The Journal of Infectious Diseases

MAJOR ARTICLE

Guillain-Barré Syndrome After High-Dose Influenza Vaccine Administration in the United States, 2018–2019 Season

Silvia Perez-Vilar,[1,a] Mao Hu,[2] Eric Weintraub,[3] Deepa Arya,[1,a] Bradley Lufkin,[2] Tanya Myers,[3] Emily Jane Woo,[1] An-Chi Lo,[2] Steve Chu,[4] Madeline Swarr,[2] Jiemin Liao,[2] Michael Wernecke,[2] Tom MaCurdy,[2,5] Jeffrey Kelman,[4] Steven Anderson,[1] Jonathan Duffy,[3] and Richard A. Forshee[1]

[1]Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA, [2]Acumen LLC, Burlingame, California, USA, [3]Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, Georgia, USA, [4]Centers for Medicare & Medicaid Services, Washington, DC, USA, [5]Department of Economics, Stanford University, Stanford, California, USA

Background. The Vaccine Safety Datalink (VSD) identified a statistical signal for an increased risk of Guillain-Barré syndrome (GBS) in days 1–42 after 2018–2019 high-dose influenza vaccine (IIV3-HD) administration. We evaluated the signal using Medicare.

Methods. We conducted early- and end-of-season claims-based self-controlled risk interval analyses among Medicare beneficiaries ages ≥65 years, using days 8–21 and 1–42 postvaccination as risk windows and days 43–84 as control window. The VSD conducted chart-confirmed analyses.

Results. Among 7 453 690 IIV3-HD vaccinations, we did not detect a statistically significant increased GBS risk for either the 8- to 21-day (odds ratio [OR], 1.85; 95% confidence interval [CI], 0.99–3.44) or 1- to 42-day (OR, 1.31; 95% CI, 0.78–2.18) risk windows. The findings from the end-of-season analyses were fully consistent with the early-season analyses for both the 8- to 21-day (OR, 1.64; 95% CI, 0.92–2.91) and 1- to 42-day (OR, 1.12; 95% CI, 0.70–1.79) risk windows. The VSD's chart-confirmed analysis, involving 646 996 IIV3-HD vaccinations, with 1 case each in the risk and control windows, yielded a relative risk of 1.00 (95% CI, 0.06–15.99).

Conclusions. The Medicare analyses did not exclude an association between IIV3-HD and GBS, but it determined that, if such a risk existed, it was similar in magnitude to prior seasons. Chart-confirmed VSD results did not confirm an increased risk of GBS.

Keywords. Guillain-Barré syndrome; influenza vaccines; self-controlled risk interval; sequential tests; vaccine safety.

An association between influenza vaccination and Guillain-Barré syndrome (GBS) was first noticed during the 1976 swine influenza vaccination campaign in the United States [1–3]. Since then, several studies have assessed the GBS risk after influenza vaccination and found either no risk or small risk increases representing approximately 1 to 3 additional cases per million vaccine recipients [4–17]. The US Food and Drug Administration (FDA) and the Centers for Medicare & Medicaid Services (CMS), in collaboration with Acumen LLC, have used claims data to actively monitor the GBS risk after influenza vaccination for every influenza season since 2008 [9, 10, 15–19]. The Vaccine Safety Datalink (VSD), a collaborative project between the Centers for Disease Control and Prevention (CDC) and 8 integrated healthcare organizations, monitors GBS after influenza vaccination since 2009, using electronic health records [20, 21].

In 2009, the FDA licensed the high-dose influenza vaccine ([IIV3-HD] Fluzone High-Dose) for use in individuals ages ≥65 years using accelerated approval regulations [22]. The IIV3-HD is an injectable inactivated trivalent egg-based influenza vaccine containing 4 times more influenza hemagglutinin antigen than standard-dose vaccines. Some studies have shown higher effectiveness for IIV3-HD compared with standard-dose vaccines for the prevention of influenza-related medical encounters, hospitalizations, and death in most seasons [23–25]. During the 2015–2016 and 2016–2017 seasons, FDA and CMS identified a slightly elevated GBS risk for IIV3-HD in days 8–21 postvaccination, consistent with the risk noted in the US package insert [15]; however, the 2017–2018 surveillance did not identify an elevated risk [16].

Although in prior seasons the VSD had not detected an increased GBS risk after IIV3-HD, it did identify a statistical signal early in the 2018–2019 season. The FDA and CMS, in collaboration with the CDC, rapidly investigated the GBS risk after 2018–2019 IIV3-HD and all seasonal influenza vaccinations combined, using the Medicare database, a larger database for

Received 31 March 2020; editorial decision 6 July 2020; accepted 9 September 2020; published online November 2, 2020.

[a]Present Affiliation: Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland.

Presented in part: Advisory Committee on Immunization Practices (ACIP) Meeting, June 26–27, 2019, Atlanta, GA; 35th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, August 24–28, 2019, Philadelphia, PA.

Correspondence: Richard A. Forshee, PhD, Center for Biologics Evaluation and Research, US Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Room 1226, Silver Spring, MD 20993 (richard.forshee@fda.hhs.gov).

The Journal of Infectious Diseases® 2020;XX:1–10

DOI: 10.1093/infdis/jiaa543

the target study population than the ones available to the VSD. This manuscript describes the results of these investigations.

METHODS

Rapid Cycle Analysis in the Vaccine Safety Datalink

The VSD conducted rapid cycle analysis [26] to sequentially monitor, on a weekly basis, the risk of GBS and other selected adverse events among individuals ages ≥6 months vaccinated with any seasonal influenza vaccine from July 1, 2018 through April 3, 2019, using current-vs-historical and self-controlled risk interval (SCRI) designs [27, 28]. The methods we describe here focus on the investigation of GBS risk in days 1–42 after IIV3-HD administration among individuals ages ≥65 years.

Data Sources (Vaccine Safety Datalink)

The analyses used data from the following VSD sites: HealthPartners Institute (Minneapolis, MN), Marshfield Clinic Research Institute (Marshfield, WI), and Kaiser Permanente of the following: Colorado (Denver), Northwest (Portland, OR), Northern California (Oakland, CA), Southern California (Pasadena, CA), and Washington (Seattle, WA).

Exposure and Outcome Definition (Vaccine Safety Datalink)

The VSD used electronic vaccine registries to capture influenza vaccine administrations using the current HL7 standard CVX codes (Supplementary Material S1) [29]. Where appropriate, the VSD used the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code 357.0 and the *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) code G61.0, to identify all first-in-365-days potential GBS cases from the inpatient, outpatient clinic, and emergency room settings. To account for partially elapsed risk windows and late-arriving data, the VSD adopted previously described methods [30, 31]. Because the VSD identified a statistical signal, they conducted a per-protocol chart review of all potential GBS cases to confirm disease onset and classify cases according to the GBS case definition developed by the Brighton Collaboration (BC) [32].

Statistical Analyses (Vaccine Safety Datalink)

To provide real-time monitoring of GBS risk, the VSD used a Poisson-based maximized sequential probability ratio test (maxSPRT) stratified by site to compare the observed number of GBS cases in the 1–42 days after IIV3-HD administration with the number expected based upon historical rates of GBS occurring within 1–42 days after administration of trivalent and quadrivalent influenza vaccines in prior seasons (2012–2016) [30, 33]. The VSD also conducted SCRI analyses using a sequential method binomial maxSPRT [30, 33], comparing the number of GBS cases in days 1–42 postvaccination (risk window) with that in days 43–84 postvaccination (control window). For both the Poisson and SCRI analyses, the VSD defined a statistical signal when the log-likelihood ratio test statistic exceeded the prespecified critical value [20, 21]. After chart review, the VSD conducted an end-of-season nonsequential SCRI analysis comparing the number of confirmed GBS cases identified in the risk window versus that in the control window.

Self-Controlled Risk Interval Analyses in Medicare

After the VSD statistical signal, the FDA, CMS, and Acumen LLC, in collaboration with the CDC, to conduct a per-protocol early-season SCRI analysis [34] to assess the GBS risk after IIV3-HD and all seasonal influenza vaccines combined administered from August 11, 2018 through November 9, 2018, to Medicare beneficiaries ages ≥65 years enrolled in Medicare Fee-for-Service (FFS) Parts A (hospitalization) and B (outpatient medical care) (Figure 1). As further evaluation of the early season results, we conducted a per-protocol end-of-season SCRI analysis including influenza vaccinations administered through June 29, 2019 (Supplementary Material S2).

Data Sources (Medicare)

We used Medicare enrollment and claims data [35]. In the early-season analyses, we included claims observed through March 15, 2019 (week 31), which allowed us to capture approximately 84% of IIV3-HD administrations with approximately 96% claims maturity (probability of observing GBS cases in the control window given that they had occurred), using November 9, 2018 as vaccination cutoff date (Supplementary Material S3). In the end-of-season analyses, we included claims observed through September 27, 2019 (including approximately 100% of IIV3-HD administrations with approximately 99.9% claims maturity).

Exposure and Outcome Definition (Medicare)

We defined exposure as the beneficiary's first influenza vaccination within the study period, and we defined an incident GBS case as a vaccinated beneficiary discharged from a hospital during days 1–84 postvaccination with a GBS diagnosis (ICD-10-CM code G61.0) in first diagnosis position. We required continuous enrollment for 183 days before vaccination through the end of the control window or death, whichever occurred earlier (Supplementary Material S4). If a beneficiary died before the end of the observation period, we included the entire planned person-time of the individual. We excluded beneficiaries if there was one of the following: (1) a GBS diagnosis in any position/setting during the 183 days prevaccination or on the influenza vaccination date or (2) a GBS diagnosis in any setting more than 7 days before the primary-coded GBS hospitalization. To minimize measurement error, we assigned each GBS case's "earliest onset date" as either the hospitalization date or as the date of the first GBS claim in any position/setting in the 7 days prior [16]. We used Healthcare Common Procedure Coding System and Current Procedural Terminology codes from outpatient claims to identify administered vaccines (Supplementary Material S5 and S6). We also searched Part D (prescription drug coverage)

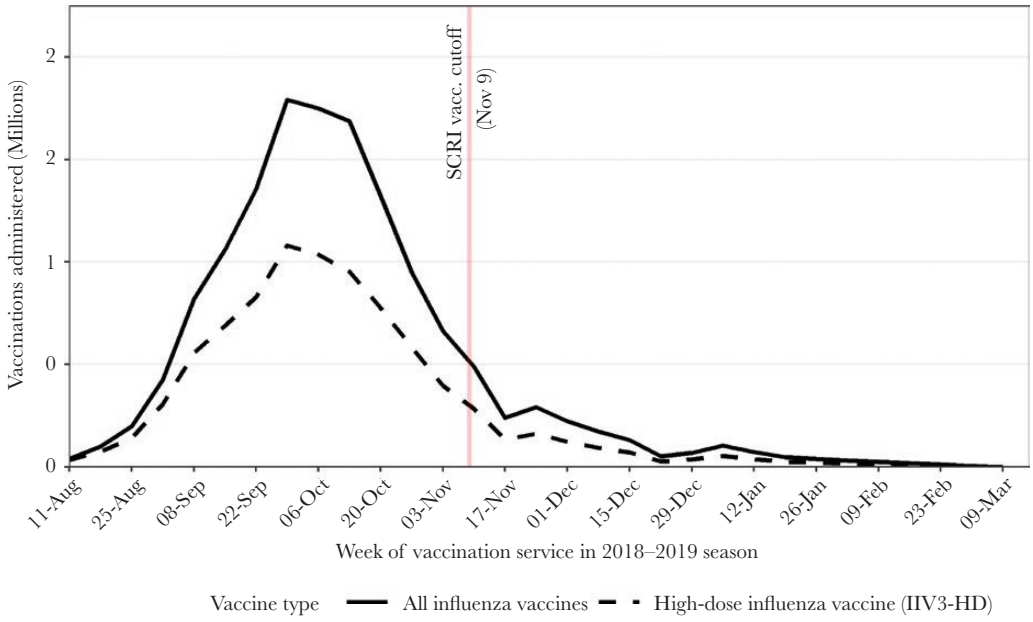

Figure 1. Medicare Fee-for-Service population number of overall seasonal and high-dose influenza vaccine administrations in the early-season surveillance population by vaccination week. SCRI, self-controlled risk interval.

claims for concomitant vaccines using National Drug Codes (Supplementary Material S7).

Statistical Analyses (Medicare)

We completed crude and seasonality-adjusted SCRI analyses [23, 24, 36] using claims-based GBS cases. We used days 8–21 and 1–42 postvaccination as primary and secondary risk windows, respectively, and days 43–84 postvaccination as control window. We selected days 8–21 postvaccination as primary risk window because prior studies' findings showed higher risk in this window [1, 10, 11, 15, 16]. For the early-season analyses, we also used imputed chart-confirmed cases. The imputed quantitative bias analysis sampled chart-confirmed GBS cases with probability equal to the positive predictive value (PPV) of 71.2%, derived from the medical record review we conducted during the 2015–2016 influenza season [15]; odds ratio (OR) estimates were combined after repeating the imputation process 1000 times [37]. To adjust for seasonality, we used the CDC's virologic surveillance data [38]. We used conditional logistic regression to calculate the ORs with 95% confidence intervals (CIs), offset by length of observation time. We calculated attributable risk (AR) as the difference in the number of GBS cases observed in the risk and control windows, divided by the total number of vaccinated beneficiaries. Details on the calculation of the ORs, AR, seasonality adjustment, and PPV-imputed quantitative bias analysis are described elsewhere [16, 23, 39]. Our power calculations showed that our early analyses would have 99% power to detect an OR of 4.0, 92% power to detect an OR of 3.0, and 56% power to detect an OR of 2.0 in the primary risk window (Supplementary Material S8.1).

We conducted the Medicare study as part of the SafeRx Project, a joint initiative of CMS and the FDA [40]. The Research Involving Human Subjects Committee of the FDA's Center for Biologics Evaluation and Research approved the surveillance. For the VSD study, the institutional review boards of each participating site approved the study. The analyses were conducted using R 3.3.4 (R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Rapid Cycle Analysis in the Vaccine Safety Datalink

A total of 646 996 (45.9%) members received IIV3-HD, with a median age of 73 years (interquartile range [IQR], 69–79 years). Descriptive statistics by vaccine type are shown in Table 1.

Self-Controlled Risk Interval Analysis

During the week of December 9, 2018, the VSD detected a statistical signal for GBS after IIV3-HD using the binomial SCRI method. By then, the VSD sites had administered 614 200 doses of IIV3-HD and observed 5 GBS cases within days 1–42 after IIV3-HD versus zero cases in the 43- to 84-day comparison window (Table 2). This resulted in a relative risk (RR) of 11 and a corresponding log-likelihood ratio (LLR) of 3.47 that exceeded the critical value of 3.39.

As of April 3, 2019 (final VSD surveillance week), there were 9 potential GBS cases within 1–84 days after 645 362 IIV3-HD doses; 8 cases occurred during days 1–42 postvaccination, and 1 case occurred during days 43–84 postvaccination. After chart review, the VSD confirmed 1 GBS case in the risk window (onset on day 1), classified as BC

Table 1. Beneficiaries' characteristics, Vaccine Safety Datalink, Influenza Vaccinated Populations Ages ≥65 Years From July 1, 2018 to April 3, 2019

Beneficiaries' Characteristics	All Influenza-Vaccinated Beneficiaries		Vaccine Type													
			High-Dose[a] (IIV3-HD)		Standard Dose						Adjuvanted (aIIV3)		Cell-Cultured (ccIIV4)		Recombinant (RIV4)	
					Trivalent (IIV3)		Quadrivalent (IIV4)		IIV3/IIV4							
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Influenza-vaccinated beneficiaries	1 410 974	100%	646 996	100%	36 775	100%	558 907	100%	595 682	100%	27 449	100%	114 387	100%	26 460	100%
Age (years)																
Mean (SD)	74 (8.3)	-	74.4 (8.1)	-	73.9 (8.3)	-	73.7 (7.9)	-	73.7 (8)	-	72.9 (8.2)	-	73.9 (8.0)	-	73.5 (8.2)	-
Median (IQR)	72 (68–78)	-	73 (69–79)	-	72 (68–79)	-	72 (68–78)	-	72 (68–78)	-	71 (68–76)	-	72 (68–78)	-	72 (68–78)	-
65–74	853 049	60.5%	378 257	58.5%	22 841	62.1%	347 431	62.2%	370 272	62.2%	18 310	66.7%	69 487	60.7%	16 723	63.2%
75–84	410 980	29.1%	195 773	30.3%	9461	25.7%	158 063	28.3%	167 524	28.1%	7066	25.7%	33 365	29.2%	7252	27.4%
≥85	146 945	10.4%	72 966	11.3%	4473	12.2%	53 413	9.6%	57 886	9.7%	2073	7.6%	11 535	10.1%	2485	9.4%
Sex[b]																
Male	630 283	44.7%	286 373	44.3%	16 208	44.1%	251 545	45.0%	267 753	44.9%	11 989	43.7%	52 451	45.9%	11 717	44.3%
Female	780 676	55.3%	360 615	55.7%	20 567	55.9%	307 358	55.0%	327 925	55.1%	15 458	56.3%	61 935	54.1%	14 743	55.7%
Concomitant Vaccination																
No	1 303 855	92.4%	594 235	91.8%	35 431	96.3%	518 113	92.7%	553 544	92.9%	24 824	90.4%	106 983	93.5%	24 269	91.7%
Any	107 119	7.6%	52 761	8.2%	1344	3.7%	40 794	7.3%	42 138	7.1%	2625	9.6%	7404	6.5%	2191	8.3%

Abbreviations: IIV3-HD, high-dose influenza vaccine; IQR, interquartile range; SD, standard deviation.

[a]The total number of high-dose vaccinations is slightly higher in the descriptive analysis than in the statistical sequential analysis due to missing variables.

[b]A very small number of records are missing sex.

Level 2, and 1 in the control window (onset on day 61), classified as BC Level 1. The VSD ruled out other 7 cases because they either were historical cases (n = 2), had alternative diagnoses (n = 2), symptom onset before or on vaccination day (n = 2), or lack of evidence for a GBS diagnosis (n = 1). The end-of-season nonsequential chart-confirmed SCRI analysis involved 646 996 IIV3-HD vaccinations and yielded a RR of 1.00 (95% CI, 0.06–15.99) (Tables 1 and 2).

Current-Versus-Historical Poisson Analysis

During the week in which the VSD identified a statistical signal using the SCRI method (December 9, 2018), the current-vs-historical Poisson analysis did not signal. Because of the more stringent data-lag adjustment required when implementing the binomial SCRI method, there was 1 additional case in the current-vs-historical Poisson, which led to 6 cases identified in the 42-day risk window vs 3.89 expected cases. The RR was 1.54 and the LLR was 0.49, which did not exceed the critical value of 3.03. The end-of-season current-vs-historical Poisson analysis did not signal after observing 8 cases versus an expected number of 4.99 cases, with a corresponding RR of 1.60 and LLR of 0.76.

Self-Controlled Risk Interval Analyses in Medicare

For the early-season analyses, the study population included 12 159 346 influenza-vaccinated beneficiaries. Of them, 7 453 690 (61.3%) received IIV3-HD. Among those vaccinated with IIV3-HD, the median age was 75 years (IQR, 70–81 years), 58% were women, and 91% did not receive other vaccinations in the same day. The end-of season study population included 14 437 945 beneficiaries vaccinated with any influenza vaccine; of them, 8 667 640 (60.0%) received IIV3-HD. Descriptive statistics by vaccine type are shown in Table 3 and Supplementary Material S9.

Primary Risk Window (8–21 Days Postvaccination)

For the early-season analyses, we identified 16 GBS claims in the primary risk window after IIV3-HD and 26 in the control window (Figure 2), resulting in an OR of 1.85 (95% CI, 0.99–3.44) and an AR of 0.98 (95% CI, −0.02 to 1.82) per million influenza-vaccinated beneficiaries (Table 4). We obtained an OR of 1.84 (95% CI, 0.78–4.31) in the PPV-imputed quantitative bias analysis. For the end-of-season analysis, we identified 18 and 33 GBS claims after IIV3-HD in the primary risk and control windows, respectively, resulting in an OR of 1.64 (95% CI, 0.92–2.91) and an AR of 0.81 (95% CI, −0.14 to 1.63) per million influenza-vaccinated beneficiaries (Figure 3; Table 4).

For the early-season analyses, we obtained an OR of 1.57 (95% CI, 0.94–2.63) for all influenza vaccines combined and an AR of 0.66 (95% CI, −0.09 to 1.33) per million vaccinated beneficiaries; the OR we obtained in the PPV-imputed quantitative bias analyses was 1.56 (95% CI, 0.78–3.15). In the end-of-season analysis, we observed an OR of 1.58 (95% CI, 1.00–2.51) and an AR of 0.72 (95% CI, 0.00–1.36) per million influenza-vaccinated beneficiaries.

Table 2. Vaccine Safety Datalink Rapid Cycle and End-of-Season Analysis Results

Analysis		Early Analysis (December 9, 2018)	End-of-Season Analysis (April 3, 2019)
Number of IIV3-HD Administrations		614 200	645 362
Sequential self-controlled risk interval analysis	GBS cases[a] in days 1–42 postvaccination (risk window)	5	-
	GBS cases[a] in days 43–84 postvaccination (control window)	0	-
	Relative risk	11	-
	LLR/critical value	3.47/3.39	-
Nonsequential self-controlled risk interval analysis	Chart-confirmed GBS cases in days 1–42 postvaccination (risk window)	-	1
	Chart-confirmed GBS cases in days 43–84 postvaccination (control window)	-	1
	Relative risk	-	1
	95% CI	-	(0.06–15.99)
Current-vs-historical Poisson analysis	Observed GBS cases[a]	6	8
	Expected GBS cases[b]	3.89	4.99
	Relative risk	1.54	1.6
	LLR/critical value	0.49/3.03	0.76/3.03

Abbreviations: CI, confidence interval; GBS, Guillain-Barré syndrome; IIV3-HD, High-dose influenza vaccine; LLR, log-likelihood ratio of the maximized sequential probability ratio test.

[a]*International Classification of Diseases, Tenth Revision* (ICD-10) coded cases.

[b]Expected GBS cases were calculated based on site-specific historical rates (combined rate across all sites: 9.04 per million vaccinations in ages ≥65 years). *International Classification of Diseases, Nineth Revision* and ICD-10 coded cases.

Secondary Risk Window (1–42 Days Postvaccination)

For the early-season analyses, we identified 34 GBS claims in the secondary risk window after IIV3-HD vaccination and 26 claims in the control window (Figure 2), resulting in an OR of 1.31 (95% CI, 0.78–2.18) and an AR of 1.07 (95% CI, −0.97 to 2.99) per million influenza-vaccinated beneficiaries (Table 4). We obtained an OR of 1.31 (95% CI, 0.65–2.61) in the PPV-imputed quantitative bias analyses. For the end-of-season

Table 3. Beneficiaries' characteristics, Medicare Fee-for-Service, Influenza Vaccinated Populations Ages ≥65 Years From August 11, 2018 to November 9, 2018

			Vaccine Type													
					Standard-Dose											
Beneficiaries' Characteristics	All Influenza-Vaccinated Beneficiaries[a]		High-Dose (IIV3-HD)		Trivalent (IIV3)		Quadrivalent (IIV4)		IIV3/IIV4[b]		Adjuvanted (aIIV3)		Cell-Cultured (ccIIV4)		Recombinant (RIV4)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Influenza-vaccinated beneficiaries	12 159 346	100%	7 453 690	100%	145 885	100%	1 349 289	100%	1 706 604	100%	1 933 837	100%	718 773	100%	233 843	100%
Age (Years)																
Mean (SD)	76.0 (7.6)	-	75.8 (7.5)	-	78.4 (8.6)	-	75.9 (7.9)	-	76.4 (8.1)	-	75.8 (7.5)	-	76.8 (8.0)	-	75.8 (7.6)	-
Median (IQR)	75 (70–81)	-	75 (70–81)	-	77 (71–85)	-	75 (69–81)	-	75 (70–82)	-	75 (70–81)	-	76 (70–82)	-	74 (70–81)	-
65–74	5 989 095	49.3%	3 716 843	49.9%	56 169	38.5%	673 761	49.9%	811 725	47.6%	966 785	50.0%	325 868	45.3%	117 119	50.1%
75–84	4 276 389	35.2%	2 633 263	35.3%	51 440	35.3%	455 085	33.7%	579 584	34.0%	685 777	35.5%	257 482	35.8%	81 358	34.8%
≥85	1 893 862	15.6%	1 103 584	14.8%	38 276	26.2%	220 443	16.3%	315 295	18.5%	281 275	14.5%	135 423	18.8%	35 366	15.1%
Sex																
Male	5 057 329	41.6%	3 129 465	42.0%	56 282	38.6%	548 461	40.6%	684 995	40.1%	809 998	41.9%	290 922	40.5%	97 411	41.7%
Female	7 102 017	58.4%	4 324 225	58.0%	89 603	61.4%	800 828	59.4%	1 021 609	59.9%	1 123 839	58.1%	427 851	59.5%	136 432	58.3%
Concomitant Vaccination																
No	11 119 723	91.5%	6 756 652	90.6%	139 956	95.9%	1 253 704	92.9%	1 595 479	93.5%	1 768 136	91.4%	684 537	95.2%	212 696	91.0%
Any	1 039 623	8.5%	697 038	9.4%	5929	4.1%	95 585	7.1%	111 125	6.5%	165 701	8.6%	34 236	4.8%	21 147	9.0%

Abbreviations: IIV3-HD, high-dose influenza vaccine; IQR, interquartile range; SD, standard deviation.

[a]The total number of influenza-vaccinated beneficiaries includes those beneficiaries with general or administration codes only or multiple vaccination types on the same day.

[b]The IIV3/IIV4 category is inclusive of standard-dose vaccine codes for IIV3 and IIV4 vaccines, but additionally includes those standard-dose vaccine codes for which it is unclear whether they were specifically trivalent or quadrivalent (see Supplementary Table S4).

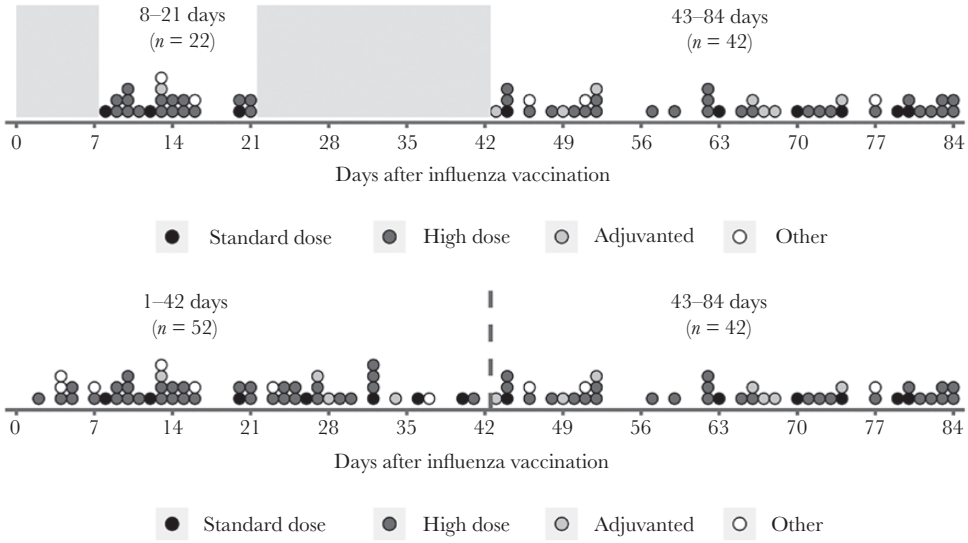

Figure 2. Medicare Fee-for-Service population early-season self-controlled risk interval analysis, interval between influenza vaccination and Guillain-Barré syndrome diagnosis, beneficiaries ages ≥65 years, high-dose and all seasonal influenza vaccines combined; risk windows are 8–21 and 1–42 days postvaccination; control window is 43–84 days postvaccination.

analysis, we identified 37 and 33 GBS claims in the secondary risk and control windows, respectively (Figure 3), resulting in an OR of 1.12 (95% CI, 0.70–1.79) and an AR of 0.46 (95% CI, −1.42 to 2.29) per million influenza-vaccinated beneficiaries.

For the early-season analyses for all seasonal vaccines combined, we identified 52 GBS claims in the risk window and 42 in the control window (Figure 2), yielding an OR of 1.24 (95% CI, 0.82–1.86) and an AR of 0.82 (95% CI, −0.74 to 2.32) per million vaccinations. The PPV-imputed quantitative bias analyses produced similar results (Table 4). In the end-of-season analysis, we obtained an OR of 1.19 (95% CI, 0.82–1.71) and an AR of 0.69 (95% CI, −0.77 to 2.11) per million influenza-vaccinated beneficiaries. Seasonality adjustments did not appreciably change any of our estimates (Supplementary Material S10).

DISCUSSION

The VSD and Medicare analyses did not find statistically significant increased GBS risks for IIV3-HD during the 2018–2019 season. The VSD rapid cycle analyses found that the LLR exceeded the critical value for IIV3-HD, but not for other influenza vaccines, and only when using binomial SCRI methods. When the VSD detected the statistical signal, the FDA, CMS, and CDC rapidly refined it in a larger database. In the early-season analyses using Medicare data, we found nonstatistically significant slightly elevated ORs, similar in magnitude to those observed in prior seasons [15, 16]. The findings from the Medicare end-of-season analyses were consistent with those from the early-season analyses. The chart review in the VSD confirmed 1 GBS case in the risk window and 1 in the control window, for an RR of 1.0; thus, the VSD did not confirm the initial statistical signal. This may be explained because the VSD case definition for GBS was highly sensitive. The Medicare analyses including all 2018–2019 influenza vaccines combined found slightly elevated borderline statistically significant ORs in the 8- to 21-day risk window. As in prior seasons [1, 10, 11, 15, 16], in the 8- to 21-day risk window we identified a GBS rate slightly higher than that in the 42-day risk window.

Given that most seasonal influenza vaccines are administered during a short period early in the season, the rapid identification and evaluation of safety signals, as done here, can inform timely regulatory and public health decision making. The results of our early-season Medicare analyses may be sensitive to our choice of an early cutoff date; we restricted analyses to beneficiaries vaccinated up to November 9, 2018, so GBS cases in both risk and control windows would have a high probability of being observed by March 15, 2019. By this vaccination cutoff, approximately 84% of vaccinations were expected to have occurred, which translated into an SCRI analysis with approximately 81% of all the control window GBS cases for the season. We chose the November 9, 2018 cutoff of as a trade-off between bias and precision. An earlier cutoff date would have included fewer vaccinations with higher claims maturity, resulting in less biased but more imprecise estimates. For the early-season analyses, we did not conduct chart review, which would have added substantial time to the effort, relying instead on the relatively high (71.2%) PPV of the ICD-10-CM GBS diagnosis code in primary discharge diagnosis position obtained during our 2015–2016 season investigation [15]. It is reassuring that the results of the VSD's chart-confirmed nonsequential SCRI analyses were consistent with the Medicare results. In addition, we performed chart-confirmed end-of-season SCRI analyses in the Medicare database. Results including

Table 4. Medicare Fee-for-Service Population Early-Season and End-of-Season Self-Controlled Risk Interval Analysis Results: Odds Ratios and Attributable Risks Among Influenza-Vaccinated Beneficiaries Ages ≥65 Years, 2018–2019[a]

Population	Number of GBS Cases		Odds Ratio	Odds Ratio 95% CI	*P* Value	Attributable Risk (Per Million Vaccinations)	Attributable Risk (Per Million Vaccinations) 95% CI
	Risk Window	Control Window					
Early-Season: High-Dose Influenza-Vaccinated Beneficiaries							
Risk Window: Days 8–21 Postvaccination							
Claims-based	16	26	1.85	(0.99–3.44)	.054	0.98	(−0.02 to 1.82)
PPV-imputed quantitative bias analysis	11.38	18.47	1.84	(0.78–4.31)	.162	0.69	(−0.29 to 1.47)
Risk Window: Days 1–42 Postvaccination							
Claims-based	34	26	1.31	(0.78–2.18)	.303	1.07	(−0.97 to 2.99)
PPV-imputed quantitative bias analysis	24.21	18.58	1.31	(0.65–2.61)	.449	0.76	(−1.20 to 2.56)
End-of-Season: High-Dose Influenza-Vaccinated Beneficiaries							
Risk Window: Days 8–21 Postvaccination							
Claims-based	18	33	1.64	(0.92–2.91)	.093	0.81	(−0.14 to 1.63)
Risk Window: Days 1–42 Postvaccination							
Claims-based	37	33	1.12	(0.70–1.79)	.633	0.46	(−1.42 to 2.29)
Early-Season: Influenza-Vaccinated Beneficiaries[b]							
Risk Window: Days 8–21 Postvaccination							
Claims-based	22	42	1.57	(0.94–2.63)	.086	0.66	(−0.09 to 1.33)
PPV-imputed quantitative bias analysis	15.67	29.93	1.56	(0.78–3.15)	.211	0.46	(−0.27 to 1.09)
Risk Window: Days 1–42 Postvaccination							
Claims-based	52	42	1.24	(0.82–1.86)	.303	0.82	(−0.74 to 2.32)
PPV-imputed quantitative bias analysis	37.03	30.01	1.24	(0.71–2.14)	.449	0.58	(−0.92 to 2.00)
End-of-Season: Influenza-Vaccinated Beneficiaries[b]							
Risk Window: Days 8–21 Postvaccination							
Claims-based	28	53	1.58	(1.00–2.51)	.049[b]	0.72	(0.00–1.36)
Risk Window: Days 1–42 Postvaccination							
Claims-based	63	53	1.19	(0.82–1.71)	.354	0.69	(−0.77 to 2.11)

Abbreviations: CI, confidence interval; GBS, Guillain-Barré syndrome; PPV, positive predictive value.

[a]Seasonality-adjusted results are presented in Supplementary Table S10.

[b]With any influenza vaccine (including high-dose influenza vaccine).

all influenza vaccines were consistent with our main analyses (Supplementary Material S11); we had insufficient power for the IIV3-HD analyses.

The VSD and Medicare FFS data have complementary capabilities. The VSD population includes more than 9 million individuals annually [27]. Among them, approximately 5.5 million received 2018–2019 influenza vaccinations [28]. Because it includes all ages, VSD is able to perform surveillance among persons <65 years of age, few of whom are enrolled in Medicare. The VSD also includes Medicare beneficiaries enrolled in Part C (Medicare Advantage), representing over one third of the overall Medicare population (Part C beneficiaries are not included in the Medicare FFS data used by the FDA-CMS collaboration). However, given that multiple influenza vaccines are indicated for use in different age groups in the United States, VSD surveillance may be insufficiently powered to assess small associations between GBS and some seasonal influenza vaccines. However, it provides direct access to medical records, essential for case confirmation. For a rare condition such as GBS, the VSD could detect an overall increased GBS risk of 1 per million within 10 weeks of the start of vaccination [41]. In contrast, the Medicare database contains a much larger and uniform population.

It includes >60 million individuals, with >17 million FFS influenza vaccine recipients, providing ample power for evaluating rare outcomes. It is particularly well suited for assessing vaccine safety because it is the largest cohort of US older adults with individually linked data containing demographic, diagnostic, and vaccination information. Furthermore, it is a single-payer system, which should decrease data source heterogeneity. However, one limitation is that there may be underascertainment of vaccinations administered outside of Medicare [42]. Thus, we restricted our analyses to influenza-vaccinated FFS beneficiaries. An additional potential limitation for our Medicare analyses is that we only included cases with hospital discharge diagnoses of GBS in the primary position, which could have led to an underestimation of GBS cases. However, GBS is a

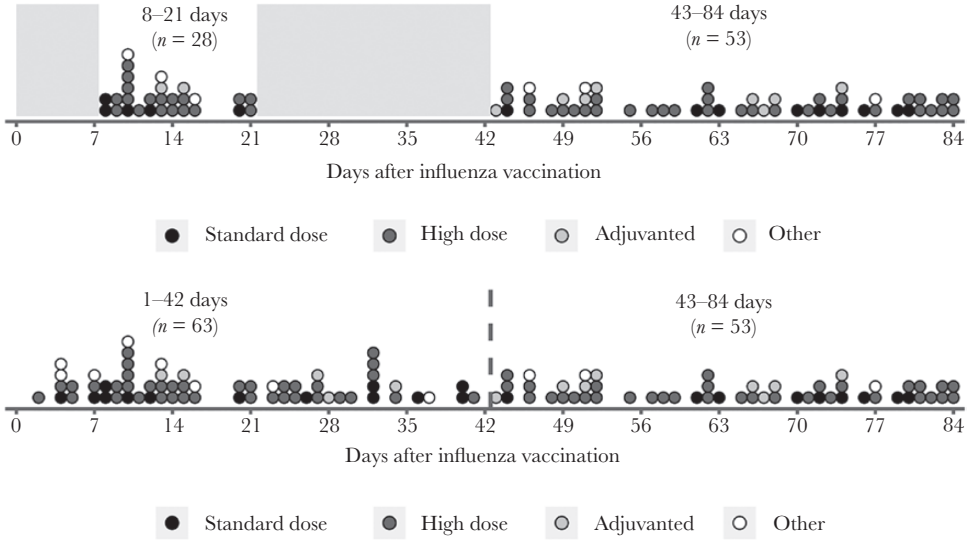

Figure 3. Medicare Fee-for-Service population end-of-season self-controlled risk interval analysis, interval between influenza vaccination and Guillain-Barré syndrome diagnosis, beneficiaries ages ≥65 years, high-dose and all seasonal influenza vaccines combined; risk windows is 8–21 and 1–42 days postvaccination; control window is 43–84 days postvaccination.

well defined acute disease with serious clinical sequelae that usually requires hospitalization rapidly [10]. In addition, prior FDA-CMS 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 the first diagnosis position (68.2%) [10]. Another limitation is that, by defining the inclusion criteria with respect to vaccination (as opposed to GBS onset), we could have biased the analysis towards finding more cases in the risk window. We used this requirement because of the importance of including beneficiaries as comparable as possible with respect to their GBS experience before vaccination date, given the known association of GBS with prior influenza vaccinations [1, 9–12, 14, 15, 22]. In addition, GBS is a very rare disease, and recurrent GBS is even more rare. However, to address this concern, we conducted a sensitivity analysis for which we required 183 days of clean period before the GBS hospitalization, thus standardizing the clean period requirement for all cases. The results of this analysis (data not shown) exactly matched results using our original case definition. Moreover, because of power limitations, our protocol did not include an analysis restricted to GBS cases without respiratory or gastrointestinal illness within 42 days before GBS onset, which have been shown as potential confounders in prior studies [43]. However, as part of the chart-confirmed supplementary analyses, we noted a history of antecedent respiratory or gastrointestinal illness within 42 days before onset of GBS symptoms in 23 (36%) of 64 chart-confirmed GBS cases. Although numbers were small, we additionally determined there was a potential imbalance in the number of such cases in the risk and control periods (data not shown). The impact of these confounders should be further investigated in subsequent multiseason analyses.

CONCLUSIONS

This collaborative effort, in which the VSD detected an early statistical signal that was rapidly evaluated in both VSD and Medicare, did not exclude an association between 2018–2019 IIV3-HD and GBS, but it determined that, if such risk existed, it was low, similar in magnitude to that observed in prior seasons [15, 16]. This reassuring finding highlights the benefits of providing timely GBS surveillance results and the robustness of federal surveillance efforts. Our findings were consistent with the US package insert of all influenza vaccines that warn—although with inconclusive evidence—of a minimally increased GBS risk. Despite slightly elevated GBS risk estimates for some seasons, the benefits of influenza vaccines in preventing influenza morbidity and mortality heavily outweigh these potential GBS risks.

Supplementary Data

Supplementary materials are available at The *Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. We thank Drs. Rositsa Dimova and Douglas Pratt (US Food and Drug Administration) for insightful review of the manuscript and Shruti Parulekar, Patrick Leonard, Manzi Ngaiza, and Yoganand Chillarige (Acumen LLC) for support with analytics and coordination. The Vaccine Safety Datalink thanks Oluwatosin Olaiya, Dr. Steven J. Jacobsen, and each site: HealthPartners Institute (Minneapolis, MN), Marshfield Clinic

Research Institute (Marshfield, WI), and Kaiser Permanente of Colorado (Denver), Northwest (Portland, OR), Northern California (Oakland, CA), Southern California (Pasadena, CA), and Washington (Seattle, WA).

Disclaimer. The manuscript was subject to administrative review before submission, but this review did not alter its content. The views expressed are those of the authors and not necessarily those of the Department of Health and Human Services, the US Food and Drug Administration, the Centers for Disease Control and Prevention, or the Centers for Medicare & Medicaid Services.

Financial support. The US Food and Drug Administration and the Centers for Medicare & Medicaid Services funded this study through an interagency agreement. The US Centers for Disease Control and Prevention Vaccine Safety Datalink IDIQ contract supported the Vaccine Safety Datalink work.

Potential conflicts of interest. The authors are employees or contractors of the US Food and Drug Administration, the Centers for Disease Control and Prevention, or the Centers for Medicare & Medicaid Services. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, et al. Guillain-Barré syndrome following vaccination in the national influenza immunization program, United States, 1976–1977. Am J Epidemiol **1979**; 110:105–23.
2. Langmuir AD. Guillain-Barré syndrome: the swine influenza virus vaccine incident in the United States of America, 1976-77: preliminary communication. J R Soc Med **1979**; 72:660–9.
3. Langmuir AD, Bregman DJ, Kurland LT, Nathanson N, Victor M. An epidemiologic and clinical evaluation of Guillain-Barré syndrome reported in association with the administration of swine influenza vaccines. Am J Epidemiol **1984**; 119:841–79.
4. Hurwitz ES, Schonberger LB, Nelson DB, Holman RC. Guillain-Barre syndrome and the 1978–1979 influenza vaccine. N Engl J Med **1981**; 304:1557–61.
5. Kaplan JE, Katona P, Hurwitz ES, Schonberger LB. Guillain-Barre syndrome in the United States, 1979–1980 and 1980–1981. Lack of an association with influenza vaccination. JAMA **1982**; 248:698–700.
6. Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barre syndrome and the 1992–1993 and 1993–1994 influenza vaccines. N Engl J Med **1998**; 339:1797–802.
7. Roscelli JD, Bass JW, Pang L. Guillain-Barre syndrome and influenza vaccination in the US Army, 1980–1988. Am J Epidemiol **1991**; 133:952–5.
8. Juurlink DN, Stukel TA, Kwong J, et al. Guillain-Barré syndrome after influenza vaccination in adults: a population-based study. Arch Intern Med **2006**; 166:2217–21.
9. Burwen DR, Sandhu SK, MaCurdy TE, et al. Surveillance for Guillain-Barré syndrome after influenza vaccination among the medicare population, 2009–2010. Am J Public Health **2012**; 102:1921–7.
10. Polakowski LL, Sandhu SK, Martin DB, et al. Chart-confirmed Guillain-Barre syndrome after 2009 H1N1 influenza vaccination among the Medicare population, 2009–2010. Am J Epidemiol **2013**; 178:962–73.
11. Dodd CN, Romio SA, Black S, et al. International collaboration to assess the risk of Guillain Barré syndrome following influenza A (H1N1) 2009 monovalent vaccines. Vaccine **2013**; 31:4448–58.
12. Salmon DA, Proschan M, Forshee R, et al. Association between Guillain-Barre syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta-analysis. Lancet **2013**; 381:1461–8.
13. Baxter R, Bakshi N, Fireman B, et al. Lack of association of Guillain-Barré syndrome with vaccinations. Clin Infect Dis **2013**; 57:197–204.
14. Romio S, Weibel D, Dieleman JP, et al. Guillain-Barre syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccines: a multinational self-controlled case series in Europe. PLoS One **2014**; 9:e82222.
15. Arya D, Said M, Izurieta HS, et al. Surveillance for Guillain-Barré syndrome after 2015–2016 and 2016–2017 influenza vaccination of medicare beneficiaries. Vaccine **2019**; 37:6543–49.
16. Perez-Vilar S, Wernecke M, Arya D, et al. Surveillance for Guillain-Barre syndrome after influenza vaccination among U.S. Medicare beneficiaries during the 2017–2018 season. Vaccine **2019**; 37:3856–65.
17. Sandhu SK, Hua W, MaCurdy TE, et al. Near real-time surveillance for Guillain-Barre syndrome after influenza vaccination among the Medicare population, 2010/11 to 2013/14. Vaccine **2017**; 35:2986–92.
18. Forshee RA, Hu M, Arya D, et al. A simulation study of the statistical power and signaling characteristics of an early season sequential test for influenza vaccine safety. Pharmacoepidemiol Drug Saf **2019**; 28:1077–85.
19. MaCurdy T. Updating sequential probability ratio test for real-time surveillance of vaccine/drug safety. In: ASA Biopharmaceutical Section Statistics Workshop. Washington DC; **2012**.
20. Li R, Stewart B, McNeil MM, et al. Post licensure surveillance of influenza vaccines in the Vaccine Safety Datalink in the 2013–2014 and 2014–2015 seasons. Pharmacoepidemiol Drug Saf **2016**; 25:928–34.
21. Greene SK, Kulldorff M, Lewis EM, et al. Near real-time surveillance for influenza vaccine safety: proof-of-concept

in the Vaccine Safety Datalink Project. Am J Epidemiol **2010**; 171:177–88.
22. U.S. Food and Drug Administration. Fluzone, fluzone high-dose and fluzone intradermal. Available at: https://www.fda.gov/vaccines-blood-biologics/vaccines/fluzone-fluzone-high-dose-and-fluzone-intradermal. Accessed 28 April 2019.
23. Izurieta HS, Thadani N, Shay DK, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. Lancet Infect Dis **2015**; 15:293–300.
24. Shay DK, Chillarige Y, Kelman J, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines among US medicare beneficiaries in preventing postinfluenza deaths during 2012–2013 and 2013–2014. J Infect Dis **2017**; 215:510–7.
25. Lu Y, Chillarige Y, Izurieta HS, et al. Effect of age on relative effectiveness of high-dose versus standard-dose influenza vaccines among US medicare beneficiaries aged ≥65 years. J Infect Dis **2019**; 220:1511–20.
26. Centers for Disease Control and Prevention. Vaccine Safety Datalink (VSD). Available at: https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html. Accessed 18 October 2019.
27. Moro PL, Li R, Haber P, Weintraub E, Cano M. Surveillance systems and methods for monitoring the post-marketing safety of influenza vaccines at the Centers for Disease Control and Prevention. Expert Opin Drug Saf **2016**; 15:1175–83.
28. Centers for Disease Control and Prevention. Advisory Committee on Immunization Practices (ACIP). Summary Report. June 26-27, 2019, Atlanta, GA. Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-2019-06-508.pdf. Accessed 5 October 2020.
29. Centers for Disease Control and Prevention. IIS: Current HL7 Standard Code Set CVX -- Vaccines Administered. Available at: https://www2a.cdc.gov/vaccines/iis/iisstandards/vaccines.asp?rpt=cvx. Accessed 18 October 2019.
30. Lee GM, Greene SK, Weintraub ES, et al.; Vaccine Safety Datalink Project. H1N1 and seasonal influenza vaccine safety in the vaccine safety datalink project. Am J Prev Med **2011**; 41:121–8.
31. Greene SK, Kulldorff M, Yin R, et al. Near real-time vaccine safety surveillance with partially accrued data. Pharmacoepidemiol Drug Saf **2011**; 20:583–90.
32. Sejvar JJ, Kohl KS, Gidudu J, et al.; Brighton Collaboration GBS Working Group. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine **2011**; 29:599–612.
33. Kulldorff M, Davis RL, Kolczak M, Lewis E, Lieu T, Platt R. A maximized sequential probability ratio test for drug and vaccine safety surveillance. Sequential Anal **2011**; 30:58–78.
34. Whitaker HJ, Ghebremichael-Weldeselassie Y, Douglas IJ, Smeeth L, Farrington CP. Investigating the assumptions of the self-controlled case series method. Stat Med **2018**; 37:643–58.
35. Centers for Medicare & Medicaid Services. Medicare Learning Network. MLN Matters Number: SE0605. Explanation of Systems Used by Medicare to Process Your Claims. Available at: https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/downloads/SE0605.pdf. Accessed 29 June 2019.
36. Vellozzi C, Iqbal S, Broder K. Guillain-Barre syndrome, influenza, and influenza vaccination: the epidemiologic evidence. Clin Infect Dis **2014**; 58:1149–55.
37. Rubin DB, Schenker N. Multiple imputation for interval estimation from simple random samples with ignorable nonresponse. J Am Stat Assoc **1986**; 81:366–74.
38. Centers for Disease Control and Prevention. National, regional, and state level outpatient illness and viral surveillance. Available at: https://gis.cdc.gov/grasp/fluview/fluportaldashboard.html. Accessed 15 November 2018.
39. Izurieta HS, Chillarige Y, Kelman J, et al. Relative effectiveness of cell-cultured and egg-based influenza vaccines among the U.S. elderly, 2017–18. J Infect Dis **2019**; 220:1255–64.
40. U.S. Food and Drug Administration. Report to Congress. The Sentinel Initiative–A National Strategy for Monitoring Medical Product Safety. Available at: https://www.fda.gov/media/82208/download. Accessed 10 January 2020.
41. McNeil MM, Gee J, Weintraub ES, et al. The Vaccine Safety Datalink: successes and challenges monitoring vaccine safety. Vaccine **2014**; 32:5390–8.
42. Lochner KA, Wynne MA, Wheatcroft GH, Worrall CM, Kelman JA. Medicare claims versus beneficiary self-report for influenza vaccination surveillance. Am J Prev Med **2015**; 48:384–91.
43. Greene SK, Rett MD, Vellozzi C, et al. Guillain-Barré syndrome, influenza vaccination, and antecedent respiratory and gastrointestinal infections: a case-centered analysis in the vaccine safety datalink, 2009–2011. PLoS One **2013**; 8:e67185.