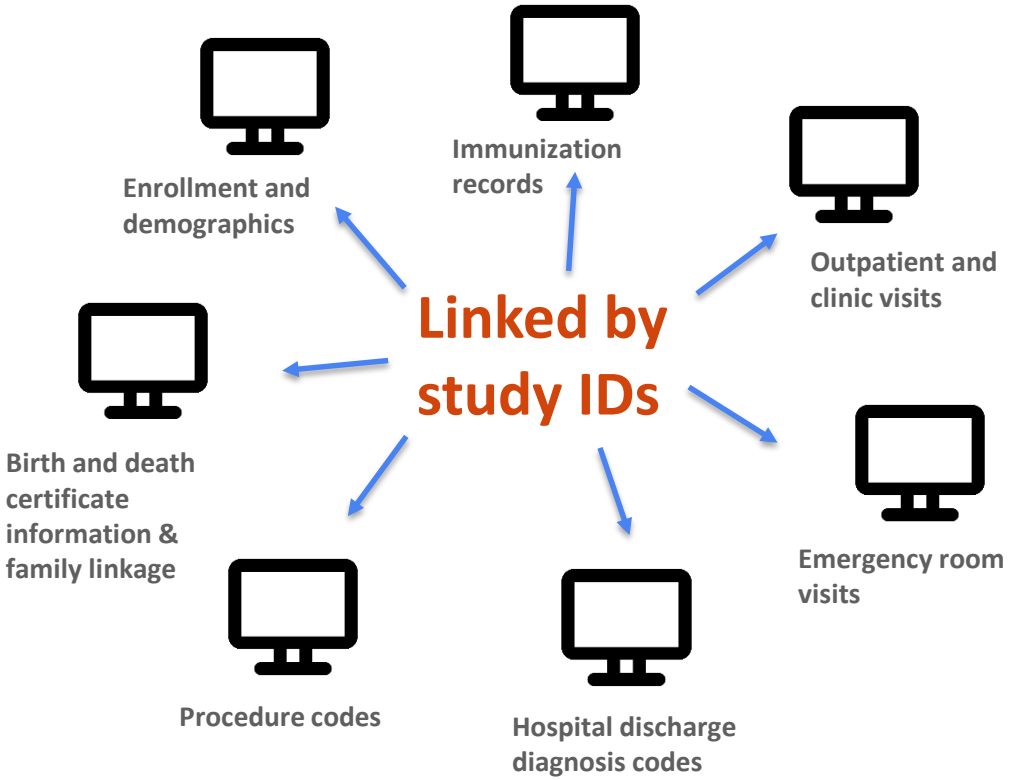


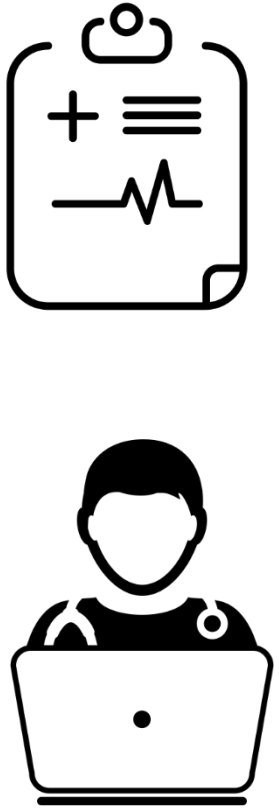
8 participating integrated healthcare organizations

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
- Links vaccination data to health outcome data
- Used for surveillance and research

VSD electronic files + chart review

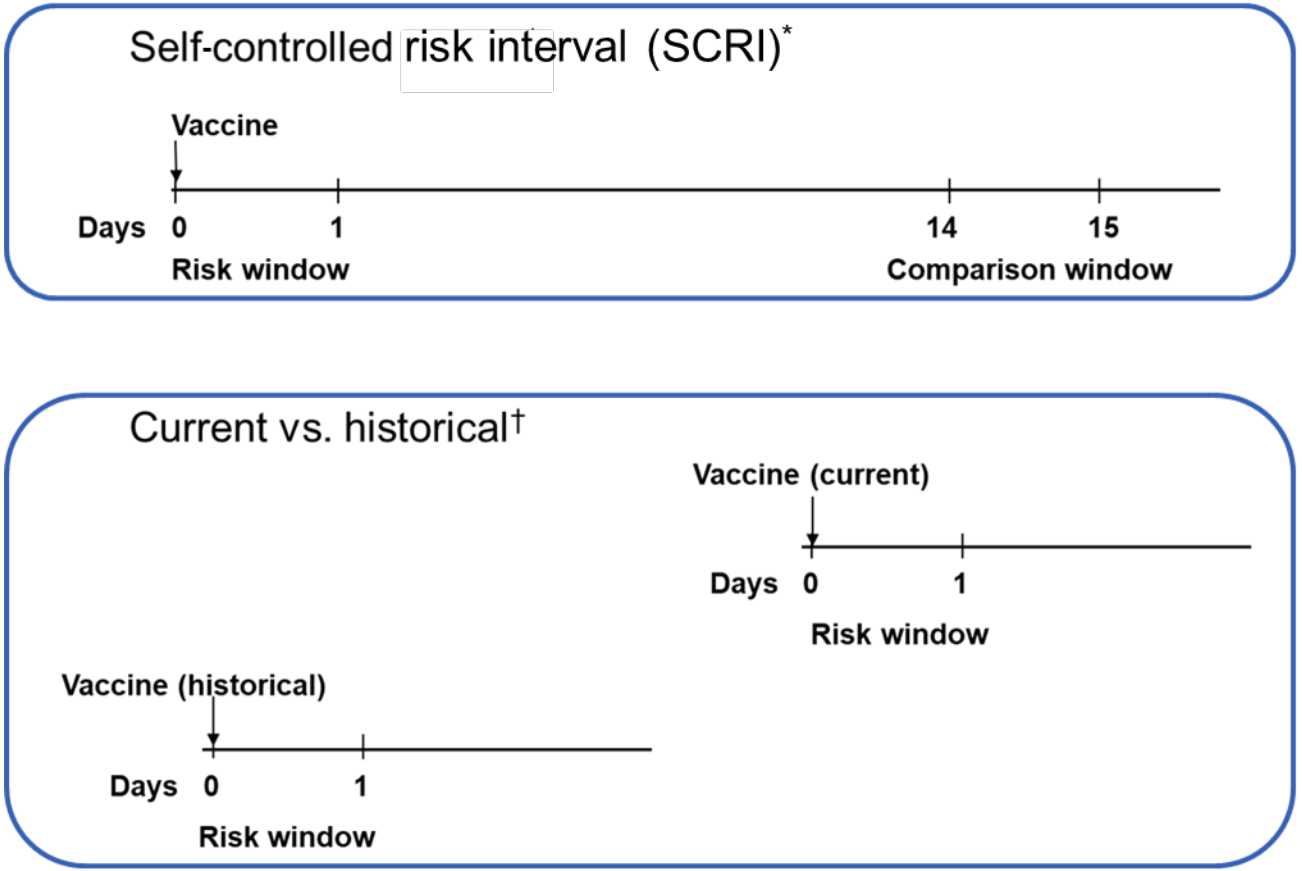




Images created by Wilson Joseph, Megan Mitchell, Ananth, and Iga from the noun project

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 surveillance tool

- A surveillance activity (signal detection and signal refinement), which is not the same as an epidemiologic study (signal evaluation, causality assessment)
- Near real-time vaccine-safety monitoring (using sequential monitoring techniques)
- Employs an automated analysis of ICD-coded diagnoses from administrative data
- 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 further evaluations, including 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 in VSD through April 3, 2019; percentages subject to rounding

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						

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

- Following signal assessment and end-of-season analysis:
  - Statistical signals for **anaphylaxis** following IIV4 and ccIIV4 ruled out (0 cases confirmed following chart review)
  - Chart review confirmed only a small number of **Bell's palsy** cases following ccIIV4 in 4-17 year olds (3 vs 1), with resultant unstable relative risk estimate (RR=3.0, 95% CI 0.31-28.8)

Final SCRI analysis of confirmed febrile seizure cases showed an elevated IRR in children aged 6-23 and 24-59 months

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

Attributable risk was less than that observed in some previous influenza seasons and less than the febrile seizure risk associated with MMR or PCV

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 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/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

Study Information

Flu-vaccinated beneficiaries vaccinated between August 11, 2018 and November 9, 2018

More than 12 million beneficiaries in total. More than 7 million who received high dose influenza vaccine.

There were 64 GBS claims in total, 42 of which were in beneficiaries who received high dose influenza vaccine.

Key Findings

None of the results from the SCRI analyses found a statistically significant relationship between flu vaccination and an increased risk of GBS;

In the primary analysis using days 8-21 as the risk window, the highest point estimate was an odds ratio of 1.85 for the association between vaccination with the high-dose flu vaccine and GBS. The 95% confidence interval was (0.99, 3.44) with a p-value of 0.054. The attributable risk was 0.98 per million vaccinations.

Initial Interpretation

While not statistically significant, the point estimate and confidence interval cannot rule out some association between HD flu vaccination and GBS. The end of season analysis could show a statistically significant association if the additional data allow a more precise estimate.

However, the magnitude of the odds ratio is similar to what has been observed in previous seasons.

The attributable risk is consistent with the labeled risk of GBS.

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 of VSD monitoring for influenza vaccine, 2018-2019

- Following signal assessment and end-of-season analysis:
  - Statistical signals for anaphylaxis following IIV4 and ccIIV4 ruled out
  - Follow-up of statistical signal for Bell's palsy following ccIIV4 in 4-17 year olds confirmed only a small number of cases resulting in unstable risk estimates
  - In children less than 5 years old, found an increased risk of febrile seizures following IIV4 similar to some previous influenza seasons
  - 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 with labeled risk of GBS

Clinical Research Studies in Progress

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

Vaccine safety monitoring

vaccine safety experts

CISA

Clinical Immunization Safety Assessment

7 participating medical research centers*

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

*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

†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 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

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Extra slides

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.

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

Risk interval	Age group	vaccine doses	Obs. # events	Exp. # events	RR	Log likelihood ratio (LLR)	Critical value of LLR
0-2 days	≥6 mo	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	Obs. # cases	Exp. # cases	RR	Log likelihood ratio (LLR)	Critical value of LLR
0-2 days	≥4 yr	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

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

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 yr	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 yr	645,362	8	1	8	---	---

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

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)