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Surveillance for Guillain-Barré syndrome after influenza vaccination among U.S. Medicare beneficiaries during the 2017–2018 season

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ABSTRACT

Background: The U.S. Food and Drug Administration and the Centers for Medicare & Medicaid Services have been actively monitoring the risk of Guillain-Barré syndrome (GBS) following influenza vaccination among Fee-for-Service (FFS) Medicare beneficiaries every season since 2008. We present our evaluation of the GBS risk following influenza vaccinations during the 2017–2018 season.

Methods: We implemented a multilayered approach to active safety surveillance that included near real-time surveillance early in the season, comparing GBS rates post-vaccination during the 2017–2018 season with rates from five prior seasons using the Updating Sequential Probability Ratio Test (USPRT), and end-of-season self-controlled risk interval (SCRI) analyses.

Results: We identified approximately 16 million influenza vaccinations. The near real-time surveillance did not signal for a potential 2.5-fold increased GBS risk either in days 8–21 or 1–42 post-influenza vaccination. In the SCRI analyses, we did not detect statistically significant increased GBS risks among influenza-vaccinated Medicare beneficiaries ≥65 years for either the 8–21 or 1–42-day risk windows for all seasonal vaccines combined, high-dose vaccine, or standard-dose vaccines; we did detect an increased GBS risk in days 8–21 post-vaccination for individuals vaccinated with the adjuvanted vaccine (OR: 3.75; 95% CI: 1.01, 13.96), although this finding was not statistically significant after multiplicity adjustment ($p = 0.146$).

Conclusions: Our multilayered surveillance approach—which allows for early detection of elevated GBS risk and provides reliable end-of-season SCRI estimates of effect size—did not identify an increased GBS risk following 2017–2018 influenza vaccinations. The slightly increased GBS risk with the adjuvanted vaccine, which was not statistically significant following multiplicity adjustment, is consistent with the package inserts of all U.S.-licensed influenza vaccines, which warn of a potential low increased GBS risk. The benefits of influenza vaccines in preventing morbidity and mortality heavily outweigh this potential risk.

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1. Introduction

Influenza vaccine safety monitoring is challenging because vaccine antigens change each season based on recommended influenza strains, and because new vaccines, produced with a diversity of manufacturing techniques, are frequently entering the U.S. market [1]. Given that most seasonal influenza vaccinations are administered during a short vaccination period, monitoring results should be produced rapidly to inform timely regulatory action. During the vaccination campaign for the 1976 swine influenza A(H1N1) pandemic threat, the risk of Guillain-Barré syndrome (GBS) [2–6] increased by nearly eight-fold during the six weeks post-vaccination and by approximately 18-fold during the two to three weeks post-vaccination with the monovalent A/New

Abbreviations: aIIV3, adjuvanted influenza vaccine; AR, attributable risk; CI, confidence interval; CMS, Centers for Medicare & Medicaid Services; CWF, Common Working File; FDA, U.S. Food and Drug Administration; FFS, Fee-for-Service; GBS, Guillain-Barré syndrome; IIV3-HD, inactivated trivalent high-dose vaccine; IIV3 +IIV4, inactivated trivalent and quadrivalent standard-dose vaccines; OR, odds ratio; PPV, positive predictive value; SCRI, self-controlled risk interval; SSD, Shared Systems Data; USPRT, updating sequential probability ratio test; VSD, Vaccine Safety Datalink.

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Jersey H1N1(swine) influenza vaccine used [7–9]. During seasonal influenza epidemics since 1976, several studies have assessed the GBS risk following inactivated influenza vaccination and found either no GBS risk or small risk increases representing approximately one to two additional cases per million vaccinees [10–17]. During the 2009–2010 pandemic, influenza A (H1N1) 2009 monovalent inactivated vaccines were associated in some studies with a small increased GBS risk, which translated to approximately one to three excess GBS cases per million vaccinees [18–22]. The U. S. Food and Drug Administration (FDA) and the Centers for Medicare & Medicaid Services (CMS), in collaboration with Acumen LLC, have been actively monitoring the GBS risk following influenza vaccination among Medicare beneficiaries for every influenza season since 2008 [23]. We used a multilayered approach to active safety surveillance, which consisted of near real-time surveillance for early detection of a high GBS risk, regular monitoring of GBS rates post-vaccination, and an end-of-season analysis aimed at obtaining the least biased risk estimate for the season. This multilayered approach is part of FDA's broader vaccine safety surveillance system. We summarize here the findings of our 2017–2018 active surveillance in Medicare.

2. Methods

We monitored GBS risk for days 8–21 and 1–42 following influenza vaccinations administered between August 12, 2017 and June 29, 2018 to U.S. Medicare beneficiaries enrolled in Fee-for-Service (FFS) Medicare Parts A (hospitalization) and B (outpatient medical care). We used days 8–21 post-vaccination as primary risk window because findings from prior studies, including those from the 1976 swine influenza vaccine, showed higher GBS risk in this window than in the 1–42 days post-vaccination window [9,10,19,21].

2.1. Data sources

Our surveillance system relied on Medicare enrollment and claims data. The observability of a GBS case depends on both, the clinical delay (period between time of vaccination and GBS occurrence in a clinical setting) and the processing delay (period between GBS occurrence and observation of its claim). Medicare claims data undergo three stages of processing: enumeration, adjudication, and final payment. We used two sources of claims data to identify influenza vaccinations and GBS diagnoses from the Inpatient (IP) and outpatient files: the weekly Common Working File (CWF), the claims data source used during previous seasons (available after adjudication), and the Shared Systems Data (SSD), which consists of claims sourced from an earlier point in CMS's data processing (after enumeration), which we used for near real-time surveillance for the first time this season. The delay between vaccination exposure and observation of GBS claims in the database causes real-time surveillance to contend with incomplete data—a challenge that using SSD helps address. For the end-of-season analyses, we used CWF data because these analyses were not conducted in near real-time.

We used Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT) codes from outpatient claims to identify influenza vaccinations and concomitantly administered vaccines (pneumococcal, hepatitis B, zoster, and tetanus toxoid-containing vaccines) (Supplementary materials; S-1, S-2). We also searched Part D (prescription drug coverage) claims for concomitant vaccine National Drug Codes (NDC) (Supplementary materials; S-3).

We identified GBS claims from the inpatient and outpatient settings using the International Classification of Diseases, Ninth Revision, Clinical modification (ICD-9-CM) code 357.0 (until September 30, 2015) and the International Classification of Diseases, Tenth Revision, Clinical modification (ICD-10-CM) code G61.0.

2.2. Near real-time surveillance

Our near real-time surveillance included all beneficiaries who received any influenza vaccine during the 2017–2018 influenza season. We required continuous enrollment in Medicare Parts A and B from the day of vaccination until the end of the relevant risk window, GBS event, or death, whichever occurred earlier. We defined exposure as the beneficiary's first influenza vaccination within the study period, and GBS occurrence as a primary-coded GBS hospitalization within the risk window post-vaccination. Beneficiaries with codes for two different types of influenza vaccines (<0.1%) were included in the primary analysis but excluded from the vaccine-type subgroup analyses.

We implemented a cohort design and conducted continuous weekly sequential testing using the Updating Sequential Probability Ratio Test (USPRT) method [20,24,25] to assess whether the observed GBS risk in the 8–21 and 1–42 post-vaccination risk windows was elevated relative to the GBS rate from the five prior influenza seasons (2012–2013 season to 2016–2017 season). The critical limit used in testing is adjusted for the delay in data acquisition [20,24,25]. Similar to the Vaccine Safety Datalink's (VSD) maxSPRT Poisson and binomial methods, USPRT consists of a series of tests conducted sequentially, with the overall test signaling if one of the individual tests is rejected. However, USPRT adjusts for the delay in the observation of GBS cases due to claims processing, which may be more appropriate for insurer databases where the delay is expected to be longer than in provider-based databases used in VSD. Furthermore, the VSD maxSPRT binomial method uses a control window, providing more effective control for confounding than USPRT, which uses a historical comparator.

Based on a simulation study [26], we initiated testing with data as of September 29, 2017 (week 7), by when we achieved reasonable power for the first test to detect a large effect size of interest, and ended with data as of October 27, 2017 (week 11), by when 69.7% of the season's vaccinations were administered (Fig. 1). We used an overall alpha of 0.05 apportioned equally among all tests and used Monte Carlo simulations to define a weekly testing threshold under the null hypothesis that the observed rate should not be higher than 2.5-times expected rate from historical data (our simulations indicated that a lower null hypothesis level would result in spurious signals for clinically insubstantial elevated risk) [26]. We conducted analyses for the overall population (all ages, all influenza vaccines) and for the following subgroups: (1) ≥65 years, all vaccines; (2) ≥65 years, inactivated trivalent high-dose vaccine (IIV3-HD); (3) ≥65 years, inactivated trivalent and quadrivalent standard-dose vaccines (IIV3 + IIV4).

2.3. Weekly descriptive analyses

Following completion of the near real-time surveillance, we continued assessing GBS rates post-vaccination on a weekly basis until the end of the season for the overall population (all ages, all influenza vaccines) and stratified by age groups (all ages, <65 years, ≥65 years) and vaccine types administered during the 2017–2018 season.

2.4. End-of-season analyses

We conducted end-of-season self-controlled risk interval (SCRI) [21] analyses to determine if the observed rates in the post-vaccination risk windows (days 8–21 and 1–42) were significantly higher than the GBS rates in the post-vaccination control windows (days 43–84). To deliver results at the Advisory Committee on

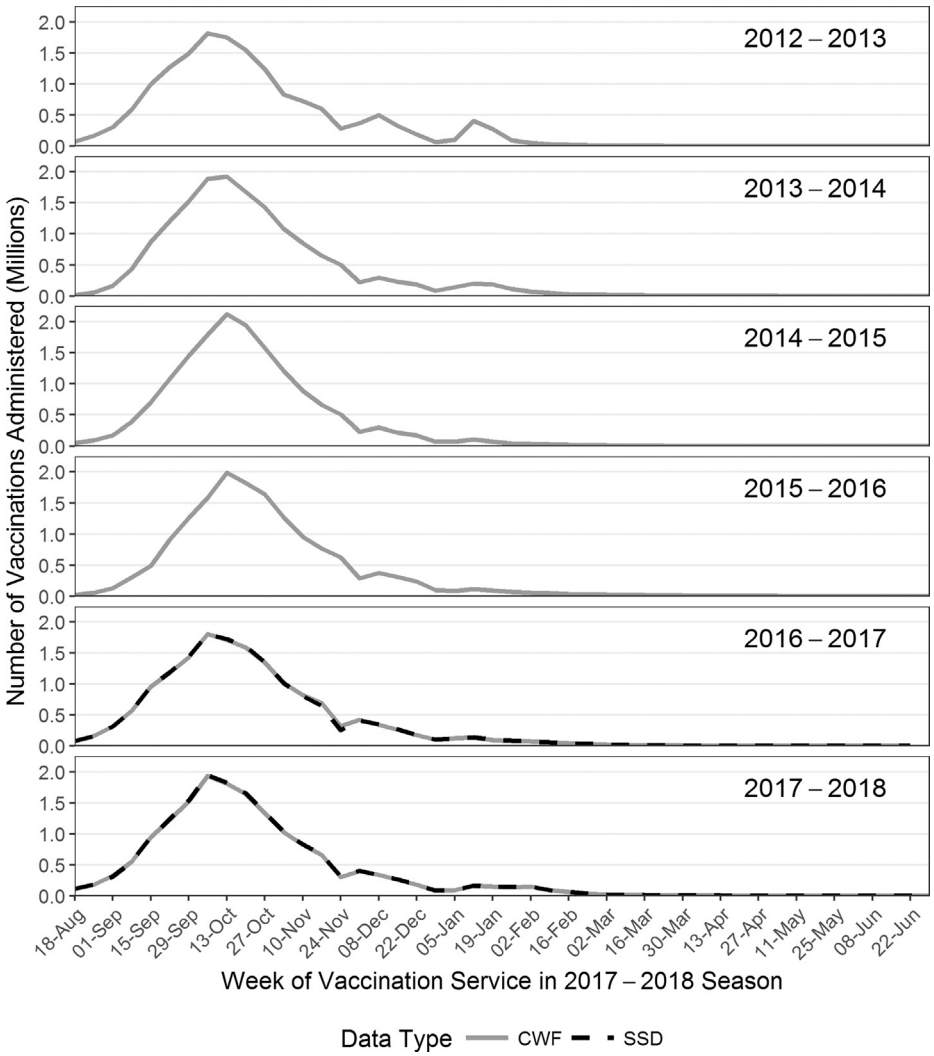

Fig. 1. Number of influenza vaccinations by vaccination week in the U.S. Fee-for-Service Medicare population; CWF data and SSD.

Immunization Practices June 2018 Meeting [27] we completed an "early vaccination cut-off" SCRI analysis wherein we used vaccination claims through January 5, 2018 (week 21) as the influenza vaccination cut-off. This cutoff captured approximately 95% of all vaccinations administered by the end of the season, and included GBS claims processed through May 18, 2018 (week 40) [27]. Specifications and results from this earlier end-of-season SCRI analysis are shown in supplementary materials (S-4, S-5). In this paper, we focus on the results produced from the final post-hoc SCRI analysis in which we used data received through September 14, 2018 to allow sufficient follow-up time for all vaccinations. The surveillance population consisted of beneficiaries ages ≥65 years who had a first GBS diagnosis within 84 days after vaccination and were discharged from the hospital with a GBS diagnosis in first diagnosis position. We required continuous enrollment for 183 days prior to the vaccination date through the end of the control window or death, whichever occurred earlier. If a beneficiary died or disenrolled prior to the end of the observation period, we still included the entire planned person-time of the individual in the risk and control windows. We excluded beneficiaries with: (1) a GBS diagnosis in any position and any setting during the 183 days pre-vaccination or on the influenza vaccination date or (2) a prior GBS claim in any setting more than seven days prior to the primary-coded GBS hospitalization. For this analysis, while exposure remained the beneficiary's first influenza vaccination within the study period, we defined an incident GBS case as the first occurrence of GBS during days 1–84 post-vaccination. We assigned each case's "earliest onset date" as either the hospitalization date or as the date of an earlier GBS claim in any position in the inpatient or outpatient settings in the seven days prior; thus, if a primary-coded GBS hospitalization occurred in the 85–91 days post-vaccination but the earliest onset date was determined to be 84 days post-vaccination or less, the case was included in the analyses.

We produced crude and seasonality-adjusted SCRI analyses [28–30] using both claims-based and imputed GBS cases. The positive predictive value (PPV) imputed bias analyses we performed simulated chart-confirmed GBS cases by sampling with probability equal to the PPV of 71.2% derived from the medical record review of GBS cases from the 2015–2016 influenza season [10]. Estimates were combined after repeating the imputation process 1000 times [31]. To adjust for seasonality, we used data from CDC's virologic surveillance to determine a weekly rate of confirmed influenza results calculated as the total positive influenza count divided by the total number of specimens submitted [32] in each of the ten U.S. Department of Health and Human Services regions across the United States. Following the definition of high and low influenza circulation for each region, the regional baseline risk was estimated from a Poisson regression model, which gives expected weekly number of GBS cases for each region. The weekly GBS

probability was then predicted for each region and combined using a weighted average to obtain the national GBS predicted probability for each week. Finally, the cumulative risk in the risk and control windows were estimated by a Poisson regression model and included in log scale as the offset term in the SCRI model.

For the 8–21 risk window, we conducted analyses stratified by concomitant vaccinations. We also conducted subgroup analyses by vaccine type (IIV3-HD, IIV3 + IIV4, and adjuvanted influenza vaccine (aIIV3)), and calculated multiplicity-adjusted p-values (q-values) using the Benjamini-Hochberg procedure [33].

We used conditional logistic regression models to calculate the odds ratios (ORs) with 95% CIs, offset by length of observation time. We calculated attributable risk (AR) as the difference in the expected number of GBS cases observed in the risk and control windows, divided by the total number of vaccinated beneficiaries. Additional details on the calculation of the ORs and AR as well as seasonality adjustment and PPV imputed bias analysis are described in Supplementary Materials S-6.

All analyses were conducted using R 3.3.4 (R Foundation for Statistical Computing, Vienna, Austria) and SAS v. 9.4 (SAS Institute Inc., Cary, NC, United States).

This study was performed as part of the SafeRx Project, a joint initiative of CMS and FDA. The Research Involving Human Subjects Committee of FDA's Center for Biologics Evaluation and Research approved the surveillance.

3. Results

3.1. Near real-time surveillance

Using CWF data, we observed approximately 1.7 million influenza vaccinations at the beginning (week 7) and approximately 7.5 million vaccinations at the end of the testing schedule (week 11). Leveraging SSD in our near real-time surveillance allowed us to observe about 0.6 million (33.6%) more vaccinations as of week 7 and about one million (13.5%) more as of week 11 than when we

Table 1
Descriptive statistics, Fee-for-Service influenza-vaccinated Medicare beneficiaries (all ages), near real-time surveillance (week 11), 2012–2018; 8–21-day window.*

	2012–2013		2013–2014		2014–2015		2015–2016		2016–2017		2017–2018	
	#	%	#	%	#	%	#	%	#	%	#	%
CWF data												
Influenza-vaccinated beneficiaries	7,445,821	100%	6,429,638	100%	7,113,172	100%	5,680,135	100%	7,324,662	100%	7,475,570	100%
Age (years)												
Mean (SD)	73.6 (10.6)	–	73.6 (10.6)	–	73.7 (10.3)	–	73.6 (10.5)	–	73.7 (10.3)	–	73.6 (10.2)	–
Median (IQR)	74 (68–81)	–	74 (68–81)	–	74 (68–81)	–	73 (68–80)	–	74 (68–80)	–	74 (68–80)	–
<65	814,643	10.9%	706,348	11.0%	716,992	10.1%	605,959	10.7%	721,947	9.9%	732,610	9.8%
65–74	3,102,897	41.7%	2,710,664	42.2%	3,093,731	43.5%	2,465,039	43.4%	3,239,693	44.2%	3,348,825	44.8%
75–84	2,458,367	33.0%	2,094,375	32.6%	2,299,577	32.3%	1,802,430	31.7%	2,317,104	31.6%	2,368,520	31.7%
≥85	1,069,914	14.4%	918,251	14.3%	1,002,872	14.1%	806,707	14.2%	1,045,918	14.3%	1,025,615	13.7%
Sex												
Male	3,098,368	41.6%	2,678,471	41.7%	2,995,427	42.1%	2,405,091	42.3%	3,090,053	42.2%	3,175,578	42.5%
Female	4,347,453	58.4%	3,751,167	58.3%	4,117,745	57.9%	3,275,044	57.7%	4,234,609	57.8%	4,299,992	57.5%
Vaccine type												
High-dose (IIV3-HD)	1,312,808	17.6%	1,599,629	24.9%	2,879,586	40.5%	2,880,772	50.7%	4,350,841	59.4%	4,603,409	61.6%
Standard, split virus (IIV3/4)	5,983,783	80.4%	4,739,829	73.7%	4,101,048	57.7%	2,701,032	47.6%	2,752,933	37.6%	1,806,254	24.2%
Adjuvanted (aIIV3)	–	–	43	<0.1%	700	<0.1%	363	<0.1%	117,100	1.6%	510,869	6.8%
Cell-based (ccIIV3/4)	59	<0.1%	1723	<0.1%	61,129	0.9%	48,350	0.9%	34,205	0.5%	410,165	5.5%
Recombinant (RIV3/4)	–	–	43	<0.1%	3159	<0.1%	1658	<0.1%	3478	<0.1%	14,039	0.2%
Intradermal (IIV3/4-ID)	25,719	0.3%	17,257	0.3%	7432	0.1%	4566	0.1%	12,877	0.2%	8680	0.1%
Other	123,452	1.7%	71,114	1.1%	60,118	0.8%	43,394	0.8%	53,228	0.7%	122,154	1.6%
SSD†												
Influenza-vaccinated beneficiaries	–	–	–	–	–	–	–	–	8,202,675	100%	8,489,974	100%
Age (years)												
Mean (SD)	–	–	–	–	–	–	–	–	73.7 (10.4)	–	73.6 (10.2)	–
Median (IQR)	–	–	–	–	–	–	–	–	73 (68–80)	–	73 (68–80)	–
<65	–	–	–	–	–	–	–	–	826,916	10.1%	838,223	9.9%
65–74	–	–	–	–	–	–	–	–	3,631,626	44.3%	3,818,324	45.0%
75–84	–	–	–	–	–	–	–	–	2,573,556	31.4%	2,668,557	31.4%
≥85	–	–	–	–	–	–	–	–	1,170,577	14.3%	1,164,870	13.7%
Sex												
Male	–	–	–	–	–	–	–	–	3,456,175	42.1%	3,595,714	42.4%
Female	–	–	–	–	–	–	–	–	4,746,500	57.9%	4,894,260	57.6%
Vaccine type												
High-dose (IIV3-HD)	–	–	–	–	–	–	–	–	4,797,326	58.5%	5,131,311	60.4%
Standard, split virus (IIV3/4)	–	–	–	–	–	–	–	–	3,123,846	38.1%	2,079,694	24.5%
Adjuvanted (aIIV3)	–	–	–	–	–	–	–	–	137,716	1.7%	607,470	7.2%
Cell-based (ccIIV3/4)	–	–	–	–	–	–	–	–	42,214	0.5%	464,290	5.5%
Recombinant (RIV3/4)	–	–	–	–	–	–	–	–	4,074	<0.1%	26,541	0.3%
Intradermal (IIV3/4-ID)	–	–	–	–	–	–	–	–	15,257	0.2%	10,237	0.1%
Other	–	–	–	–	–	–	–	–	82,242	1.0%	170,431	2.0%

Abbreviations: IQR, interquartile range; SD, standard deviation.

* Cumulative vaccinations for days 1–42 post-vaccination (secondary risk window) are slightly different (data not shown). These small differences are due to the enrollment criteria.

† Shared Systems Data was only available for the 2016–2017 and 2017–2018 seasons.

used CWF data. Descriptive statistics of influenza-vaccinated beneficiaries included in the near real-time surveillance (all ages) are shown in Table 1.

USPRT did not signal for a potential 2.5-fold increased risk of GBS either in days 8–21 or 1–42 post-influenza vaccination, compared with the five prior seasons we used as controls (Fig. 2). Results were consistent for the overall population and for all subgroup analyses (data not shown).

3.2. Weekly descriptive analyses

Following the end of the sequential testing, we continued to generate weekly descriptive statistics through the end of the season. We observed approximately 16.7 million influenza-vaccinated beneficiaries by week 46 (as of June 29, 2018). IIV3-HD accounted for 54%, IIV3 + IIV4 for 28%, aIIV3 for 9%, and cell-cultured vaccine for 6% of all 2017–2018 influenza vaccinations. We did not identify any increased GBS rate post-vaccination that required further investigation (Supplementary materials S-7).

3.3. End-of-season analyses

Upon the conclusion of the season, we conducted SCRI analyses, obtaining the least biased risk estimates for the season. We included a total of 14,169,847 influenza-vaccinated beneficiaries ages ≥65 years (median age: 74 years; interquartile range: 70–81 years). A total of 60.1% beneficiaries received IIV3-HD, 58.5% were women, and 90.9% did not receive any other vaccine on the same day. Descriptive statistics of beneficiaries by vaccine type administered are shown in Table 2.

3.3.1. Primary risk window (8–21 days post-vaccination)

For all seasonal influenza vaccines combined, we identified 26 GBS claims in the primary risk window and 70 in the 43–84 days post-vaccination used as control window (Fig. 3), resulting in an unadjusted OR of 1.11 (95% CI: 0.71, 1.75) and an AR of 0.19 (95% CI: −0.59, 0.95) per million vaccinations. Seasonality-adjusted analyses produced similar results. The analyses stratified by concomitant vaccination did not show statistically significant results either (Table 3).

We did not identify a statistically significant increased GBS risk for IIV3-HD (OR: 0.89 (95% CI: 0.48, 1.65)) per million vaccinations) or for IIV3 + IIV4 (OR: 1.00 (95% CI: 0.36, 2.75)). For aIIV3, there were five GBS claims in the primary risk window and four in the control window, resulting in an increased GBS risk (OR: 3.75 (95% CI: 1.01, 13.96); AR: 2.50 (95% CI: 0.02, 3.75) per million vaccinations). This result, however, was not robust after multiplicity adjustment (q = 0.15).

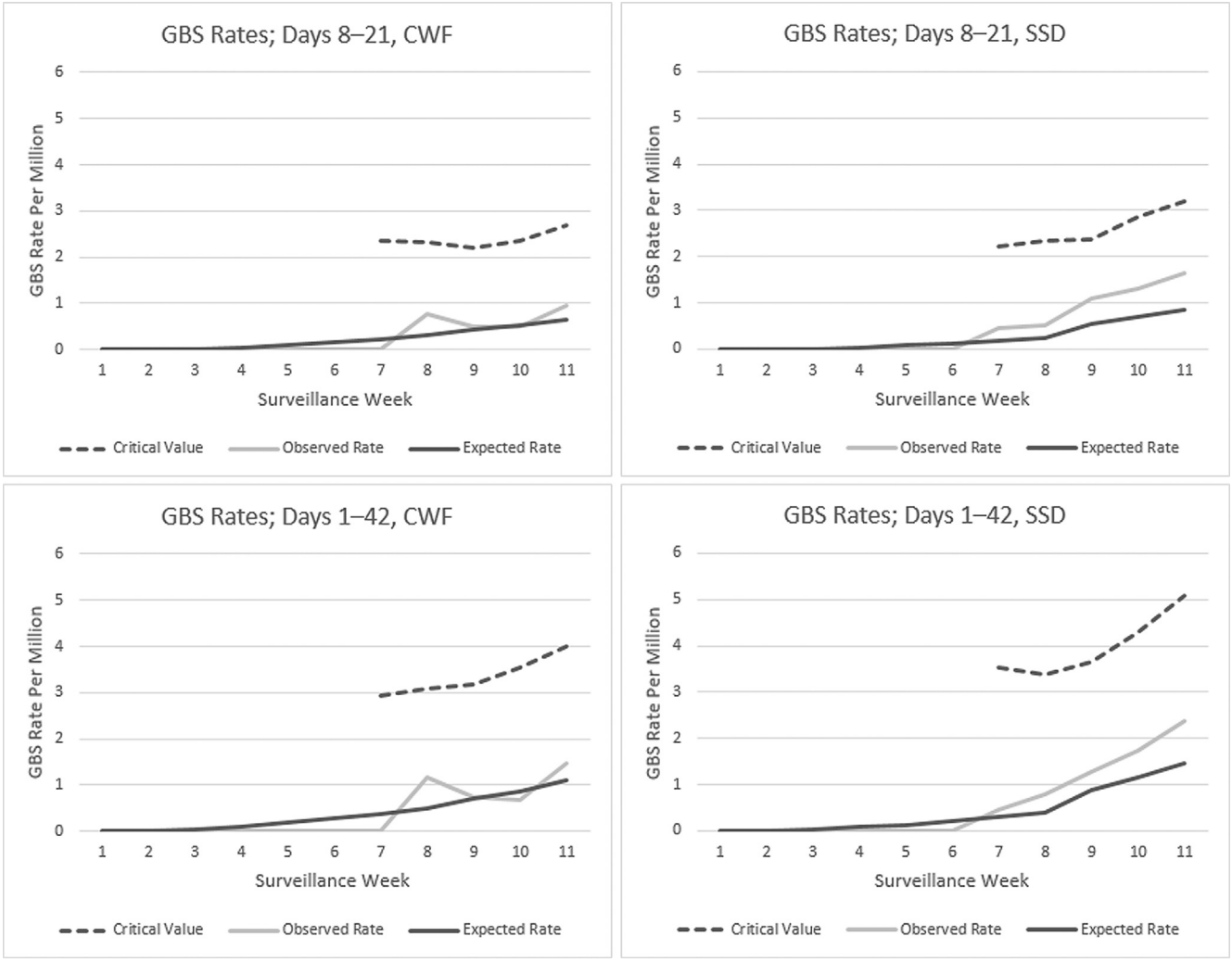

Fig. 2. Near real-time surveillance: GBS rates (weeks 7–11); all vaccines, all ages, risk windows: 8–21 and 1–42 days post-vaccination; CWF data and SSD.

Table 2
Descriptive statistics, Fee-for-Service Medicare influenza-vaccinated beneficiaries ages ≥65 years, end-of-season self-controlled risk interval analyses, by vaccine type, 2017–2018 (CWF data).

Subgroup	Vaccine type																	
	High-dose (IIV3-HD)		Standard-dose (IIV3 + IIV4)						Adjuvanted (aIIV3)		Cell-cultured (ccIIV4)		Recombinant				Intradermal (IIV4-ID)	
			Trivalent (IIV3)		Quadrivalent (IIV4)		IIV3/IIV4*						RIV3		RIV4			
	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
Influenza-vaccinated beneficiaries	8,521,267	100%	668,269	100%	1,915,039	100%	496,243	100%	1,464,557	100%	679,277	100%	5,469	100%	53,959	100%	13,300	100%
Age (years)																		
Mean (SD)	75.7 (7.5)	–	76.8 (8.2)	–	75.7 (7.8)	–	77.5 (8.5)	–	75.8 (7.6)	–	76.1 (7.8)	–	77.5 (8.7)	–	76.0 (7.7)	–	78.1 (8.9)	–
Median (IQR)	74 (70–81)	–	75 (70–83)	–	74 (69–81)	–	76 (70–84)	–	74 (70–81)	–	75 (70–81)	–	76 (70–84)	–	75 (70–81)	–	77 (70–85)	–
65–74	4,327,153	50.8%	309,486	46.3%	981,809	51.3%	213,821	43.1%	739,602	50.5%	332,878	49.0%	2401	43.9%	26,815	49.7%	5469	41.1%
75–84	2,940,618	34.5%	226,948	34.0%	630,455	32.9%	168,047	33.9%	498,161	34.0%	232,096	34.2%	1764	32.3%	18,608	34.5%	4263	32.1%
≥85	1,253,496	14.7%	131,835	19.7%	302,775	15.8%	114,375	23.0%	226,794	15.5%	114,303	16.8%	1304	23.8%	8536	15.8%	3568	26.8%
Sex																		
Male	3,577,685	42.0%	264,949	39.6%	788,115	41.2%	193,343	39.0%	607,734	41.5%	276,447	40.7%	1967	36.0%	22,411	41.5%	5169	38.9%
Female	4,943,582	58.0%	403,320	60.4%	1,126,924	58.8%	302,900	61.0%	856,823	58.5%	402,830	59.3%	3502	64.0%	31,548	58.5%	8131	61.1%
Concomitant vaccination																		
No	7,680,048	90.1%	629,078	94.1%	1,741,199	90.9%	463,545	93.4%	1,336,631	91.3%	634,594	93.4%	5059	92.5%	48,998	90.8%	12,598	94.7%
Any	841,219	9.9%	39,191	5.9%	173,840	9.1%	32,698	6.6%	127,926	8.7%	44,683	6.6%	410	7.5%	4961	9.2%	702	5.3%
PCV13	460,950	5.4%	18,210	2.7%	87,844	4.6%	15,147	3.1%	73,203	5.0%	23,220	3.4%	193	3.5%	2753	5.1%	273	2.1%
PSV23	305,585	3.6%	16,551	2.5%	68,522	3.6%	13,764	2.8%	43,522	3.0%	17,269	2.5%	174	3.2%	1769	3.3%	287	2.2%

Abbreviations: IQR, interquartile range; PCV13, Pneumococcal conjugate vaccine; PSV23, Pneumococcal polysaccharide vaccine; SD, standard deviation.
* Standard vaccine codes for which it is unclear whether they were specifically trivalent or quadrivalent.

3.3.2. Secondary risk window (1–42 days post-vaccination)

For all seasonal vaccines combined, we identified 70 GBS claims in the risk window and 70 in the control window (Fig. 3), yielding an OR of 1.00 (95% CI: 0.72, 1.39) and an AR of 0.00 (95% CI: −1.62, 1.62) per million vaccinations. Seasonality-adjusted analyses produced similar results (Table 3).

Results from the imputed analyses, none of which were statistically significant, are shown in Table 3.

4. Discussion

Overall, our findings did not indicate increased GBS risk following 2017–2018 influenza vaccinations. Our near real-time surveillance did not show signals for an increased GBS risk in days 8–21 and 1–42 post-vaccination compared with the five prior historical seasons used as controls, using a 2.5-fold risk threshold. Our end-of-season analyses, conducted among beneficiaries ages ≥65 years, did not find an increased GBS risk for the 2017–2018 seasonal influenza vaccines during days 8–21 and 1–42 post-vaccination compared with the control window. However, we did identify a slightly increased GBS risk in days 8–21 post-vaccination for aIIV3 in the unadjusted analysis, which was not statistically significant following multiplicity adjustment.

Our findings were similar to those obtained from other studies. CDC's VSD 2017–2018 rapid cycle analysis, which used both SCRI and current versus historical designs to evaluate the GBS risk during days 1–42 post-vaccination among 2.1 million IIV3 and 2.3 million IIV4 recipients ages ≥6 months, found that log-likelihood ratios that did not exceed the critical value [27]. Because the study included only 254,436 aIIV3 recipients, it was underpowered to evaluate the GBS risk following aIIV3.

FDA approved aIIV3 (Fluad®, standard-dose trivalent MF59 adjuvanted influenza vaccine, Seqirus Inc.), the first U.S. licensed seasonal adjuvanted influenza vaccine for use in adults ages ≥65 years, under accelerated approval regulations on November 24, 2015 [34]. As with all other U.S. approved influenza vaccines, the aIIV3's package insert warns of a potential excess GBS risk, slightly higher than one additional case per one million persons vaccinated [35]. As a comparator for our aIIV3 results, a recent review in the Vaccine Adverse Event Reporting System (VAERS) comprising data from July 2016 to June 2018 identified a total of four GBS cases, resulting in approximately two reported cases for every three million doses of aIIV3 distributed in the United States [36]. Thus, our finding of a potential slightly elevated GBS risk for aIIV3, considered within the context of other existing data, is not unexpected. During the 2009–2010 pandemic, some studies found lower GBS risk estimates for adjuvanted vaccines than for non-adjuvanted vaccines [18,19,37–43]. One possible explanation for the apparent (non-significant) risk difference between the (AS03) adjuvanted and non-adjuvanted vaccines found was the higher amount of influenza antigen in non-adjuvanted vaccines, although other factors could have also contributed [19]. In contrast to our study, these studies mostly included data from the ASO3-adjuvanted pandemic vaccine, which contained one third of the antigen amount found in the non-adjuvanted standard dose or the MF59-adjuvanted pandemic vaccine and showed high protection against influenza [44]. Also, this year's analysis of IIV3-HD was not consistent with previous years' surveillance. Unlike the past two seasons, our 2017–2018 surveillance did not identify an elevated GBS risk in days 8–21 post-vaccination with IIV3-HD. It is unknown whether the change in the H1N1 component, which, for the first time since the 2009–2010 pandemic, did not include the (a) H1N1 pandemic virus, contributed to this finding. However, despite potentially slightly elevated GBS risk estimates, the benefits of influenza vaccines in preventing influenza morbidity and

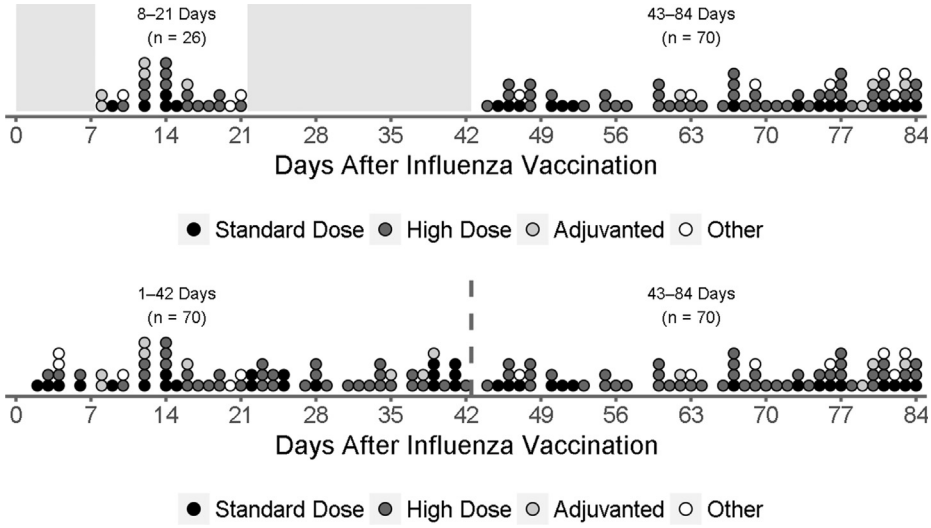

Fig. 3. Interval between influenza vaccination and GBS diagnosis among beneficiaries ages ≥65 years included in the end-of-season self-controlled risk interval analyses: all vaccines; risk windows: 8–21 and 1–42 days post-vaccination, control window: 43–84 days post-vaccination. The X-axis represents time interval in days post-vaccination. Day 0 is vaccination day. Y-axis represents number of GBS cases by vaccine type.

Table 3
End-of-season self-controlled risk interval analysis results: Odds ratios and attributable risks among influenza-vaccinated beneficiaries ages ≥65 years, 2017–2018.

Population	Number of GBS cases		Odds ratio	Odds ratio 95% CI	p-value*	Adjusted p-value*	Attributable risk (per million vaccinations)	Attributable risk (per million vaccinations) 95% CI
	Risk window	Control window						
Risk window: days 8–21 post-vaccination								
Influenza-vaccinated beneficiaries								
Claims-identified	26	70	1.11	(0.71, 1.75)	0.638	–	0.19	(−0.59, 0.95)
PPV imputed bias analysis	18.42	49.77	1.10	(0.59, 2.05)	0.756	–	0.12	(−0.63, 0.85)
Seasonality-adjusted influenza-vaccinated beneficiaries								
Claims-identified	26	70	1.13	(0.72, 1.78)	0.590	–	0.22	(−0.56, 0.97)
PPV imputed bias analysis	18.42	49.77	1.12	(0.60, 2.09)	0.719	–	0.14	(−0.61, 0.87)
Standard-dose influenza-vaccinated beneficiaries (IIV3 + IIV4)								
Claims-identified	5	15	1.00	(0.36, 2.75)	1.000	1.000	0.00	(−1.52, 1.52)
PPV imputed bias analysis	3.57	10.69	0.97	(0.23, 4.07)	0.966	1.000	−0.04	(−1.45, 1.40)
High-dose influenza-vaccinated beneficiaries (IIV3-HD)								
Claims-identified	13	44	0.89	(0.48, 1.65)	0.702	1.000	−0.20	(−1.15, 0.79)
PPV imputed bias analysis	9.23	31.28	0.87	(0.37, 2.07)	0.757	1.000	−0.16	(−1.07, 0.81)
Adjuvanted trivalent influenza-vaccinated beneficiaries (aIIV3)								
Claims-identified	5	4	3.75*	(1.01, 13.96)	0.049	0.146	2.50	(0.02, 3.75)
PPV imputed bias analysis	3.50	2.85	4.30	(0.00, ∞)	1.000	1.000	1.89	(-∞, ∞)
Influenza-vaccinated with concomitant vaccination								
Claims-identified	2	11	0.55	(0.12, 2.46)	0.430	–	−1.29	(−3.43, 1.85)
PPV imputed bias analysis	1.53	7.78	0.57	(0.08, 4.17)	0.578	–	−0.88	(−2.72, 1.95)
Influenza-vaccinated without concomitant vaccination								
Claims-identified	24	59	1.22	(0.76, 1.96)	0.411	–	0.34	(−0.46, 1.10)
PPV imputed bias analysis	17.04	41.99	1.21	(0.63, 2.33)	0.568	–	0.23	(−0.55, 0.96)
Risk window: days 1–42 post-vaccination								
Influenza-vaccinated beneficiaries								
Claims-identified	70	70	1.00	(0.72, 1.39)	1.000	–	0.00	(−1.62, 1.62)
PPV imputed bias analysis	49.86	49.81	1.00	(0.64, 1.56)	0.997	–	0.00	(−1.54, 1.55)
Seasonality-adjusted influenza-vaccinated beneficiaries								
Claims-identified	70	70	1.02	(0.73, 1.41)	0.927	–	0.08	(−1.55, 1.70)
PPV imputed bias analysis	49.86	49.81	1.02	(0.65, 1.59)	0.942	–	0.06	(−1.49, 1.60)

* Significant at $p < 0.05$

mortality heavily outweigh these potential risks. Specifically, the GBS risk following influenza disease is higher than any increased GBS risk following influenza vaccination identified after the 1976 swine influenza vaccination [45,46].

Our multilayered surveillance approach allows for early detection of elevated GBS risk and provides a reliable SCRI estimate of effect size. In 2017–2018, unlike previous influenza seasons, the accelerated near real-time surveillance testing, specifically

designed to timely detect elevated GBS risk, allowed us to obtain interim results by mid-November 2017 [26]. Moreover, by using SSD, we were able to reduce claims delay for both vaccinations and GBS cases, which allowed us to increase our population size for near real-time surveillance while still maintaining consistency of results when compared to CWF data. Therefore, using SSD for near real-time surveillance permits an earlier detection of safety signals, which could expedite the public health response to any potential signal, particularly in the context of future pandemics. We further assessed the GBS risk following influenza vaccination using SCRI analyses, which control for time-fixed confounders and provide a less biased risk estimate for the season. In the 2017–2018 season, for the first time, we provided end-of-season SCRI results by early June, including approximately 95% of all vaccinations administered by the end of the season [27]. When conducting SCRI analyses early in the season, cases occurring in the risk window are more likely to be observed than those occurring in the control window, due to differential claims delays in the risk and control windows. During 2017–2018, we addressed the issue of claims delay by restricting the analyses to beneficiaries vaccinated before January 5, 2018 (week 21), so GBS cases in both the risk and control windows had a high probability of being observed by May 8, 2018 (week 40). The end-of-season SCRI analysis we performed once we had 100% of the vaccinations found the same results, (Table 3) which supports our choice of an earlier analysis. We also investigated the feasibility of conducting end-of-season SCRI analyses even earlier. We conducted a simulation study using 2017–2018 data in which we directly controlled for delay in claims, considering both clinical and processing delays, by using an adjusted offset term in the SCRI model. This adjustment, had we implemented it during this season, would have allowed us to obtain risk estimates 20 weeks earlier (by December 29, 2017) [47].

The strengths of the Medicare FFS database for assessing vaccine safety includes the largest cohort of U.S. elderly with individually linked data containing demographic, diagnostic, and vaccination information. To our knowledge, this is the largest post-marketing study to investigate GBS risk following aIIV3 administration, however, we only observed nine GBS cases, giving us a 35% power to detect an OR of 3.0 (Supplementary materials S-8). Our study, however, did not account for time-varying confounders, including preceding illness and influenza seasonality (vaccine-type analyses) [45,48]. Therefore, we cannot exclude the possibility that our finding of a slightly elevated risk for aIIV3 could be due to unadjusted confounders. Our surveillance included only FFS Medicare beneficiaries for whom an influenza vaccination claim was submitted (approximately 16 million beneficiaries). Medicare allows vaccination billing from non-traditional providers, but some under-ascertainment may have occurred; a study comparing Medicare claims versus beneficiaries self-reported influenza vaccinations found than self-reported influenza vaccinations were higher (69.4%) than vaccination claims (48.3%) [49]. Thus, the restriction to influenza-vaccinated beneficiaries in both our near real-time surveillance and end-of-season analyses helped us avoid potential bias due to claims for influenza vaccination not submitted by the beneficiary to Medicare. However, whether influenza-vaccinated beneficiaries not captured using claims data differed from our study population regarding GBS risk is unknown. Although sequential analyses using USPRT has proven useful for near real-time GBS surveillance after influenza vaccination [21,23], USPRT's use of historical data as comparators presents some limitations. These analyses do not implicitly account for time-fixed confounders and do not adjust for shifts over time in the vaccinated population such as secular trends, differences in population characteristics, or differences in influenza vaccines and concomitant vaccines being administered. Our subgroup analyses partially address shifts in age of influenza-vaccinated beneficiaries and vaccine type, but other confounding factors are left unaddressed. Also, we only included cases with hospital discharge diagnoses of GBS in the primary position, so we may have missed some GBS cases. However, prior work found that the PPV of the ICD-9-CM diagnosis code for GBS in secondary diagnosis positions was significantly lower (7.8%) than in first diagnosis position (68.2%) [21]. During this season, we did not conduct medical chart review because this would have added substantial time to the surveillance effort; we relied instead on the relatively high PPV of the ICD-10-CM diagnosis code for GBS obtained during the 2015–2016 season (71.2%) [10]. Also, in the SCRI analyses, we excluded influenza-vaccinated beneficiaries who had a GBS claim in any setting more than seven days prior to the GBS hospitalization, which could have led to an underestimation of GBS cases. Nonetheless, GBS is a well-defined acute disease with serious clinical sequelae that usually requires hospitalization rapidly [21]. However, by reassigning each case's onset date in our post-hoc SCRI analyses as the first GBS claim in any position and any setting (when it occurred within the seven days prior to the primary-code GBS hospitalization) instead of the GBS hospitalization date, when applicable, we minimized measurement error. We observed that approximately 18% of primary-coded GBS hospitalizations (regardless of influenza vaccination) in the 2017–2018 season had a previous GBS diagnosis in the seven days prior (unpublished data). Prior work also showed that 75% of cases had a GBS hospitalization admission date within seven days of GBS onset [21].

In summary, our multilayered approach—which allows for early detection of elevated GBS risk before all seasonal vaccinations have occurred and provides a reliable end-of-season SCRI estimate of effect size—did not identify an increased GBS risk following the ensemble of 2017–2018 influenza vaccinations. The increased GBS risk found in our SCRI analyses following vaccination with aIIV3, which became not statistically significant after multiplicity adjustment, will benefit from continued monitoring in coming seasons. These findings are consistent with the package insert of all influenza vaccines distributed in the United States, which warn, although with inconclusive evidence for a causal relationship, of a minimally increased GBS risk. The benefits of influenza vaccines in preventing morbidity and mortality heavily outweigh this potential risk.

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Conflicts of interest

None declared.

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Disclaimer

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.05.041.

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