

BRIEF REPORT

Absence of associations between influenza vaccines and increased risks of seizures, Guillain–Barré syndrome, encephalitis, or anaphylaxis in the 2012–2013 season

Alison Tse Kawai^{1*}, Lingling Li¹, Martin Kulldorff¹, Claudia Vellozzi², Eric Weintraub², Roger Baxter³, Edward A. Belongia⁴, Matthew F. Daley⁵, Steven J. Jacobsen⁶, Allison Naleway⁷, James D. Nordin⁸ and Grace M. Lee^{1,9}

¹Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA

²Centers for Disease Control and Prevention, Immunization Safety Office, Atlanta, GA, USA

³Kaiser Permanente, Northern California, Oakland, CA, USA

⁴Marshfield Clinic Research Foundation, Marshfield, WI, USA

⁵Kaiser Permanente, Colorado, Denver, CO, USA

⁶Kaiser Permanente, Southern California, Pasadena, CA, USA

⁷Kaiser Permanente, Northwest, Portland, OR, USA

⁸Health Partners Research Foundation, Minneapolis, MN, USA

⁹Boston Children's Hospital, Boston, MA, USA

ABSTRACT

Purpose We conducted weekly surveillance for pre-specified adverse events following receipt of the 2012–2013 influenza vaccines in the Vaccine Safety Datalink (VSD).

Methods For each outcome, risk intervals (i.e., period after vaccination with a potentially increased risk) were defined on the basis of biologic plausibility and prior literature. Seizures following inactivated influenza vaccine (IIV) were monitored in children in three age groups (6–23 months, 24–59 months, and 5–17 years) using a self-controlled risk interval design. We also monitored for Guillain–Barré syndrome, encephalitis, and anaphylaxis following IIV in patients ≥6 months of age using a cohort design with historical controls. In the risk intervals following live attenuated influenza vaccine (LAIV), we collected weekly counts of Guillain–Barré syndrome, encephalitis, and anaphylaxis in patients ages 2–49. Among LAIV vaccinees, numbers of expected events based on rates in historical controls were calculated, adjusted for age and site.

Results At the end of surveillance, approximately 3.6 million first doses of IIV and 250 000 first doses of LAIV had been administered in the VSD. No elevated risks were identified in risk intervals following 2012–2013 IIV, as compared with a self-matched control interval or to historical controls. For each outcome, fewer than three events occurred in the risk interval following 2012–2013 LAIV, and we thus were unable to estimate measures of relative risks.

Conclusions No increased risk was identified for any of the pre-specified outcomes following 2012–2013 influenza vaccinations in the VSD. Published 2014. This article is a U.S. Government work and is in the public domain in the USA.

KEY WORDS—vaccine safety; influenza vaccine safety surveillance; Vaccine Safety Datalink; pharmacoepidemiology

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INTRODUCTION

During weekly surveillance of 2010–2011 seasonal influenza vaccine safety, an elevated risk for febrile seizures was found in children 6–59 months of age receiving inactivated influenza vaccine (IIV) in the Vaccine Safety Datalink (VSD), a large US cohort of

medical care organization (MCO) enrollees.¹ The risk was increased particularly among children 6–23 months of age receiving concomitant IIV and 13-valent conjugate pneumococcal vaccine (PCV13). No elevated risks were found for febrile seizures following IIV for other age groups or for outcomes following live attenuated influenza vaccine (LAIV). The Vaccine Information Statement for influenza vaccines was updated to describe an increased risk for febrile seizures in young children receiving IIV and PCV13 vaccines concomitantly.²

*Correspondence to: A. T. Kawai, Department of Population Medicine, Harvard Pilgrim Health Care Institute, 133 Brookline Ave, Boston, MA 02215 USA. Email: Alison_Kawai@HPHC.org

Because the antigenic composition of the influenza vaccine changes to reflect circulating influenza strains, the VSD has continued to conduct influenza vaccine safety surveillance annually. The trivalent IIVs for 2010–2011 included A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens.³ During the 2011–2012 influenza season, there was no change in the antigenic components of the trivalent vaccine compared with the prior year, and we also found an elevated risk of seizures in children 6–23 months of age following IIV.^{3,4} However, the 2012–2013 trivalent IIVs contained different H3N2 and B lineage antigens (A/Victoria/361/2011 (H3N2)-like, and B/Wisconsin/1/2010-like (Yamagata lineage) antigens) while still including the A/California/7/2009 (H1N1)-like antigen contained in vaccines licensed in the prior two seasons.⁴ In addition to the change in antigenic components, potential changes in patterns of concomitant vaccination raised the possibility that the risk of adverse events might be different in 2012–2013. The purpose of this report is to describe the results of weekly prospective surveillance and analyses after completion of surveillance for the 2012–2013 influenza vaccines.

METHODS

Data sources

The Centers for Disease Control and Prevention (CDC)-sponsored VSD is a collaboration between CDC and nine MCOs, encompassing data on more than nine million members annually.⁵ Among other activities, the VSD monitors potential associations between specific vaccines and pre-specified adverse events using weekly updated data and sequential statistical analyses.^{1,5–9} Eight MCOs participated in surveillance for this report: Group Health Cooperative (Washington), Kaiser Permanente Colorado, Kaiser Permanente Northwest (Oregon), Harvard Vanguard Medical Associates, Harvard Pilgrim Health Care (Massachusetts), HealthPartners (Minnesota), Kaiser Permanente Northern California, Kaiser Permanente Southern California, and Marshfield Clinic (Wisconsin). MCOs provided computerized weekly aggregate data on demographics, immunizations, and medical encounters. Institutional review boards at CDC and each VSD site approved the study and determined that informed consent was not required.

Vaccines and outcomes

We monitored seizures, Guillain–Barré syndrome (GBS), encephalitis, and anaphylaxis following first dose 2012–2013 IIV and GBS, encephalitis, and anaphylaxis following first dose 2012–2013 LAIV. Seizures

following IIV were monitored in children in three age groups (6–23 months, 24–59 months, and 5–17 years). As other adverse events occurred rarely, all other outcomes following IIV were monitored in a composite of patients ≥ 6 months of age. All outcomes following LAIV were monitored in a composite of patients 2–49 years of age.

Outcomes were identified from electronic health records and defined using ICD-9 (International Classification of Disease, Version 9) codes (Web appendix 1). Post-vaccination risk intervals for each outcome were defined on the basis of biologic plausibility and prior literature.⁸ We defined the post-vaccination risk intervals as 0–1 days for seizures, 1–42 days for GBS, 1–21 days for encephalitis, and 0–2 days for anaphylaxis. To avoid capturing follow-up visits, we only considered the first diagnosis within a pre-specified period (Web appendix 1) as an incident event. We also limited seizures, encephalitis, and anaphylaxis to the inpatient and emergency department settings because ICD9-codes for these conditions in the outpatient setting often represent follow-up visits rather than acute events.

Study design

For monitoring seizures following IIV, we used the self-controlled risk interval (SCRI) design, which compared the risk of a potential adverse event in a risk interval (0–1 days after vaccination) with that in a self-matched control interval beyond the risk interval at a time not likely to be biologically plausible or causally associated with vaccine (14–20 days after vaccination).^{1,8,9} A marked strength of the SCRI design is that it inherently adjusts for time invariant confounders. For outcomes with lower frequency, we used a cohort design with historical controls. For IIV and for LAIV, these outcomes included GBS, encephalitis, and anaphylaxis. In the cohort design with historical controls, the number of events in a predefined risk interval following 2012–2013 influenza vaccine was compared with the expected number on the basis of rates in historical controls, adjusted for age and site.

Analysis for surveillance of pre-specified adverse events following 2012–2013 influenza vaccines

We conducted weekly surveillance from 30 September 2012 through 9 February 2013. Surveillance was not conducted between 11 November 2012 and 29 December 2012 because of technical difficulties with transferring site data to the coordinating center. After the issue was resolved, data from prior weeks (including 11 November 2012 through 29 December

2012) continued to be retrieved and analyzed with newly accumulated data on a weekly basis.

Sequential monitoring was conducted for seizures following IIV in children in three age strata (6–23 months, 24–59 months, and 5–17 years) using the SCRI design. The binomial-based maximized sequential probability ratio test (MaxSPRT)¹⁰ was used to adjust for repeated analyses of accumulating data throughout monitoring of seizures. Upper limits and critical values were set using an alpha level of 0.05 and a one-tailed test.¹¹ Before entering each vaccine dose into the analysis, we waited until estimated lags in data accrual (i.e., time between a diagnosis and appearance in the data, allowed to vary by site and setting of diagnosis) and follow-up time after vaccination was complete.¹¹ Lags in data accrual were estimated on the basis of historical data.

We also conducted sequential monitoring for GBS, encephalitis, and anaphylaxis following IIV in patients ≥6 months of age using data from the cohort design utilizing historical controls and adjusting for age and site. To account for repeated analyses of data accumulating throughout surveillance, the Poisson-based MaxSPRT¹⁰ or the Poisson-based conditional MaxSPRT (CMaxSPRT)¹² was used. Upper limits and critical values were based on the estimated number of doses expected to be administered using an alpha level of 0.05 and a one-tailed test.^{10,12} CMaxSPRT, an extension of the Poisson-based MaxSPRT that accounts for uncertainty in historical rates, was used when the ratio of the number of observed historical events to the upper limit was less than 4, which was the case for anaphylaxis and encephalitis. We adjusted the number of counts in the historical seasons downwards to reflect the portion of the risk interval that had elapsed and the completeness of 2012–2013 data accrual, which varied by site and was estimated on the basis of historical data.¹¹

In patients 2–49 years of age receiving LAIV, we also monitored counts of GBS, encephalitis, and anaphylaxis in the post-vaccination risk intervals. For surveillance of LAIV, expected counts based on rates in historical controls were calculated, adjusted for age and site. We also accounted for the portion of the risk interval that had elapsed and the completeness of 2012–13 data accrual, which varied by site.¹¹ We did not conduct formal statistical analyses for LAIV because of low exposure and case numbers.

Analysis after surveillance completion

After surveillance ended, we analyzed data from the SCRI design with conditional Poisson models. Logistic regression, with adjustment for age and site, was utilized for the cohort design with historical

controls. The historical period included the 2005–2006 through 2009–2010 influenza seasons for all outcomes. The cohort design for 2012–2013 IIV utilized historical IIV recipients for controls, whereas the cohort design for 2012–2013 LAIV used historical LAIV recipients for controls. We only included 2012–2013 influenza vaccine doses if lags in data accrual and follow-up time were complete. Formal statistical analyses for outcomes following LAIV were not conducted because of low exposure and case numbers.

RESULTS

During surveillance, more than 3.5 million first doses of 2012–2013 IIV and 250 000 first doses of 2012–2013 LAIV were administered (Table 1). Among IIV vaccinees ages 16–23 and 24–59 months of age, the proportion of children receiving concomitant PCV13 was lower in the 2012–2013 as compared with the 2010–2011 influenza season (Web appendix 2). By contrast, in children 6–11 and 12–15 months of age receiving IIV, PCV13 was equally likely to be received concomitantly in the 2012–2013 and the 2010–2011 influenza seasons. In children 6–59 months of age receiving IIV, diphtheria–tetanus–acellular pertussis-containing vaccines were equally likely to be received concomitantly in the 2012–2013 and 2010–2011 influenza seasons.

Sequential monitoring did not identify a statistically elevated risk for seizures following IIV in children; there was also no statistically elevated risk of GBS, encephalitis, or anaphylaxis following IIV in patients ≥6 months of age (data not shown). We ascertained

Table 1. Descriptive characteristics associated with first doses of 2012–2013 inactivated influenza vaccine (IIV) and live attenuated influenza vaccine (LAIV) in the Vaccine Safety Datalink

Characteristic	Number first doses of 2012–2013 IIV(% total) N = 3 596 793	Number first doses of 2012–2013 LAIV(% total) N = 256 406
Site		
A	263 065 (7.3%)	21 206 (8.3%)
B	109 448 (3.0%)	3615 (1.4%)
C	161 456 (4.5%)	32 218 (12.6%)
D	210 631 (5.9%)	13 030 (5.1%)
E	99 703 (2.8%)	5783 (2.3%)
F	1 229 724 (34.2%)	113 175 (44.1%)
G	221 999 (6.2%)	20 760 (8.1%)
H	1 300 767 (36.2%)	46 629 (18.2%)
Age		
6–23 months	117 869 (3.3%)	—
24–59 months	118 616 (3.3%)	49 447 (19.3%)
5–17 years	467 979 (13.0%)	167 613 (65.4%)
≥18 years	2 892 329 (80.4%)	39 366 (15.4%)
Sex		
Male	2 028 310 (56.4%)	137 183 (53.5%)
Female	1 568 367 (43.6%)	119 238 (46.5%)
Unknown	116 (<0.1%)	5 (<0.1%)

Table 2. End of surveillance analysis of inactivated influenza vaccine (IIV) and live attenuated influenza vaccine (LAIV) in the Vaccine Safety Datalink, 2012–2013 influenza season

Vaccine	Outcome	Study design	Age	Number first doses in 2012–2013 season	Number cases in risk interval, 2012–2013 season	Number cases in control interval, 2012–2013 season	Number cases in risk interval/number first doses, historical seasons 2005–2006 through 2009–2010	Historical controls	Relative risk, (95%CI)*
IIV	Seizures	Self-controlled risk interval†	6–23 months	117 869	4	13	—	—	1.1 (0.4, 3.3)
			24–59 months	118 616	6	10	—	—	2.1 (0.8, 5.8)
	Guillain-Barré syndrome	Cohort with historical controls‡	5–17 years	467 979	5	11	—	—	1.6 (0.6, 4.6)
			≥6 months	2 832 064	14	—	102/11 160 450	IIV recipients	0.5 (0.3, 0.9)
LAIV	Encephalitis	Cohort with historical controls‡	≥6 months	3 169 173	8	—	35/11 160 450	IIV recipients	0.8 (0.4, 1.8)
	Anaphylaxis	Cohort with historical controls‡	≥6 months	3 303 339	7	—	18/11 160 450	IIV recipients	1.3 (0.5, 3.1)
	Guillain-Barré syndrome	Cohort with historical controls‡	2–49 years	187 497	1	—	0/338 838	LAIV recipients	—
	Encephalitis	Cohort with historical controls‡	2–49 years	218 866	2	—	1/338 838	LAIV recipients	—
	Anaphylaxis	Cohort with historical controls‡	2–49 years	232 406	0	—	2/338 838	LAIV recipients	—

*Relative risks were not computed for outcomes following LAIV because of low exposure and case numbers.

†Only vaccinees with events in the risk or control intervals were informative for the analysis; events were not entered into the analysis unless lags in data accrual (depending on site and setting) and follow-up time (risk and control intervals) were complete. The risk interval for monitoring seizures following IIV was 0–1 days post-vaccination, whereas the control interval was 14–20 days post-vaccination.

‡Adjusted for age and site. Doses in the 2012–2013 season were not entered into the analysis unless lags in data accrual (depending on site) and the risk interval length (depending on outcome) were complete. The post-vaccination risk intervals were defined as 1–42 days for Guillain-Barré syndrome, 1–21 days for encephalitis, and 0–2 days for anaphylaxis.

GBS, encephalitis, and anaphylaxis following LAIV without formal statistical analyses in patients 2–49 years of age. Less than three of each of these outcomes were observed in the risk intervals (Table 2).

In analyses conducted after the completion of surveillance, no associations were found between IIV and risk of seizures in children ages 6–23 months, 24–59 months, or 5–17 years using a SCRI design (Table 2). Furthermore, IIV was not associated with elevated risk of encephalitis, anaphylaxis, or GBS in children or adults ages ≥ 6 months using a cohort design with historical controls (Table 2). In fact, IIV was associated with a statistically significant decreased risk of GBS (RR 0.5, 95%CI 0.3, 0.9).

DISCUSSION

The VSD conducted weekly surveillance of over 3.5 million first doses of 2012–2013 IIV and over 250 000 first doses of 2012–2013 LAIV. In children 16–23 and 24–59 months of age, IIV was less likely to be administered concomitantly with PCV13 in the 2012–2013 season than in the 2010–2011 season. This is presumably because of the March 2010 recommendation by the US Advisory Committee on Immunization Practices (ACIP) for children 14–59 months of age with four prior doses of seven-valent pneumococcal conjugate vaccine (PCV7) to receive a dose of PCV13, which was licensed in February 2010 and succeeded PCV7.¹³ No association between IIV and seizures was found in children in any age group (6–23 months, 24–59 months, or 5–17 years). IIV was also not associated with increased risk of GBS, encephalitis, or anaphylaxis in patients ≥ 6 months of age. Furthermore, fewer than three events were observed in the risk intervals for GBS, encephalitis, and anaphylaxis following LAIV in children and adults 2–49 years of age.

The lack of association between 2012–2013 IIV and seizures in children 6–23 months of age contrasts with findings from the 2010–2011 and 2011–2012 influenza seasons in the VSD, which found a 2.4-fold (95%CI 1.2-fold to 4.7-fold) increased risk of chart-confirmed febrile seizures among 6–59 month old children in the 2010–2011 season¹ and a similarly increased risk during the 2011–2012 season.⁴ Similar methodology, including study designs and outcome definitions, was used in the 2010–2011, 2011–2012, and 2012–2013 seasons, so the discordant findings cannot be attributed to differences in methods. As in the 2010–2011 and 2011–2012 seasons, we did not use outpatient visits to identify post-vaccination seizures because a prior study in the VSD found that the positive predictive value for seizure codes occurring in young

children in the outpatient setting was less than 20%.¹⁴ Our use of the SCRI design for all three seasons was also a strength because this approach inherently adjusts for time invariant confounders. During all three seasons, only one manufacturer had influenza vaccine products licensed for use in children less than 2 years of age, so the discordant findings were less likely to be because of a manufacturer-specific issue. The lack of an IIV-seizure association during the 2012–2013 season could potentially be due to the different strains contained in the 2010–2011/2011–2012 and 2012–2013 seasons, though we are unable to test this hypothesis, and it is unclear whether the changes in H3N2 and B strains would be sufficient to alter the risk for febrile seizures. The different findings over three influenza seasons highlight the importance of annual surveillance to assess influenza vaccine safety.

Findings should be interpreted in context of limitations. First, due to low event counts, we were unable to estimate measures of relative risks for LAIV. Second, although the cohort design with historical controls is more statistically powerful than the SCRI design for monitoring rare events, it may be biased if the historical comparator group does not reflect the true baseline risk. Because some studies have reported an association between 2009 H1N1 vaccine and GBS,¹⁵ we did not include individuals who only received 2009 H1N1 vaccines in our background rate estimates. However, some 2009 IIV vaccinees in our historical comparator group may have also received 2009 H1N1 vaccine. Thus, the apparent protective association between 2012–2013 IIV and GBS in the cohort design may be due to falsely elevated rates in our historical comparator group.

In conclusion, no safety concerns were identified in influenza vaccine safety surveillance during the 2012–2013 season in the VSD. These findings support the ACIP recommendation for influenza vaccination in persons ages ≥ 6 months of age.⁴ The VSD will continue to monitor the safety of influenza vaccines in future influenza seasons.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

CONFLICT OF INTEREST

RB has received research grants from Sanofi Pasteur, Novartis, GSK, and Protein Sciences. EB receives research support from MedImmune LLC. AN has received research funding from GlaxoSmithKline. The other authors do not have any conflicts of interest to report.

KEY POINTS

- Weekly surveillance for pre-specified adverse events following receipt of 2012–2013 influenza vaccines was conducted in the Vaccine Safety Datalink.
- No elevated risks for seizures, GBS, encephalitis, and anaphylaxis were identified in risk intervals following 2012–2013 inactivated influenza vaccine, as compared with a self-matched control interval or to historical controls.
- Less than three counts of seizures, GBS, encephalitis, and anaphylaxis occurred in the risk intervals following 2012–2013 live attenuated influenza vaccine.
- No increased risk was identified for any of the pre-specified outcomes following 2012–2013 influenza vaccinations in the Vaccine Safety Datalink.

ETHICS STATEMENT

Institutional review boards at CDC and each participating VSD site approved the study and determined that informed consent was not required.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's website.

Influenza Vaccine Safety Surveillance, 2012-13 Season

Web appendix 1. Outcome definitions for safety surveillance of influenza vaccines in the Vaccine Safety Datalink, 2012-13 influenza season

Outcome	ICD9 codes	Settings	Look back period and settings to define incidence	Other exclusions	Risk interval	Control Interval ¹
Seizures	780.3, 780.31, 780.32, 780.39	Inpatient, ED	6 months in inpatient, ED, or clinic setting	None	0-1 days	14-20 days
Guillain-Barré syndrome	357.0	Inpatient, ED, or outpatient	1 year in inpatient, ED, or clinic setting	None	1-42 days	----
Encephalitis	323.5*, 323.6*, 323.8*, 323.9, 341.2*	Inpatient or ED	1 year in inpatient, ED, or clinic setting	Exclude if associated with any of the following codes in 0-7 days after the index diagnosis: 047.0-047.1, 048, 049.0-049.8, 053*, 056*, 320*	1-21 days	----
Anaphylaxis	995.0 999.4	Inpatient or ED	6 months in inpatient or ED setting	None	0-2 days	----

¹Only applies to the self-controlled risk interval design, which was used to monitor seizures following inactivated influenza vaccine (IIV); does not apply to the cohort design with historical controls, which was used to monitor Guillain-Barré syndrome, encephalitis, and anaphylaxis following IIV and all outcomes following live attenuated influenza vaccine.

Influenza Vaccine Safety Surveillance, 2012-13 Season

Web appendix 2. Vaccines administered concomitantly with 1st dose 2012-13 IIV and 1st dose 2010-11 IIV by age in the Vaccine Safety Datalink

	Number 1 st IIV doses administered with concomitant vaccines of interest, by age and influenza season (% of IIV doses administered in age group during season)							
	6-11 months		12-15 months		16-23 months		24-59 months	
Vaccines administered concomitantly with IIV	2010-11 Season N=49,446	2012-13 Season N=47,372	2010-11 Season N=27,048	2012-13 Season N=28,168	2010-11 Season N=40,234	2012-13 Season N=42,329	2010-11 Season N=118,821	2012-13 Season N=118,616
13-valent pneumococcal conjugate vaccine ¹	27,484 (55.6%)	26,011 (54.9%)	12,138 (44.9%)	12,333 (43.8%)	7,821 (19.4%)	4,220 (10.0%)	22,749 (19.1%)	2,567 (2.2%)
Diphtheria-tetanus-acellular pertussis-containing vaccine ¹	27,828 (56.3%)	26,943 (56.9%)	9,667 (35.7%)	8,937 (31.7%)	9,563 (23.8%)	9,845 (23.3%)	12,151 (10.2%)	11,719 (9.9%)

¹With or without other concomitant vaccines