End-of-Season Update: 2016-2017 Influenza Vaccine Safety Monitoring

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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.

U.S. influenza vaccine abbreviations*

Vaccine	Abbreviation
Trivalent inactivated influenza vaccine	IIV3
Quadrivalent inactivated influenza vaccine	IIV4
High-dose trivalent inactivated influenza vaccine (approved for use in individuals 65+ years old)	IIV3-HD
Intradermal trivalent and quadrivalent inactivated influenza vaccines	IIV3-ID IIV4-ID
Cell culture-based trivalent and quadrivalent inactivated influenza vaccine	ccIIV3 ccIIV4
Recombinant trivalent and quadrivalent inactivated influenza vaccine	RIV3 RIV4
Adjuvanted trivalent inactivated influenza vaccine (approved for use in individuals 65+ years old)	aIIV3

*IIV is commonly used when discussing inactivated influenza vaccines as a general category

Vaccine Adverse Event Reporting System (VAERS) surveillance for the 2016-2017 influenza season

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

Strengths

- National data; accepts reports from anyone
- Rapid signal detection
- Can detect rare adverse events
- Collects information about vaccine, characteristics of vaccinee, adverse event†

Limitations

- Reporting bias
- Inconsistent data quality and completeness
- Lack of unvaccinated comparison group
- Generally cannot assess if vaccine caused an AE

*VAERS website: http://vaers.hhs.gov
†Some reports have no adverse event

VAERS surveillance: methods

- Includes U.S. influenza vaccine reports received in VAERS through May 26, 2017 (vaccinated July 1, 2016 through May 1, 2017)
- Signs, symptoms and diagnoses are coded using Medical Dictionary for Regulatory Activities (MedDRA) terms
- Clinical review of reports (includes review of medical records when available) was performed for:
  - All serious* reports after IIV3, IIV3-HD, IIV4, IIV4-ID, ccIIV3, RIV3, aIIV3
  - Anaphylaxis reports in persons with a history of egg allergy
  - Pregnancy reports for spontaneous abortion, stillbirth, congenital anomalies, and serious pregnancy reports
- Empirical Bayesian data mining to detect disproportional reporting for vaccine-adverse event pairings

*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, 2016-2017

	IIV3 N (%)	IIV4 N (%)	IIV3-HD N (%)
Total reports*	1,370	4,236	2,033
Serious reports†	61 (4%)	258 (6%)	90 (4%)
Non-serious reports	1,309 (96%)	3,978 (94%)	1,943 (96%)
Guillain-Barré syndrome (GBS)	14 (1%)	51 (1%)	19 (0.9%)
Anaphylaxis‡	3 (0.2%)	27^ (0.6%)	3 (0.2%)

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

*U.S. primary reports (foreign reports excluded), all ages

†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

‡Onset interval 0-1 days post vaccination for anaphylaxis

^Three IIV4 anaphylaxis reports were in persons with a history of egg allergy

U.S. reports to VAERS following ccIIV4, RIV3, aIIV3 and IIV4-ID, 2016-2017

	ccIIV4 N (%)	RIV3 N (%)	aIIV3 N(%)	IIV4-ID N(%)
Total reports*	361	41	100	65
Serious reports†	13 (4%)	3 (7%)	0	3 (5%)
Non-serious reports	348 (96%)	38 (93%)	100 (100%)	62 (95%)
Guillain-Barré syndrome (GBS)	4 (1%)	0	0	0
Anaphylaxis‡	1 (0.3%)	2^ (5%)	0	2 (3%)

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

*U.S. primary reports (foreign reports excluded), all ages

†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

‡Onset interval 0-1 days post vaccination for anaphylaxis

^One RIV3 anaphylaxis report was in a person with a history of egg allergy

Anaphylaxis reports* in patients with history of egg allergy

Age (yrs)	Sex (M/F)	Vaccine	Medical history	Onset interval	AE symptoms, treatment, outcome	Brighton level†
6	F	Fluzone (IIV4)	• Asthma, eczema, Food allergies to eggs (signs symptoms not reported), peanut, wheat, corn, shellfish • Received "a flu shot" (unknown type) 2 years prior with no reactions	30-35 min	• Hives, tachycardic, no wheezing	3
37	F	Flublok (RIV3) RIV3 is egg free	• Hives to "flu shots" (unknown type) in the past • Diarrhea and hives after eating eggs (and poultry) • Latex allergies, symptoms include swelling and itching	Within minutes	• Swelling of upper throat, difficulty swallowing, pruritus in tongue, throat, and chest • Loss of consciousness • Given Benadryl, epinephrine (3 shots), albuterol and ipratropium	1

* End-of-Season Update: 2016-2017 Influenza Vaccine Safety Monitoring

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

Anaphylaxis reports* in patients with history of egg allergy

(continued)

Age (yrs)	Sex (M/F)	Vaccine	Medical history	Onset interval	AE sSymptoms, treatment, outcome	Brighton level†
2	F	Fluzone (IIV4), Hep A	• Anaphylaxis with milk • "Positive" reaction (unspecified) to eggs, although pt. can eat eggs • Received IIV (unknown type) and Hep A vaccines in the past without problems	Within minutes	• Vomiting, red rash in back, paleness and low responsiveness • Blood pressure (BP) initially 84/40 and dropped to 70/30 • Given Epi-pen; pulse and BP improved • Given Benadryl IV, Zofran, Solu-Medrol IV and normal saline	1
18	F	Afluria (IIV4), IPV, MCV, Tdap	• Had known history of egg allergy (signs symptoms not reported) prior to receiving a "flu vaccine" (unknown type) in past • No contra-indication to receiving IIV could be identified	Within hours	• Hives, severe respiratory distress with wheezing, angioedema of face and throat swelling • Seen in urgent care, given epinephrine (2 doses) and Benadryl	1

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

Pregnancy reports in VAERS following influenza vaccination, 2016-2017

Pregnancy reports	
Total reports (n=36 for IIV3 or IIV4, n=1 for ccIIV4)	37
Median maternal age (range)	29 years (16-42)
Median gestational age (range) at vaccination, N=14 (40%) with gestational age reported	21 weeks (1-37)
Trimester of vaccination • 1st trimester • 2nd trimester • 3rd trimester	14 5 (36%) 4 (28%) 5 (36%)
Pregnancy-specific outcomes • Spontaneous abortion • Vaginal bleeding	7 (19%) 5 2
Non-pregnancy specific adverse event reports (includes the one ccIIV4 report)	18 (49%)[a]
Vaccination error reports (no adverse event)	12 (32%)[b]

[a] Includes injection site reactions/pain in extremity/joint (6), systemic reactions (4), urinary tract infection (1), non-anaphylaxis allergic reactions (3), anaphylaxis (2), influenza-like-illness (1), nausea/vomiting (1)

[b] Vaccination errors included administration of Fluzone High-Dose (3), thimerosal-containing vaccine (2), HPV vaccine (3), Fluad (1), MMR and varicella (1), IIV instead of Tdap (1), and perceived error in giving IIV to a 16-year-old female (1)

Summary of VAERS surveillance for the 2016-2017 influenza season and plans for 2017-2018

- No new safety concerns detected for IIVs, ccIIV3, RIV3, aIIV3 during the 2016-2017 influenza season
- Surveillance for the 2017-2018 influenza season will include enhanced safety monitoring* for:
  - aIIV3 (FLUAD™)
  - IIV4-ID (Fluzone® Intradermal Quadrivalent)
  - RIV4 (Flublok® Quadrivalent)
  - Pregnancy reports
  - Anaphylaxis reports in persons with history of egg allergy

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

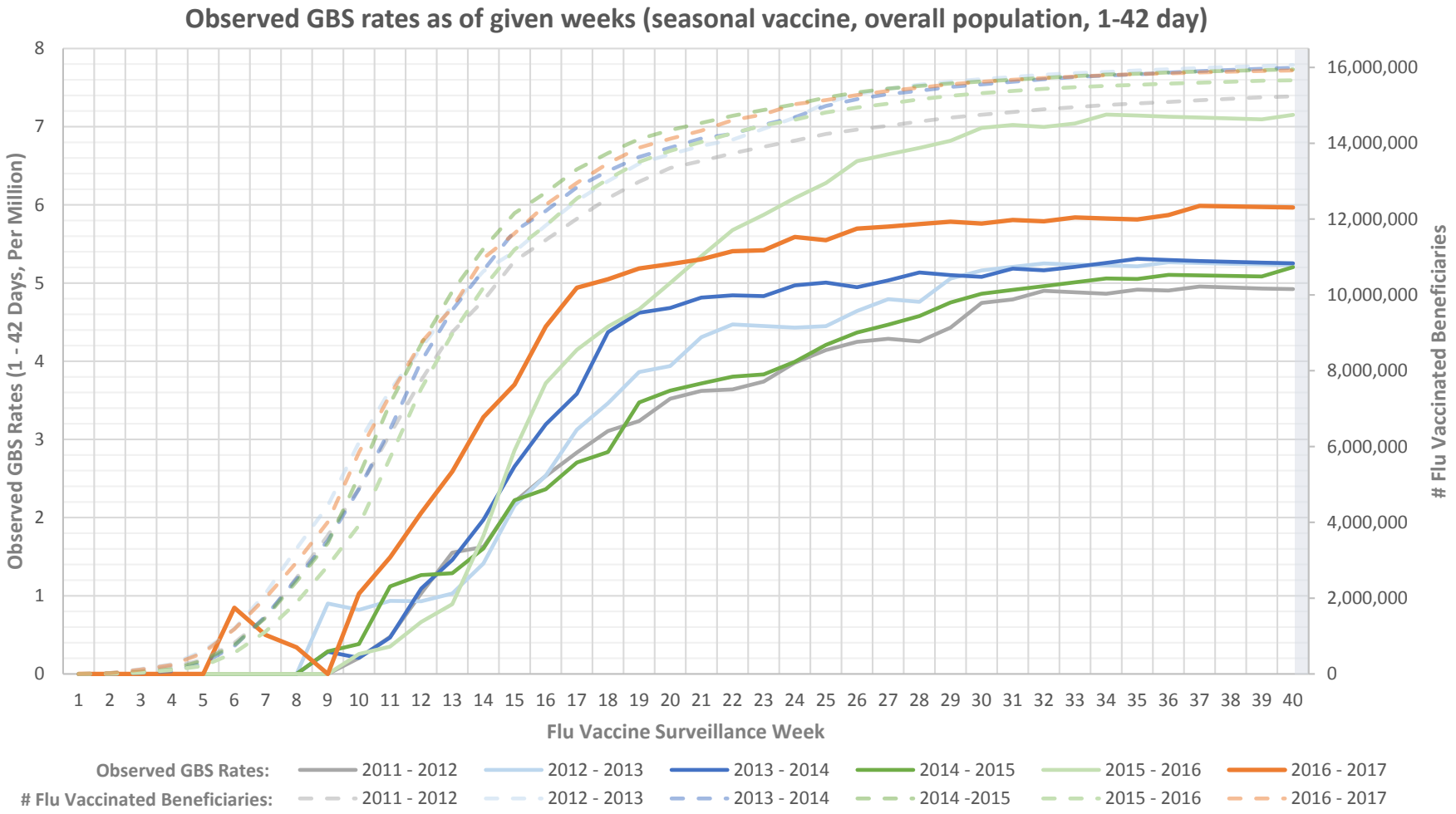
U.S. Food and Drug Administration (FDA) Surveillance for Guillain-Barré Syndrome (GBS) Following Influenza Vaccination of Medicare Beneficiaries in the 2016-2017 Influenza Season

Surveillance for Guillain-Barré Syndrome (GBS) Following Influenza Vaccination of Medicare Beneficiaries in 2016/17 Season

- Near real time surveillance[1] for GBS after influenza vaccination is conducted every influenza season by FDA in collaboration with CMS[2]
- Weekly statistical testing compared GBS rates in current season with average rate in prior five seasons (historical rate)
- In week 17 of surveillance (data as of Dec 9, 2016) current GBS rate for the primary outcome (all ages, all influenza vaccines, 1-42 day window) was greater than the historical rate
- By week 20, GBS rate in the current season declined and was very close to the historical rate

1. CMS claims data are refreshed every week; however, it may take up to 10 weeks for the claims data to mature
2. CMS, Centers for Medicare & Medicaid Services

Observed GBS Rate in 2016/17 Season Compared with the Past Five seasons (as of May 19, 2017)



Current Status

- In week 40 of surveillance (data as of May 19, 2017) GBS rate in a 6-week risk window was 5.96/million vaccinees, compared to an average of 5.70/million vaccinees for the prior five seasons

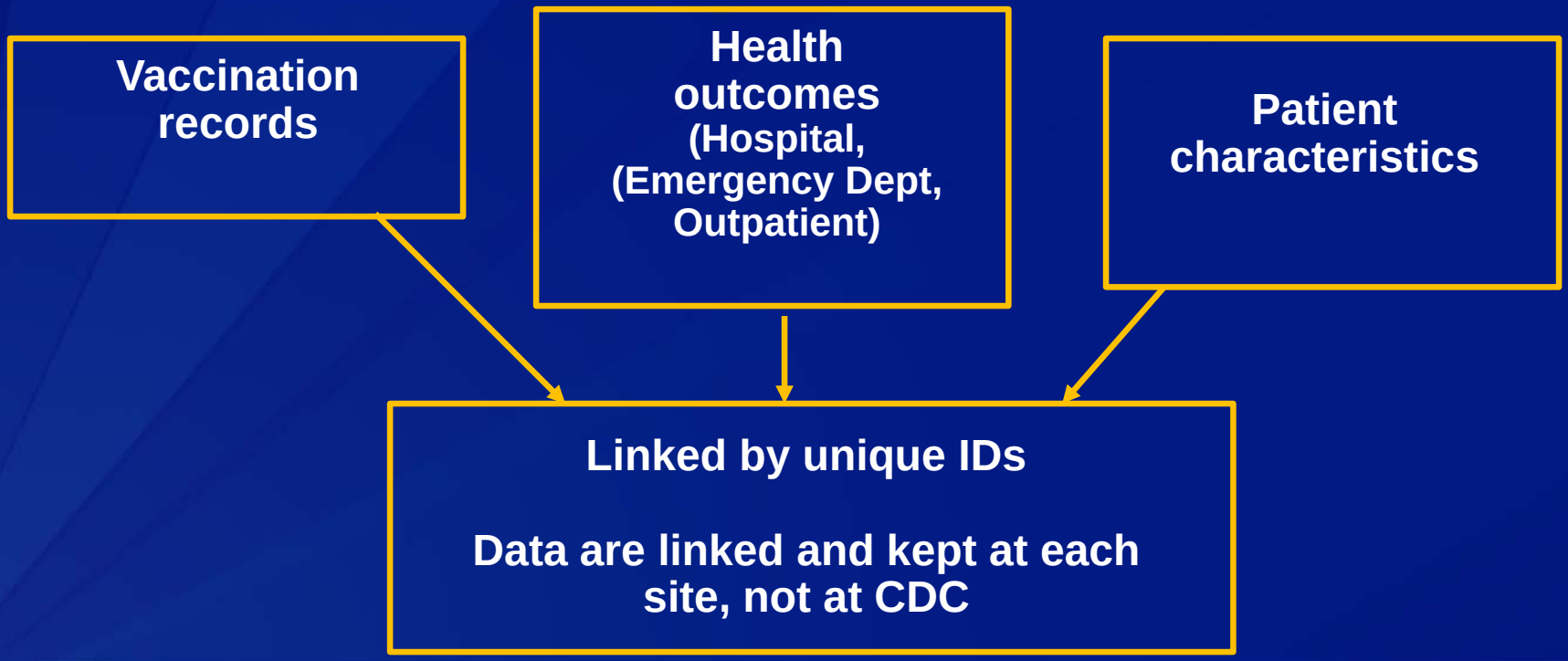
- End of season analysis, using self-controlled design, to be conducted when 99% of the fee-for-service beneficiaries have been vaccinated

- Limitations of surveillance include: comparison to historical data, claims-based analysis, no control for confounders

Vaccine Safety Datalink Rapid Cycle Analysis for the 2016-2017 influenza season

Vaccine Safety Datalink (VSD)

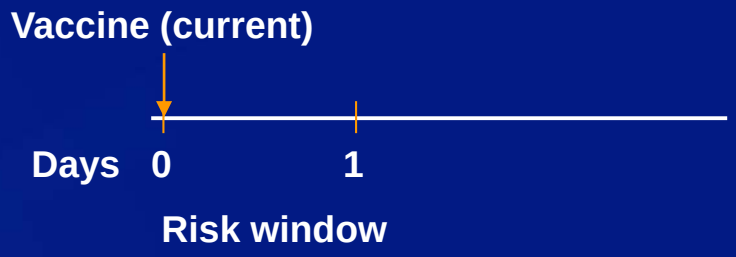
- Established in 1990
- Collaboration between CDC and 9 integrated healthcare plans
- Data on over 9 million persons per year (~3% of U.S. population)
- Links vaccination data to health outcome data

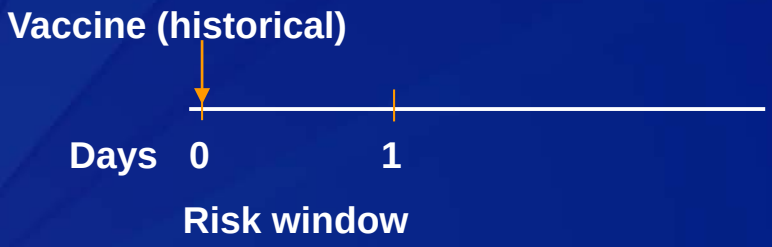


Rapid Cycle Analysis in the Vaccine Safety Datalink

Self controlled design*

Current vs. historical†





* 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 2016-2017 influenza season

Pre-specified outcome	Age group	Risk window (days)	Control window* (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

*For self-control design

Influenza vaccine doses administered in the Vaccine Safety Datalink (2016-2017 influenza season)

Vaccine	Dose 1 doses administered* in all ages
IIV3	2,655,071
IIV4	1,359,059
IIV High-Dose	456,043
ccIIV3	78,002
IIV Intradermal	5,549
RIV3	1,104
Total	4,554,828

*Doses administered through April 29, 2017, no aIIV3 doses in VSD for 2016-2017

2016-2017 VSD Rapid Cycle Analysis results for IIV3 (Binomial maxSPRT – self-control)

Pre-specified outcome	Risk interval	Age group	IIV3 doses	Events in risk window	Events in control window	Relative risk	LLR*	Critical value
Anaphylaxis	0-2	>=6 mo	2,655,071	9	4	2.25	0.9868	3.3914
Bell's palsy	1-42	<18 yr	439,764	10	25	0.40	0.0000	3.6060
		18-49 yr	1,007,035	154	231	0.67	0.0000	4.1127
		>=50 yr	1,208,272	234	373	0.63	0.0000	4.1589
Encephalitis	1-21	>=6 mo	2,655,071	17	26	1.31	0.3620	3.2958
GBS	1-42	>=6 mo	2,655,071	18	19	0.95	0.0000	3.8616
Seizures	0-1	24-59 mo	36,591	1	2	1.75	0.0972	3.0082
Transverse myelitis	1-21	>=6 mo	2,655,071	5	6	1.67	0.3468	3.2958

*Log-likelihood ratio did not exceed the critical value for any pre-specified outcomes (i.e., no signals)

2016-2017 VSD Rapid Cycle Analysis results for IIV4 (Binomial maxSPRT – self-control)

Pre-specified outcome	Risk interval	Age group	IIV4 doses	Events in risk window	Events in control window	Relative risk	LLR*	Critical value
Anaphylaxis	0-2	>=6 mo	1,359,059	2	2	1.00	0.0000	3.3914
Bell's palsy	1-42	<18 yr	520,006	13	15	0.87	0.0000	3.6060
		18-49 yr	352,236	50	78	0.64	0.0000	4.1127
		>=50 yr	486,817	116	187	0.62	0.0000	4.1589
Encephalitis	1-21	>=6 mo	1,359,059	6	5	2.40	1.0399	3.2958
GBS	1-42	>=6 mo	1,359,059	7	14	0.43	0.0000	3.8616
Seizures	0-1	6-23 mo	191,424	9	21	1.50	0.4884	3.0082
		24-59 mo	127,099	7	7	3.50	2.5837	3.0082
Transverse myelitis	1-21	>=6 mo	1,359,059	1	0	.	1.0986	3.2958

*Log-likelihood ratio did not exceed the critical value for any pre-specified outcomes (i.e., no signals)

2016-2017 VSD Rapid Cycle Analysis results for IIV3 (Poisson maxSPRT – current vs historical)

Pre-specified outcome	Risk interval	Age group	IIV3 Doses	Obs. # of AEs	Exp. # of AEs	Relative risk	LLR*	Critical value
ADEM	1-21	>=6 mo	2,655,071	0	0.93	0.00	0.00	2.94
Anaphylaxis	0-2	>=6 mo	2,655,071	9	5.75	1.57	0.78	3.17
Bell's palsy	1-42	<18 yr	439,764	10	10.34	0.97	0.00	3.55
		18-49 yr	1,019,864	154	136.60	1.13	1.06	3.93
		>=50 yr	1,208,272	234	229.05	1.02	0.05	4.09
Encephalitis	1-21	>=6 mo	2,655,071	17	9.93	1.71	2.07	3.52
GBS	1-42	>=6 mo	2,655,071	18	15.26	1.18	0.23	3.61
Seizures	0-1	6-23 mo	4,015	0	0.29	0.00	0.00	3.33
		24-59 mo	36,591	1	1.16	0.86	0.00	2.85
Transverse myelitis	1-21	>=6 mo	2,655,071	5	1.60	3.12	2.30	3.17

*Log-likelihood ratio did not exceed the critical value for any pre-specified outcomes (i.e., no signals)

2016-2017 VSD Rapid Cycle Analysis results for IIV4 (Poisson maxSPRT – current vs historical)

Pre-specified outcome	Risk interval	Age group	IIV4 doses	Obs. # of AEs	Exp. # of AEs	Relative risk	LLR*	Critical value
ADEM	1-21	>=6 mo	1,359,059	0	0.56	0.00	0.00	2.94
Anaphylaxis	0-2	>=6 mo	1,359,059	2	2.24	0.89	0.00	3.17
Bell's palsy	1-42	<18 yr	520,006	13	12.47	1.04	0.01	3.55
		18-49 yr	357,941	50	52.44	0.95	0.00	3.93
		>=50 yr	486,817	116	103.48	1.12	0.73	4.09
Encephalitis	1-21	>=6 mo	1,359,059	6	6.06	0.99	0.00	3.52
GBS	1-42	>=6 mo	1,359,059	7	8.77	0.80	0.00	3.61
Seizures	0-1	6-23 mo	191,424	9	13.53	0.67	0.00	3.33
		24-59 mo	127,099	7	3.72	1.88	1.14	2.85
Transverse myelitis	1-21	>=6 mo	1,359,059	1	0.97	1.03	0.00	3.17

*Log-likelihood ratio did not exceed the critical value for any pre-specified outcomes (i.e., no signals)

Summary of 2016-2017 Vaccine Safety Datalink influenza vaccine Rapid Cycle Analysis (RCA)

- No RCA signals in either self-controlled risk interval or current vs. historical designs for any of the pre-specified outcomes for IIV3 or IIV4
- For IIV3-High Dose
  - Limited number of doses administered in VSD for the 2016-2017 influenza season (n=450,242)
  - No statistical signals or elevated relative risks for any pre-specified outcomes being monitored (which includes Guillain-Barré syndrome) in either self-controlled risk interval or current vs. historical designs
- Data for ccIIV3, IIV Intradermal, and RIV3 are limited due to low use of these vaccines, but were generally reassuring

Vaccine Safety Datalink (VSD) influenza vaccine safety monitoring and research for 2017-2018 influenza season

- Conduct self-controlled risk interval and current vs. historical Rapid Cycle Analysis (RCA) for the pre-specified conditions:
  - Anaphylaxis, Bell's palsy, encephalitis, Guillain-Barré syndrome, seizures, transverse myelitis, acute disseminated encephalomyelitis
- Continue work on a comprehensive analysis to evaluate the risk of GBS following pH1N1-containing seasonal influenza vaccines, 2010-2016
  - Study is a follow-up to the RCA signal (in self-controlled risk interval design) for GBS following IIV3 detected during the 2015-2016 influenza season

Summary of influenza vaccine safety monitoring for 2016-2017

- No new safety concerns detected in VAERS monitoring
- Reassuring results in FDA's near real-time monitoring for GBS following influenza vaccination in Medicare beneficiaries in CMS data
- No signals for any pre-specified outcomes being monitored in Vaccine Safety Datalink (VSD) Rapid Cycle Analysis

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Thank You

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