End-of-Season Update: 2015-2016 Influenza Vaccine Safety Monitoring

Advisory Committee on Immunization Practices
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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.

US influenza vaccine abbreviations*

Vaccine	Abbreviation
Trivalent inactivated influenza vaccine	IIV3
Quadrivalent inactivated influenza vaccine	IIV4
Quadrivalent live attenuated influenza vaccine	LAIV4
High-dose trivalent inactivated influenza vaccine	IIV3-HD
Intradermal trivalent and quadrivalent inactivated influenza vaccines	IIV3-ID IIV4-ID
Cell culture-based trivalent inactivated influenza vaccine	ccIIV3
Recombinant trivalent inactivated influenza vaccine	RIV3

*IIV is commonly used when generally discussing inactivated influenza vaccines as a category and LAIV when generally discussing live attenuated influenza vaccines

Vaccine Adverse Event Reporting System (VAERS) surveillance for the 2015-2016 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†
- Data available to public

Limitations

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

*VAERS website: http://vaers.hhs.gov

†Some reports have no adverse event

VAERS surveillance: methods

- Includes US influenza vaccine reports received in VAERS through May 27, 2016 (vaccinated July 1, 2015-May 6, 2016)
- 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) were performed for:
  - All serious* reports after IIV4, IIV4-ID, LAIV4, ccIIV3, RIV3
  - All 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

*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)

†Banks et al. Comparing data mining methods on the VAERS database. Pharmacoepidemiol Drug Saf. 2005;14:601–609

US reports to VAERS following IIV3, IIV4, LAIV4 and IIV3-HD, 2015-2016

	IIV3 N (%)	IIV4 N (%)	LAIV4 N (%)	IIV3-HD N (%)
Total reports*	4,380	1,728	374	1,783
Serious reports†	201 (5)	109 (6)	21 (6)	106 (6)
Non-serious reports	4,179 (95)	1,619 (94)	353 (94)	1,677 (94)
Guillain-Barré syndrome (GBS)‡	45 (1)	19 (1)	2 (0.5)	11 (0.6)
Anaphylaxis‡	14 (0.3)	11 (0.6)	2 (0.5)	6 (0.3)

- Two reports of anaphylaxis following LAIV4 in persons with history of egg allergy#
- No data mining findings for Guillain–Barré syndrome or anaphylaxis

*US primary reports (foreign reports excluded), all ages (total N = 8,643)

†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

‡MedDRA (Medical Dictionary for Regulatory Activities) term; onset interval 0-1 days post vaccination for anaphylaxis

#One with documented allergy test result

US reports to VAERS following ccIIV3, RIV3 IIV3-ID and IIV4-ID, 2015-2016

	ccIIV3 N (%)	RIV3 N (%)	IIV3-ID N(%)	IIV4-ID N(%)
Total reports*	288	47	3	40
Serious reports†	11 (4)	1 (2)	0	2 (5)
Non-serious reports	277 (96)	46 (98)	3 (100)	38 (95)
Guillain-Barré syndrome (GBS)‡	1 (0.4)	0	0	0
Anaphylaxis‡	2 (0.7)	2 (4)	0	0

- No data mining findings for Guillain–Barré syndrome or anaphylaxis

*US 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

‡MedDRA (Medical Dictionary for Regulatory Activities) term; onset interval 0-1 days post vaccination for anaphylaxis

Pregnancy reports in VAERS following influenza vaccination, 2015-2016

	N (%)
Total reports after IIV3 or IIV4	58
Median maternal age (range) in years	32 (14-44)
Median gestational age (range) in weeks at vaccination, N=17 (29%) with gestational age reported	20 (4-38)
Trimester of vaccination • 1st trimester • 2nd trimester • 3rd trimester	17 6 (35) 6 (35) 5 (29)
Pregnancy-specific outcomes • Spontaneous abortion • Stillbirth • Vaginal bleeding	8 (14) 5 1 2
Non-pregnancy specific reports	29 (50)*
No adverse event	21 (36)
Total reports after LAIV4 • No adverse event • Abdominal pain • Nasal congestion/sore throat	7 5 1 1

* Includes injection site reactions/pain in extremity/joint pain (14), systemic reactions (7), neurological conditions (4), non-anaphylaxis allergic reactions (3), diarrhea, nausea, and vomiting (1)

Summary of VAERS surveillance for the 2015-2016 influenza season and plans for 2016-2017

- No new safety concerns detected for IIVs, LAIV4, ccIIV3 or RIV3 during the 2015-2016 influenza season
- Surveillance for the 2016-2017 influenza season will include enhanced safety monitoring* for:
  - Adjuvanted influenza vaccine (Fluad®)
  - IIV4-ID (Fluzone® Intradermal 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

US Food and Drug Administration (FDA) near real-time surveillance for Guillain-Barré syndrome following influenza vaccination in Medicare beneficiaries for the 2015-2016 influenza season

Near real-time surveillance for Guillain-Barré Syndrome (GBS) following 2015-2016 influenza vaccination in Medicare beneficiaries

- FDA conducts near real-time surveillance for GBS following influenza vaccination every influenza season in collaboration with the Centers for Medicare & Medicaid Services (CMS)
- Weekly statistical testing compares GBS rates in the current season with rates in the prior three seasons in the Medicare database
- During 2015-2016 season there 15.4 million IIV* administrations

*Includes IIV products combined

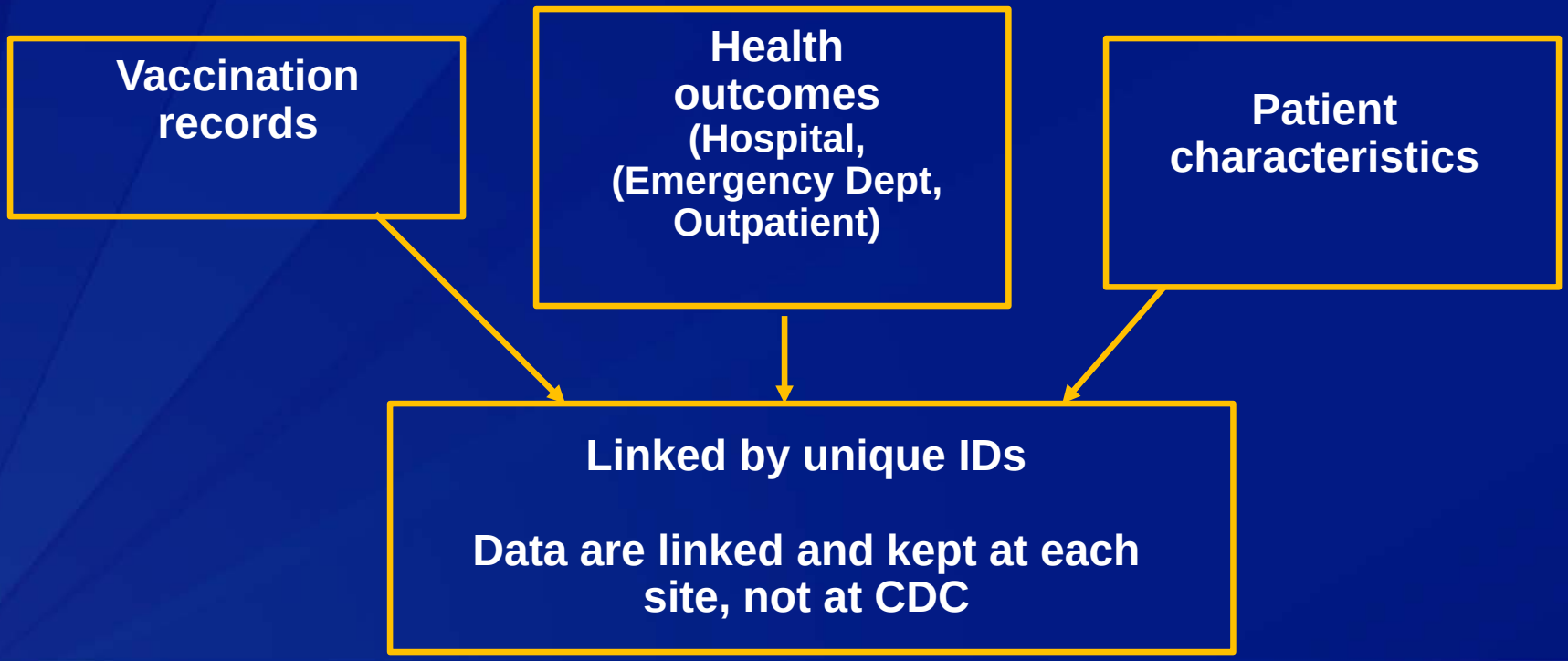
Near real-time surveillance for Guillain-Barré Syndrome (GBS) following 2015-2016 influenza vaccination in Medicare beneficiaries

- 2015-2016 season surveillance showed a GBS rate increase following IIV of small magnitude
  - 7.25 cases/million IIV vaccinees in comparison to an average of 5.45 cases/million IIV vaccinees for the past three seasons
- Limitations of surveillance include
  - Comparison of current to historical data
  - Claims-based analysis
  - Change from ICD-9 in the previous seasons to ICD-10 in the 2015-16 season
  - No control for confounders
- End-of-season analysis using self-controlled designs has been initiated

Vaccine Safety Datalink end-of-season analysis for the 2015-2016 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 US population)
- Links vaccination data to health outcome data



Vaccine Safety Datalink end-of-season analysis (2015-2016 influenza season outcomes)

Pre-specified outcome	Age group	Risk window (days)	Control window* (days)
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	≥6 mos	1-42	43-84
Seizures	6-23 mos 24-59 mos	0-1 for IIV 0-14 for LAIV	14-20 for IIV 15-29 for LAIV
Transverse myelitis	≥6 mos	1-21	-56 to -15

*For self-control design

Influenza vaccine doses administered in the Vaccine Safety Datalink (2015-2016 influenza season)

Vaccine	Dose 1 doses administered* in all ages
IIV3	3,100,856
IIV4	297,924
IIV High-Dose	301,359
LAIV4	195,815
ccIIV3	173,646
RIV3	23,340
IIV Intradermal	4,988

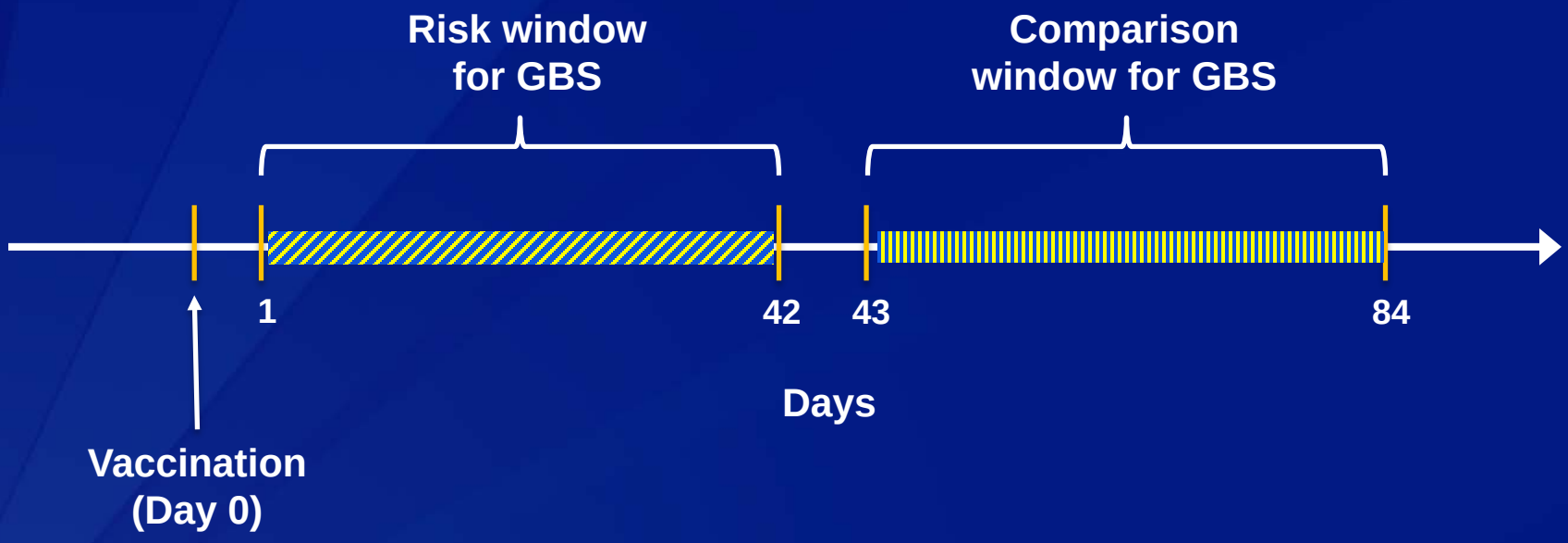
*Doses administered through May 1, 2016

2015-2016 Vaccine Safety Datalink (VSD) influenza end-of-season analysis

- Because of the transition from ICD-9 to ICD-10 in 2015, VSD analysis was limited to analysis of ICD-10 data, specifically IIV3 doses administered after October 1, 2015
- Conducted self controlled risk interval (SCRI) analysis*
- Guillain-Barré syndrome (GBS) SCRI parameters (GBS is the signaling outcome in 2015-2016)
  - Risk window: days 1-42
  - Comparison window: days 43-84
  - Incident definition: first occurrence in a year

* Each patient serves as his/her own control, looking at events in risk window and events in comparison window

2015-2016 Vaccine Safety Datalink (VSD) end-of-season analysis for influenza vaccine and Guillain-Barré syndrome (GBS) – self controlled risk interval (SCRI) design



* Each patient serves as his/her own control, looking at events in risk window and events in comparison window

2015-2016 Vaccine Safety Datalink (VSD) influenza end-of-season* analysis for Guillain-Barré syndrome (GBS)

Model† (SCRI with IIV3)	Cases in risk window (1-42 days)	Cases in comparison window (43-84 days)	RR	95% CI	P-value
>6 months	27	8	3.38	(1.53, 7.43)	0.0025
<65 years	14	4	3.5	(1.15, 10.63)	0.0271
65+ years	13	4	3.25	(1.06, 9.97)	0.0393
Inpatient or ED, >6 months	18	6	3	(1.19, 7.56)	0.0198
Inpatient or ED, >6 months (quick chart review)	11	3	3.67	(1.02, 13.14)	0.0461

*Approximately ~3.1 million IIV3 doses administered for the 2015-2016 influenza season

†Data in the first four rows is automated, ICD-10 data; data in the last row has received a quick chart review that includes an electronic medical record review to confirm case is an incident case and was diagnosed by a neurologist

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2014-2015 season‡	18	13	1.38	(0.68, 2.83)	0.3713

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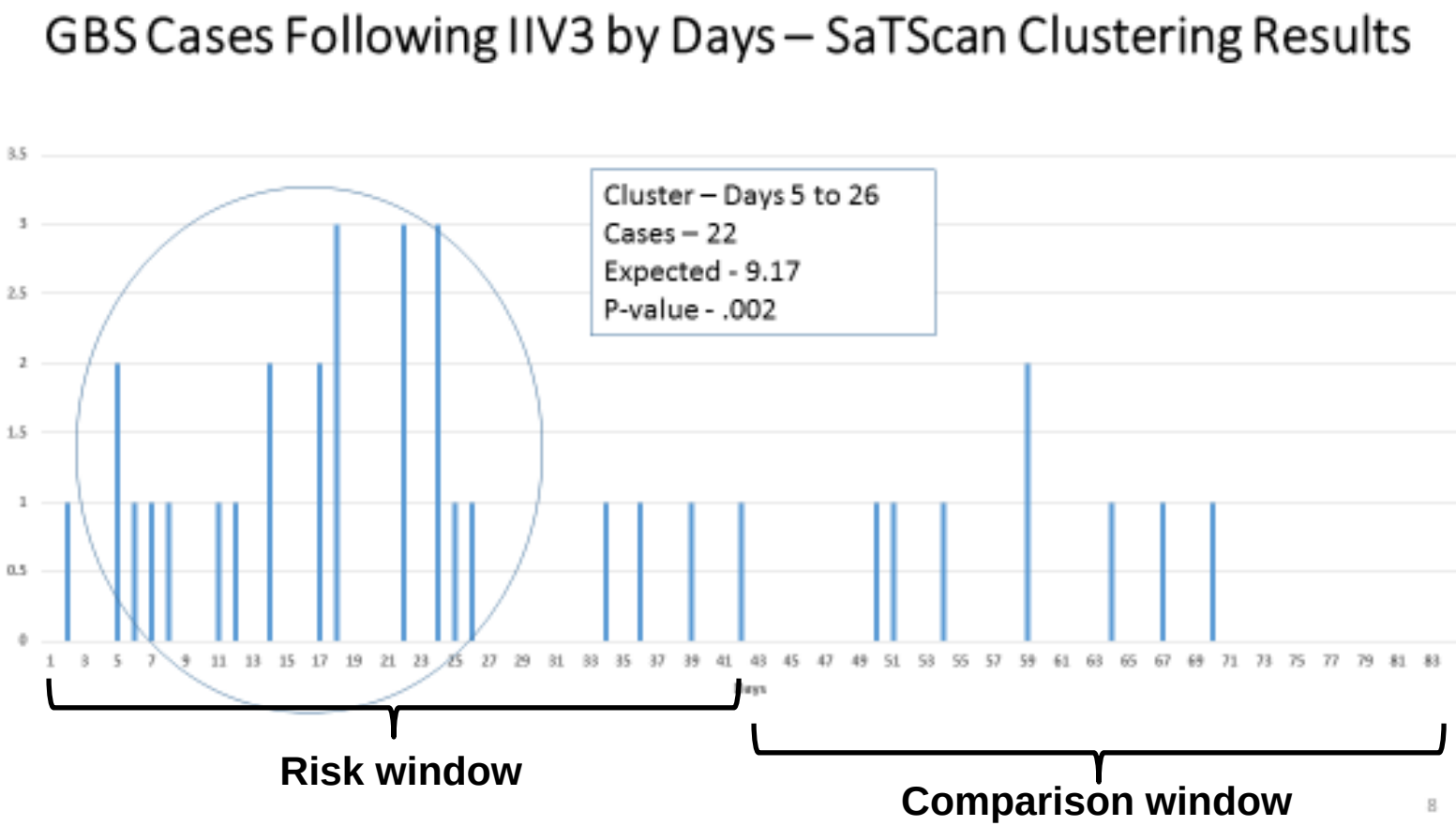
‡2014-2015 influenza season data in the last row includes automated, ICD-9 data for >6months

Guillain-Barré syndrome (GBS) SaTScan clustering results in the Vaccine Safety Datalink using automated data for the 2015-2016 influenza season



Summary of 2015-2016 Vaccine Safety Datalink (VSD) influenza end-of-season analysis for Guillain-Barré syndrome (GBS)

- VSD identified a significantly elevated relative risk of 3.67 (95% CI: 1.02, 13.14) using the SCRI* method in the quick chart review analysis
- The corresponding attributable risk for GBS following IIV3 is approximately 2.6 additional GBS cases per million doses administered
- Next Steps
  - VSD will continue to further evaluate the association by
    - Conducting chart review of all GBS cases (inpatient, emergency department and outpatient)
    - Conducting a case centered analysis that adjusts for seasonality of both IIV3 administration and of GBS, and other potential confounders

*Self controlled risk interval

Summary of influenza vaccine safety monitoring for the 2015-2016 season

- No new safety concerns detected in VAERS surveillance
- FDA surveillance for Guillian-Barré syndrome (GBS) following influenza vaccination in Medicare beneficiaries
  - Showed a GBS rate following IIV of 7.25 cases per million compared to an average of 5.45 for the prior three seasons
  - Further assessment using self controlled methods in progress
- CDC Vaccine Safety Datalink (VSD) end-of-season analysis
  - Signal was identified for GBS following IIV3 in the SCRI* design
  - Estimated attributable risk is 2.6 GBS cases per million IIV3 doses administered
  - Signal assessment using detailed chart review and case centered analysis is in progress
- Preliminary GBS risk estimate appears consistent with that observed in some previous influenza seasons

*Self controlled risk interval

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Thank You

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