End-of-Season Update: 2017-2018 Influenza Vaccine Safety Monitoring

June 2018 Advisory Committee on Immunization Practices (ACIP) meeting

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June 20, 2018

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

U.S. influenza vaccine abbreviations[1]

Abbreviation	Vaccine
IIV3	Trivalent inactivated influenza vaccine
IIV4	Quadrivalent inactivated influenza vaccine
IIV3-HD	High-dose trivalent inactivated influenza vaccine (approved for use in individuals 65+ years old)
IIV3-ID, IIV4-ID	Intradermal trivalent and quadrivalent inactivated influenza vaccines
ccIIV3, ccIIV4	Cell culture-based trivalent and quadrivalent inactivated influenza vaccine
RIV3, RIV4	Recombinant trivalent and 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

Vaccine Adverse Event Reporting System (VAERS) surveillance for the 2017-2018 influenza season

Vaccine Adverse Event Reporting System (VAERS)[1]

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

As a hypothesis generating system, VAERS identifies potential vaccine safety concerns that can be studied in more robust data systems

[1]Co-managed by CDC and FDA (http://vaers.hhs.gov)

VAERS surveillance: methods

- U.S. influenza vaccine reports received through May 11, 2018 (vaccinated July 1, 2017 through April 30, 2018)
- 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, and serious pregnancy reports
  - 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 or permanent disability (FDA routinely reviews all serious reports)

U.S. reports to VAERS following IIV3, IIV4, and IIV3-HD, 2017-2018

-	IIV3 N (%)	IIV4 N (%)	IIV3-HD N (%)
Total reports[1]	571	4,307	2,413
Non-serious reports	539 (94%)	4,044 (94%)	2,325 (96%)
Serious reports[2]	32 (6%)	263 (6%)	88 (4%)
Guillain-Barré syndrome (GBS)	7 (1.2%)	54 (1.3%)	12 (0.5%)
Anaphylaxis[3]	4[4] (0.7%)	27[4] (0.6%)	3[4] (0.1%)

- No data mining signals for Guillain-Barré syndrome or anaphylaxis 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 or permanent disability; [3]Onset interval 0-1 days post vaccination for anaphylaxis; [4]One IIV3, six IIV4, and one IIV3-HD anaphylaxis reports were in persons with a history of egg allergy

U.S. reports to VAERS following ccIIV4, aIIV3, RIV3, RIV4 and IIV4-ID, 2017-2018

	ccIIV4 N (%)	aIIV3 N (%)	RIV3 N (%)	RIV4 N (%)	IIV4-ID N (%)
Total reports[1]	924	503	43	47	67
Non-serious reports	888 (96%)	485 (96%)	42 (98%)	44 (94%)	64 (96%)
Serious reports[2]	36 (4%)	18 (4%)	1 (2%)	3 (6%)	3 (4%)
Guillain-Barré syndrome (GBS)	9 (1%)	3 (0.6%)	0 (0%)	0 (0%)	0 (0%)
Anaphylaxis[3]	6[4] (0.7%)	0 (0%)	0 (0%)	1[4] (2%)	2 (3%)

- No data mining signals for Guillain-Barré syndrome or anaphylaxis in association with ccIIV4, aIIV3, RIV3, RIV4, or IIV4-ID

[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 or permanent disability; [3]Onset interval 0-1 days post vaccination for anaphylaxis; [4]Three ccIIV4 reports and the single RIV4 anaphylaxis report were in persons with a history of egg allergy

Reports to VAERS following vaccination during pregnancy, 2017-2018

Report Type	N
Total reports (IIV4=23, ccIIV4=17, IIV3=9, RIV4=2, aIIV3=1, unknown brand=7)	59
Median maternal age (range) at vaccination	31 years (17-43)
Median gestational age (range) at vaccination, n=43 with GA reported	16 weeks (2-39)
Trimester of vaccination, n=46 reports with trimester documented • 1st trimester • 2nd trimester • 3rd trimester	 20 (44%) 12 (26%) 14 (30%)
Pregnancy-specific adverse event reports • Spontaneous abortion (8) • Preterm delivery (1) • Morning sickness (2) • Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome (1) • Uterine inversion (1)	13 (22%)
Non-pregnancy specific adverse event reports	19 (32%)[1]
No adverse event documented in report	27 (46%)[2]

[1] Non-anaphylaxis allergic reaction (9), injection site reaction/pain in extremity (5), shoulder injury related to vaccine administration (1), tingling in arm (1), multiple sclerosis (1), epistaxis (1), shoulder dystocia in infant (1)

[2]12 vaccination errors where the following were given: Fluzone High-Dose (2), Fluad (1), MMR or varicella (2), HPV (1), thimerosal-containing vaccine (1) , influenza vaccine instead of Tdap (1), expired vaccine (1), two doses of Flulaval given 3 weeks apart

Summary of VAERS monitoring

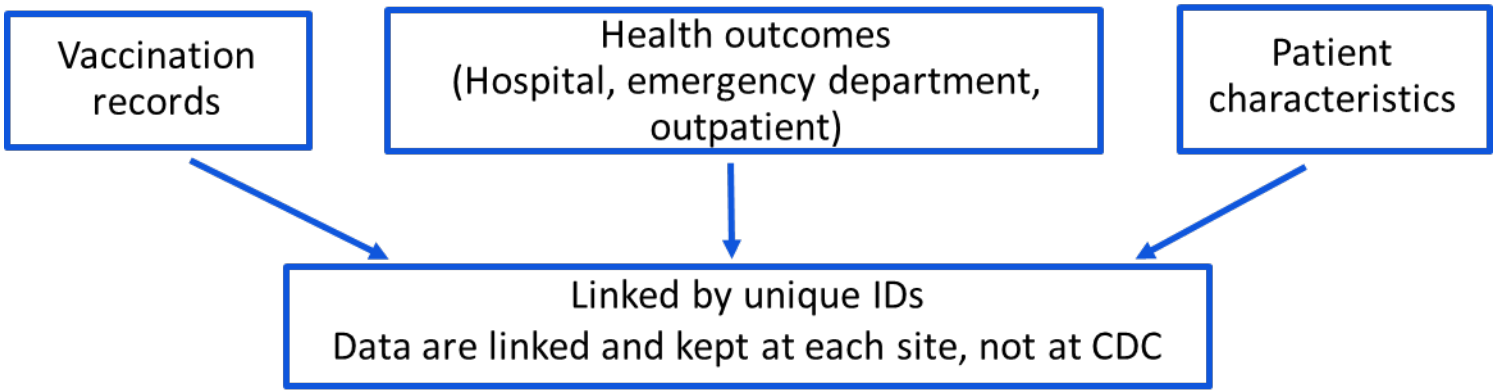
- No new safety concerns detected for IIV3/IIV4, IIV3-HD, ccIIV4, aIIV3, RIV3/RIV4, or IIV4-ID during the 2017-2018 influenza season
- Surveillance for the 2018-2019 influenza season will include enhanced safety monitoring[1] for:
  - aIIV3 (FLUAD®)
  - RIV4 (Flublok® Quadrivalent)
  - Pregnancy reports
  - 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

Vaccine Safety Datalink Rapid Cycle Analysis for the 2017-2018 influenza season

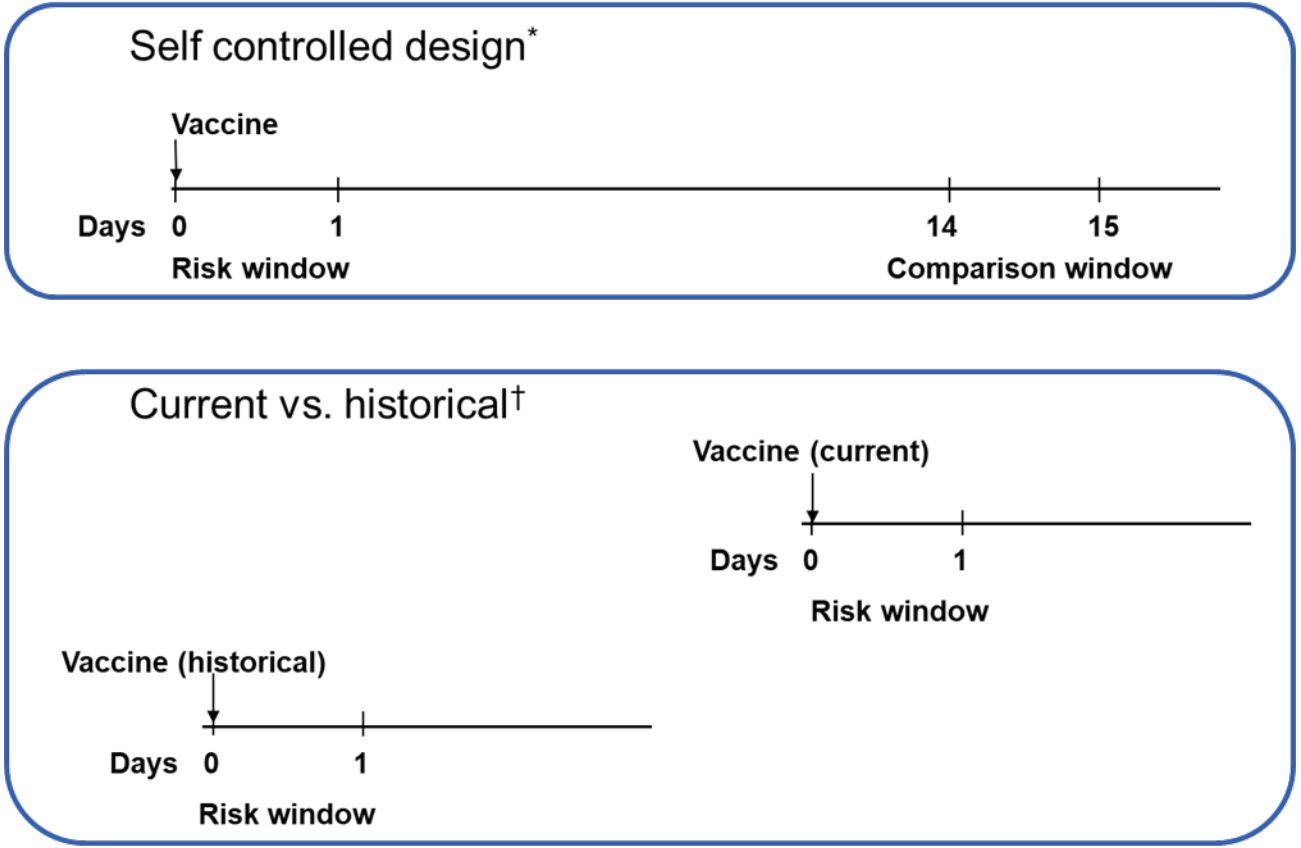
Vaccine Safety Datalink (VSD)

- Established in 1990
- Collaboration between CDC and several integrated healthcare plans
- Data on over 10 million persons per year (~3% of U.S. population)
- Links vaccination data to health outcome data



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 IIV3 and 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

Vaccine Safety Datalink Rapid Cycle Analysis outcomes for the 2017-2018 influenza season

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

[1]For self-controlled risk interval design

Influenza vaccine doses administered in the VSD (2017-2018 influenza season)

Vaccine	Dose 1 doses administered[1] in all ages
IIV3	2,109,217 (39%)
IIV4	2,368,274 (44%)
IIV3 High-Dose	415,324 (8%)
ccIIV3/ccIIV4	187,577 (4%)
aIIV3	254,436 (5%)
RIV3/RIV4	3,892 (0.07%)
IIV4 Intradermal	6,103 (0.11%)
Total	**5,344,823**

[1]Doses administered through April 11, 2018; percentages subject to rounding errors

2017-2018 VSD Rapid Cycle Analysis results for IIV3 (self-controlled risk interval design)

Pre-specified outcome	Risk interval	Age group	IIV3 doses	Events in risk window	Events in control window	Relative risk	LLR[1]	Critical value
Anaphylaxis	0-2	>=6 mo	2,109,217	4	2	2	0.3398	3.3914
Bell's palsy	1-42	<18 yr	302,076	11	13	0.8462	0	4.051
		18-49 yr	893,372	127	171	0.756	0	4.1478
		>=50 yr	913,769	196	316	0.6203	0	4.1589
Encephalitis	1-21	>=6 mo	2,109,217	1	18	0.1111	0	3.3298
GBS	1-42	>=6 mo	2,109,217	7	16	0.4375	0	3.4657
Seizures	0-1	6-23 mo	4,254	0	0	N/A	-	-
		24-59 mo	19,827	0	0	N/A	-	-
Transverse myelitis	1-21	>=6 mo	2,109,217	0	0	N/A	-	-

[1]Log-likelihood ratio did not exceed the critical value for any pre-specified outcomes

2017-2018 VSD Rapid Cycle Analysis results for IIV4 (self-controlled risk interval design)

Pre-specified outcome	Risk interval	Age group	IIV4 doses	Events in risk window	Events in control window	Relative risk	LLR1*	Critical value
Anaphylaxis	0-2	>=6 mo	2,368,274	10	6	1.6667	0.5053	3.3914
Bell's palsy	1-42	<18 yr	773,840	19	27	0.7037	0	3.3914
		18-49 yr	734,968	102	142	0.7183	0	3.4657
		>=50 yr	859,466	167	327	0.5107	0	3.656
Encephalitis	1-21	>=6 mo	2,368,274	8	18	0.8889	0	3.2958
GBS	1-42	>=6 mo	2,368,274	12	12	1	0	3.3914
Seizures	0-1	6-23 mo	196,699	8	22	1.2727	0.1641	3.0082
		24-59 mo	168,165	6	13	1.6154	0.4421	3.0082
Transverse myelitis	1-21	>=6 mo	2,368,274	2	3	1.3333	0.0486	3.2958

[1]Log-likelihood ratio did not exceed the critical value for any pre-specified outcomes

2017-2018 VSD Rapid Cycle Analysis results for IIV3 (current vs. historical design)

Pre-specified outcome	Risk interval	Age group	IIV3 Doses	Obs. # of AEs	Exp. # of AEs	Relative risk	LLR[1]	Critical value
ADEM	1-21	>=6 mo	2,093,446	1	0.55	1.83	0.15	3.03
Anaphylaxis	0-2	>=6 mo	2,093,446	5	4.94	1.01	0	3.67
Bell's palsy	1-42	<18 yr	301,397	11	6.84	1.61	1.07	3.86
		18-49 yr	910,220	128	124.54	1.03	0.05	4.22
		>=50 yr	905,453	196	173.83	1.13	1.36	4.34
Encephalitis	1-21	>=6 mo	2,093,446	2	9.11	0.22	0	3.82
GBS	1-42	>=6 mo	2,093,446	7	13.00	0.54	0	3.91
Seizures	0-1	6-23 mo	4,254	0	0.29	0	0	3.75
		24-59 mo	19,827	0	0.57	0	0	3.46
Transverse myelitis	1-21	>=6 mo	2,093,446	0	1.57	0	0	3.39

[1]Log-likelihood ratio did not exceed the critical value for any pre-specified outcomes

2017-2018 VSD Rapid Cycle Analysis results for IIV4 (current vs. historical design)

Pre-specified outcome	Risk interval	Age group	IIV4 doses	Obs. # of AEs	Exp. # of AEs	Relative risk	LLR[1]	Critical value
ADEM	1-21	>=6 mo	2,197,805	1	0.71	1.4	0.05	3.03
Anaphylaxis	0-2	>=6 mo	2,197,805	11	4.20	2.62	3.8	3.67
Bell's palsy	1-42	<18 yr	734,899	19	17.24	1.1	0.09	3.86
		18-49 yr	671,239	102	94.75	1.08	0.27	4.22
		>=50 yr	797,160	167	165.68	1.01	0.01	4.34
Encephalitis	1-21	>=6 mo	2,197,805	10	10.51	0.95	0	3.82
GBS	1-42	>=6 mo	2,197,805	12	15.82	0.76	0	3.91
Seizures	0-1	6-23 mo	196,552	8	13.16	0.61	0	3.75
		24-59 mo	161,417	6	4.48	1.34	0.23	3.46
Transverse myelitis	1-21	>=6 mo	2,197,805	2	1.96	1.02	0	3.39

[1]Log-likelihood ratio exceeded the critical value for anaphylaxis (meets threshold for a "statistical signal"); log-likelihood ratio did not exceed the critical value for any other pre-specified outcomes

Assessment of statistical signal for anaphylaxis in 2017-2018 VSD RCA for IIV4 (current vs. historical design)

- Statistical signal detected the week starting Oct 15, 2017
  - 9 anaphylaxis cases observed, 1.13 cases expected (RR 8.00)
    - By week starting Nov 5, 2017, 10 cases observed, 2.06 cases expected (RR 4.84)
- Chart review of the 10 anaphylaxis cases
  - 9 cases had symptom onset prior to vaccination (5 with possible or probable environmental triggers)
  - 1 probable case with onset at ~12 hours and no other suspected triggers
- Signal was not confirmed after chart review; 1 additional anaphylaxis case detected in the week starting Jan 7, 2018 and was not reviewed

Summary of 2017-2018 Vaccine Safety Datalink influenza vaccine Rapid Cycle Analysis (RCA)

- No confirmed RCA signals in either self-controlled risk interval or current vs. historical designs
- Data for IIV3-High Dose, ccIIV3/ccIIV4, aIIV3, RIV3/RIV4 and IIV4-ID limited due to low use, but were generally reassuring

Vaccine Safety Datalink (VSD) influenza vaccine safety monitoring and research for 2018-2019 influenza season

- Conduct self-controlled risk interval and current vs. historical Rapid Cycle Analysis (RCA)
  - Same pre-specified conditions and risk intervals
  - Will combine standard dose IIV3 and IIV4 into a single vaccine category for monitoring, but if statistical signals are detected we will analyze these vaccine types separately

FDA's monitoring of Guillain-Barré syndrome (GBS) following influenza vaccination among Medicare beneficiaries

2017-2018 season

Tom Shimabukuro on behalf of the Surveillance Team
ACIP meeting, June 20-21, 2018

FDA's surveillance approach

Active surveillance: Medicare data

USPRT: Updating Sequential Probability Ratio Test (MaCurdy, 2012; Burwen, 2012; Franks, 2014)

Medicare data

Fee-for-Service beneficiaries (Medicare Parts A and B)

Influenza vaccination and GBS diagnosis information comes from:

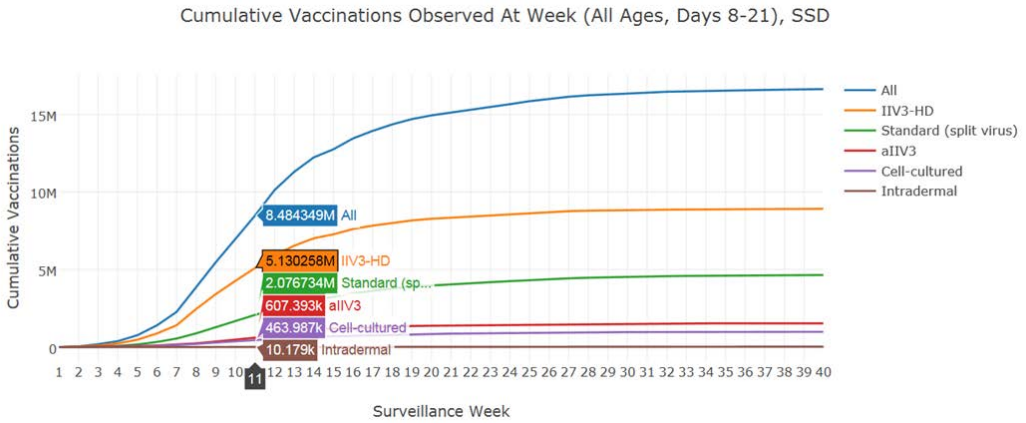
- **Common Working File (CWF) Data**
  - Updated weekly
- **Shared Systems Data (SSD)**
  - Updated daily
  - Sourced from an earlier point in CMS's data processing than CWF

Near real-time surveillance
Methods

[1] MaCurdy, 2012; Burwen, 2012; Franks, 2014;
[2] Manuscript under preparation

- Sequential testing using USPRT[1]
- 5-year historical cohort as comparison group
- One-sided alpha of 0.05 apportioned equally using a constant alpha-spending plan among 5 pre-established consecutive weekly tests (weeks 7-11)2
- Risk windows of days 8-21 (primary) and days 1-42 post-vaccination
- Null hypothesis: The observed rate should not be higher than 2.5 times the expected rate based on historical data[2]
- Overall analyses: all ages, all influenza vaccines
- Subgroup analyses: ≥65 years, all vaccines; ≥ 65 years, IIV3-High-dose; ≥ 65 years, inactivated standard dose (split virus) vaccine (IIV3/IIV4)

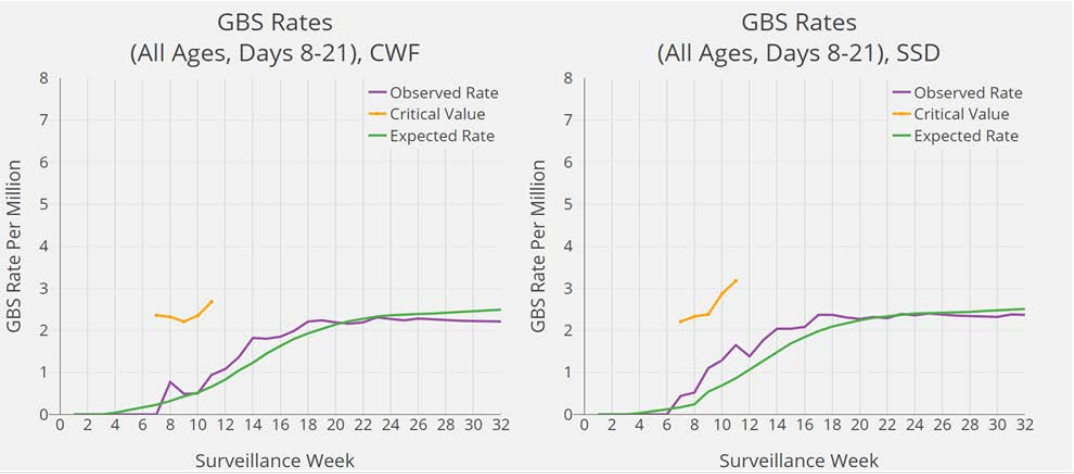
Near real-time surveillance Results



Cumulative vaccinations for 2017-18 observed at week 11; all vaccines and by vaccine type, all ages, days 8-21 (primary risk window)

Near real-time surveillance Results

Results of the 2017-18 near real-time surveillance do not show signals for a potential 2.5-fold increased risk of GBS in days 8-21 and 1-42 post-vaccination (data not shown) compared with the five prior historical seasons used as controls (2012-13 to 2016-17), either in the overall analyses (all ages, all influenza vaccines), or in the subgroup analyses (≥65 years, all vaccines; ≥65 years, IIV3-HD; ≥65 years, inactivated standard dose (split virus) vaccine (IIV3 and IIV4).



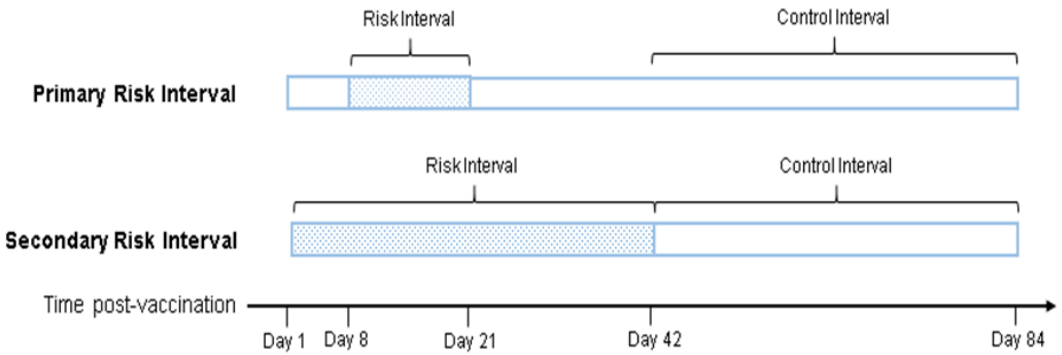
Perez-Vilar et al., Conference on Vaccinology Research, Bethesda, MD, April 23-25, 2018

End-of-season SCRI analyses
Methods

Population:

Fee-for-service beneficiaries ages ≥ 65 years

In the SCRI approach, each influenza-vaccinated beneficiary serves as their own control as we assess a beneficiary's risk of experiencing an outcome (GBS) after exposure (i.e., influenza vaccination) compared to the same beneficiary's risk of experiencing an outcome during a non-exposed time period. The study population for SCRI includes all exposed individuals, but only GBS cases contribute to the risk estimation



End-of-season SCRI analyses
Methods

- Vaccination data up to January 5th (approximately 95% of total vaccinees)

- GBS cases up to May 18th (among eligible vaccinees)

End-of-season SCRI analyses

Results

Vaccine type	Flu-Vaccinated Beneficiaries Number (%)
All vaccines combined	13,389,946 (100%)
High dose vaccine (HD)	8,148,446 (61%)
Standard dose (split virus) vaccine (IIV3 and IIV4)	2,844,565 (21%)
Adjuvanted trivalent vaccine (aIIV3)	1,374,935 (10%)

End-of-season SCRI analyses
Methods (claims-based)

Primary risk window (8-21 days)

SCRI analyses	Cases Risk Window (Days 8-21)	Cases Control Window (Days 43-84)	Odds Ratio (95% CI)	Attributable Risk (95%CI) (per million vaccinations)
Unadjusted analyses	23	66	1.05 (0.65, 1.68)	0.07 (-0.71, 0.85)
Seasonality -adjusted analyses	23	66	1.15 (0.71, 1.84)	0.23 (-0.56, 1.00)

Secondary risk window (1-42 days)

SCRI analyses	Cases Risk Window (Days 1-42)	Cases Control Window (Days 43-84)	Odds Ratio (95% CI)	Attributable Risk (95%CI) (per million vaccinations)
Unadjusted analyses	66	66	1.00 (0.71, 1.41)	0.00 (-1.67, 1.67)
Seasonality -adjusted analyses	66	66	1.09 (0.77, 1.53)	0.42 (-1.25, 2.08)

Conclusions

- Our near real-time surveillance did not show a risk of GBS higher than the pre-specified testing threshold (≥2.5-fold increased risk of GBS compared with the five prior historical seasons used as controls)
- Our end-of-season SCRI analyses using all seasonal influenza vaccines did not show any statistically significant GBS risk in the 8-21 and 1-42 days post-vaccination, with or without seasonality adjustments. Analyses by vaccine type are ongoing
- Unlike previous influenza seasons, the accelerated near real-time surveillance testing we introduced for 2017-2018 allowed us to quickly provide final interim results to FDA leadership in early December 2017
- Using SSD for the first time this season permitted us to reduce claims delay for both vaccinations and GBS cases, thus allowing for the use of larger numbers for analysis while still maintaining consistency of results when compared to CWF

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CISA study: Safety and Immunogenicity of FLUAD® vs. Fluzone® High-Dose in Older Adults: Update First Season (2017-2018), cont.

- Enrolled and randomized **279** participants during the first season
- Safety review
  - Safety panel of three vaccine safety experts who are not study investigators reviewed interim safety data on June 6, 2018
  - Each panel member concluded there were no substantial safety concerns observed

CISA study: Fever after simultaneous versus sequential vaccination in young children (ClinicalTrials.gov: NCT03165981)

- Design: randomized clinical trial (open label)
  - Children aged 12-16 months randomized 1:1 to receive simultaneous or sequential schedule

Schedule	Visit 1[1]	Visit 2 (2 weeks later)
Simultaneous	PCV13, DTaP, and IIV4	Health education (dental care)
Sequential	PCV13 and DTaP	IIV4 and health education

  - Primary outcome: Any fever on day 1 and/or day 2 following Visit 1 and/or Visit 2
- Enrolled and randomized **221** children (goal 280) during 2017-18 season[2]: paused early for widespread influenza activity; analysis in progress

[1]Can get other "non-study" vaccines at visit 1

[2]Duke University (Lead), Kaiser Permanente Northern California

Acknowledgments

CDC Immunization Safety Office

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Thank you

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