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Surveillance for Guillain-Barré syndrome after 2015–2016 and 2016–2017 influenza vaccination of Medicare beneficiaries

Deepa P. Arya [a,*,1], Maria A. Said [a,2], Hector S. Izurieta [a], Silvia Perez-Vilar [a], Craig Zinderman [a], Michael Wernecke [b], Michael Alexander [b,3], Taylor White [b,4], I-Hsuan Su [b,5], Bradley Lufkin [b], Thomas MaCurdy [b,c], Jeffrey Kelman [d], Richard Forshee [a]

[a] Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA
[b] Acumen, LLC, Burlingame, CA, USA
[c] Stanford University, Stanford, CA, USA
[d] Centers for Medicare & Medicaid Services, Washington, DC, USA

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ABSTRACT

Background: Guillain-Barré syndrome (GBS) is a serious acute demyelinating disease, an increased risk of which was found after the 1976 swine flu vaccinations. The U.S. Food and Drug Administration, in collaboration with the Centers for Medicare & Medicaid Services, has been conducting active surveillance for GBS after influenza vaccinations of Medicare Fee-For-Service beneficiaries since 2009.

Methods: We conducted active surveillance for GBS claims in the 2015–2016 and 2016–2017 influenza seasons using the Updating Sequential Probability Ratio Test (USPRT) to monitor for signals of GBS risk. We performed self-controlled risk interval (SCRI) analyses at the end of both seasons, including chart confirmation in the 2015–2016 season, to estimate the odds ratio of GBS risk. We used 1–42 and 8–21 days post-vaccination as primary and secondary risk windows, respectively, and 43–84 days post-vaccination as the control window.

Results: Over 13 million beneficiaries were vaccinated in each season. USPRT found a low magnitude signal for GBS in both seasons. SCRI analyses did not find excess GBS risk following any influenza vaccine for days 1–42 post-vaccination in either season. In the 2015–2016 season, for the 8–21 day window, our chart-confirmation showed an attributable GBS risk of 0.87 (95% CI: 0.16, 1.49) and 1.68 (95% CI: 0.69, 2.41) cases per million vaccinees after all seasonal and high dose (HD) vaccines, respectively, an elevated GBS risk for beneficiaries aged ≥75 years following all seasonal vaccines (OR: 2.25; 95% CI: 1.15, 4.39) and HD vaccine (OR: 3.67, 95% CI: 1.52, 8.85), and an elevated GBS risk for males who received seasonal vaccines (OR: 2.18; 95% CI: 1.15, 4.15) and HD vaccine (OR: 3.33; 95% CI: 1.35, 8.20). The finding of elevated GBS risk with advancing age and in males is consistent with literature; however, a distinction between HD and SD was a new finding. In the 2016–17 season, for the 8–21 day window, attributed cases showed an attributable GBS risk of 0.87 (95% CI: 0.03, 1.61) and 1.11 (95% CI: 0.00, 2.01) cases per million vaccinees after all seasonal and HD vaccines, respectively. We found no excess GBS risk for standard dose vaccines in the 8–21 day window in either season.

Conclusions: Our primary analysis finding of no excess GBS risk during both seasons was reassuring. The slightly elevated GBS risk, although in the expected range, in the 8–21 day window after all seasonal and high dose vaccines, but not after standard dose vaccines is hypothesis-generating because the difference may be due to vaccine factors such as antigen amount or strains in various seasons or due to host factors.

* Corresponding author at: Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD, 20993-0002, USA.
E-mail address: deepa.arya@fda.hhs.gov (D.P. Arya).
[1] Present address: Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA.
[2] Present address: Epidemiology Branch Chief at the National Park Service, Washington, DC, USA
[3] Present address: UBER, Washington, DC, USA
[4] Present address: Qlik, Los Angeles, CA, USA
[5] Present address: Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina – Chapel Hill, USA.

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1. Introduction

An association between influenza vaccination and Guillain-Barré syndrome (GBS) was first noticed during the 1976 swine flu vaccination in the U.S. [1]. Although the risk of GBS has been studied only intermittently since 1976, it has been seen that the risk does vary from year to year, never with a definitive explanation [2–5]. GBS is a spectrum of acute or subacute neuropathy characterized by varying degrees of motor weakness, sensory abnormalities, autonomic dysfunction, and characteristic findings in cerebrospinal fluid and electrodiagnostic studies [6–8]. The exact pathophysiology of GBS is not well understood; however, immune stimulation appears to play a role [8–10]. Men are almost twice as likely to be affected as women [6,7,11,12], and the incidence increases by about 20% for every 10-year age increment [7]. The estimated annual GBS incidence ranges from 2.7 to 4 per 100,000 among the elderly [6,10,13]; however, the size [14] and representativeness of the Medicare population provides sufficient power for evaluation of such a rare outcome.

The U.S. Food and Drug Administration (FDA) has been conducting passive surveillance and data mining with disproportionality measurement for GBS after influenza vaccinations. In 2008, FDA in collaboration with the Centers for Medicare & Medicaid Services (CMS) and with the assistance of Acumen, LLC, developed the near real-time surveillance methodology to actively monitor for the occurrence of GBS after influenza vaccination of Medicare beneficiaries [4,5,15]. FDA implemented the active surveillance after the 2009–2010 seasonal and H1N1 monovalent vaccines [16] and also conducted chart reviews of the GBS cases following the H1N1 monovalent vaccine [4]. Additionally, FDA's surveillance findings were presented for the 2010–2011 to 2013–2014 influenza seasons [15].

Our near real-time surveillance for GBS claims after influenza vaccination of Medicare beneficiaries in the 2015–2016 and 2016–2017 seasons showed a low magnitude signal for GBS, for which no regulatory action was required. We evaluated this signal by conducting chart reviews in the 2015–2016 season followed by self-controlled risk interval (SCRI) analyses of chart-confirmed and imputed cases. In the 2016–2017 season we conducted SCRI analyses of the claims-based GBS cases and attributed GBS cases (based on the positive predictive value (PPV) of the GBS diagnoses obtained by chart reviews in the previous season). This paper focuses on the results of the SCRI analyses for the 2015–2016 and 2016–2017 seasons.

2. Methods

2.1. Study population and data sources

We used claims data of beneficiaries enrolled in Medicare Fee-for-Service (FFS) (Parts A and B) [17]. The study population consisted of beneficiaries aged $\geq$ 65 years who received a seasonal influenza vaccine during the influenza season and had GBS in the first hospital discharge diagnosis position within 84 days after vaccination. Inclusion and exclusion criteria are shown in Supplements A1 and A2. We identified claims for influenza vaccines and vaccines administered concomitantly (pneumococcal, hepatitis B, and tetanus toxoid-containing vaccines) using Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT) codes (Supplement B, eTables B1 and B2). We identified GBS claims from the inpatient setting, using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) code 357.0 until September 30, 2015, and the International Classification of Diseases, Tenth Revision, Clinical modification (ICD-10) code G61.0 afterwards. For the 2015–2016 season, we also performed medical chart reviews for GBS cases observed via claims.

2.2. Study design and analysis

We conducted surveillance for GBS after influenza vaccination of Medicare fee-for-service (FFS) beneficiaries using the Updating Sequential Probability Ratio Test [15,18] throughout the influenza seasons and SCRI analyses at the end of the 2015–2016 and 2016–2017 seasons. The primary and secondary risk windows were 1–42 and 8–21 days post-vaccination [1,5,8,19], respectively, and the control window was 43–84 days post-vaccination.

We defined exposure as a beneficiary's first influenza vaccination during the season, and outcome as the first occurrence of GBS in the inpatient setting during the post-vaccination window of interest. For the 2015–2016 season SCRI analysis, we used chart-confirmed GBS cases. We used Brighton Collaboration's case definitions for GBS and Fisher Syndrome (FS), a variant of GBS, to classify these cases [8] and considered cases classified as Brighton Level 1, 2, or 3 as "chart-confirmed" GBS cases. For the 2016–2017 season SCRI analysis, we used attributed cases (claims-identified cases after application of the PPV from the previous season's chart-confirmed cases).

We used conditional logistic regression models to calculate the odds ratios (ORs) with 95% confidence intervals, offset by length of observation time. The models included an indicator for the risk window as the predictor variable and an offset equal to the log of the window length, which were conditioned on an identification variable for each beneficiary. The model can be written as

$$\text{logit}(p) = \beta(\text{risk window}) + \log(\text{interval}) + \text{strata}(\text{beneficiary id})$$

where p is the risk of GBS and *interval* represents the length of the respective window in days. Under this model, our null and alternative hypotheses for the two-sided hypothesis test ($\alpha = 0.05$) can be written as

$$H_0 : e^{\beta} = 1 \qquad H_{\alpha} : e^{\beta} \neq 1$$

where e^{β} gives the OR of GBS in the risk and control windows. We conducted the following subgroup analyses: demographics (age, sex, and region of residence), vaccine type (high dose (HD) and standard dose (SD)), and presence of concomitant vaccination. The only HD vaccine administered in both seasons was the inactivated trivalent high dose vaccine (60 μg hemagglutinin per strain). The SD group included inactivated trivalent and quadrivalent (15 μg hemagglutinin per strain) vaccines. We conducted crude analyses and analyses after adjustment for potential influenza infections, which were used as a proxy for seasonality [19,20]. We conducted influenza infection adjustment using "high" and "low" influenza weeks, which were assigned as such using weekly oseltamivir prescription rates as well as use rates of rapid influenza tests (RIT) followed by an oseltamivir prescription within the subsequent two days [21]. We also conducted a post hoc SCRI analysis for the 2015–2016 season after removing the cases with antecedent illness to see if our results change.

In the 2015–2016 season, we calculated the PPV for GBS diagnosed in ICD-10 as the number of chart-confirmed GBS cases expressed as a percentage of all charts obtained (January 22, 2016 cut-off by which time > 95% of the beneficiaries had been vaccinated) wherein GBS was diagnosed in ICD-10. Methods used for calculation of attributable risk, influenza infection adjustment, and imputation for missing charts are described in Supplements C1–C3. In the 2016–2017 season, we analyzed the attributed GBS cases by using the PPV obtained in the 2015–2016 season (described in Supplement D).

All analyses were conducted using R 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS v. 9.4 (SAS Institute Inc., Cary, NC).

This study was approved by the Research Involving Human Subjects Committee of FDA's Center for Biologics Evaluation and Research.

3. Results

3.1. 2015–2016 season

In the 2015–2016 season, our claims-based near real-time surveillance using the Updating Sequential Probability Ratio Test (USPRT) first revealed a GBS signal in week 16 of surveillance (as of November 29, 2015) among HD vaccinees aged ≥ 65 years as a risk of 4.87 GBS cases per million vaccinees in the 0–42 day window and as a risk of 3.30 GBS cases per million vaccinees in the 7–21 day window. Of note, in the 2015–2016 season, 0–42 and 7–21 day risk windows were used for near real-time surveillance; however, we changed the risk windows to 1–42 and 8–21 days post-vaccination for the SCRI analyses and near real-time surveillance for subsequent seasons to better align with the existing literature [5]. In the subsequent weeks we observed a GBS signal in week 26 (as of February 2, 2016) for all beneficiaries vaccinated with all seasonal vaccines as a risk of 6.77 GBS cases per million vaccinees in the 0–42 day window. Full USPRT results are not shown.

A total of 13,366,005 Medicare FFS influenza-vaccinated beneficiaries were observed for our SCRI analyses. Of these, 6,936,021 (52%) received the HD vaccine, 6,218,036 (47%) received the SD vaccines, and the remaining received other influenza vaccines (recombinant, intradermal, and cell-culture based) or only had general influenza vaccine codes but no specific codes for a vaccine type. The demographic characteristics of the influenza-vaccinated beneficiaries and the GBS cases in the two risk windows are shown in Tables 1 and 2, respectively. We found 158 claims-based GBS cases in the 84 days post-vaccination that met our study criteria. All cases except one were identified with the ICD-10 code. Three cases were observed after the January 22, 2016 cut-off, and we requested medical charts for the remaining 155 cases. We obtained 133 (85.8%) charts. Of these, we confirmed 95 by chart review as GBS cases. Our analysis showed a PPV of an inpatient diagnosis of GBS in ICD-10 of 71.21% (95% CI: 63.49%, 78.94%).

By chart abstraction we found that seven cases identified as GBS by claims had FS noted in the charts. However, none of these seven cases met the criteria for FS and four did not meet the criteria for GBS [8]. Of the remaining three cases, we excluded one due to the subject being noted as less than 65 years of age. We included the remaining two cases in the SCRI analysis. Both cases occurred in the 1–42 day risk window; one also occurred in the 8–21 day window. Even though these two remaining cases were diagnosed by the physicians as FS, they both had limb weakness in addition to FS features and were thus classified as GBS.

The results of our SCRI analyses are shown in Table 3. Our SCRI results did not show an excess GBS risk in the 1–42 day risk window either in the overall analysis or in any of the sub-analyses by vaccine type. For the secondary 8–21 day risk window, we found a statistically significant increased GBS risk in both claims-based and chart-confirmed SCRI analyses for all seasonal vaccines. For the chart-confirmed cases using the 8–21 day risk window, we found an attributable risk of GBS of 0.87 (95% CI: 0.16, 1.49) excess cases of GBS per million vaccinees for all seasonal vaccines, and 1.68 (95% CI: 0.69, 2.41) excess cases of GBS per million vaccinees for the HD vaccine. We found no excess risk for SD vaccines in any risk window. Results after influenza infection adjustments and imputation of missing charts showed similar results in both risk windows. Our analyses for concomitant vaccination did not show an excess GBS risk in the 1–42 day risk window. However, we found that in the 8–21 day window, GBS risk for chart-confirmed seasonal vaccine recipients without concomitant vaccination was statistically significant. Analyses after influenza infection adjustments mirrored these results. Stacked strip plots of the GBS cases are shown in eFig. 1 (Supplement E).

For chart-confirmed cases in the 8–21 day window, we found a statistically significant elevated GBS risk for beneficiaries aged ≥75 years following all seasonal vaccines (OR: 2.25; 95% CI: 1.15, 4.39) and HD vaccine (OR: 3.67, 95% CI: 1.52, 8.85). We did not find

Table 1
Demographic characteristics of the influenza-vaccinated beneficiaries in the 2015–2016 and 2016–2017 seasons.

Characteristics	All Influenza-Vaccinated Beneficiaries					
	2015–2016 Season			2016–2017 Season		
	Seasonal Influenza Vaccines	High Dose Vaccine	Standard DoseVaccines	Seasonal Influenza Vaccines	High DoseVaccine	Standard Dose Vaccines
Total Beneficiaries *	13,366,005	6,936,021	6,218,036	13,645,659	8,100,846	5,298,835
Sex						
Female (%)	7,874,430 (58.9)	4,037,736 (58.2)	3,707,972 (59.6)	8,019,101 (58.8)	4,719,542 (58.3)	3,150,894 (59.5)
Male (%)	5,491,575 (41.1)	2,898,285 (41.8)	2,510,064 (40.4)	5,626,558 (41.2)	3,381,304 (41.7)	2,147,941 (40.5)
Age (years)						
65–74 (%)	6,499,850 (48.6)	3,458,968 (49.9)	2,945,163 (47.4)	6,724,101 (49.3)	4,058,115 (50.1)	2,550,615 (48.1)
75–84 (%)	4,629,268 (34.6)	2,432,437 (35.1)	2,125,867 (34.2)	4,686,483 (34.3)	2,813,561 (34.7)	1,791,917 (33.8)
85+ (%)	2,236,887 (16.7)	1,044,616 (15.1)	1,147,006 (18.5)	2,235,075 (16.4)	1,229,170 (15.2)	956,303 (18.0)
Race						
White (%)	11,868,353 (88.8)	6,307,833 (90.9)	5,381,717 (86.6)	12,049,217 (88.3)	7,306,609 (90.2)	4,533,491 (85.6)
Black (%)	712,946 (5.3)	283,979 (4.1)	411,542 (6.6)	730,791 (05.4)	353,697 (04.4)	358,444 (06.8)
Other (%)	784,706 (5.9)	344,209 (5.0)	424,777 (6.8)	865,651 (06.3)	440,540 (05.4)	406,900 (07.7)
Region**						
Midwest (%)	3,089,539 (23.1)	1,689,989 (24.4)	1,363,837 (21.9)	3,173,223 (23.3)	2,004,867 (24.7)	1,120,752 (21.2)
Northeast (%)	2,664,984 (19.9)	1,337,299 (19.3)	1,278,921 (20.6)	2,702,561 (19.8)	1,557,822 (19.2)	1,089,646 (20.6)
South (%)	5,265,859 (39.4)	2,673,207 (38.5)	2,505,297 (40.3)	5,333,879 (39.1)	3,099,454 (38.3)	2,132,348 (40.2)
West (%)	2,328,831 (17.4)	1,231,207 (17.8)	1,057,793 (17.0)	2,419,958 (17.7)	1,433,242 (17.7)	945,987 (17.9)

* Total beneficiaries for each of the claims-based, chart-confirmed, and chart-confirmed + imputation analyses.
** Beneficiaries with unknown or "other" region were excluded.

Table 2
Demographic characteristics of the GBS cases after influenza vaccinations in the 2015–2016 and 2016–2017 seasons.

Characteristic	2015–2016 Season						2016–2017 Season			
	Claims-Identified		Chart-Confirmed		Chart-Confirmed + Imputation		Claims-Identified		Claims-Identified + Attributed	
	1–42 Day Window	8–21 Day Window	1–42 Day Window	8–21 Day Window	1–42 Day Window	8–21 Day Window	1–42 Day Window	8–21 Day Window	1–42 Day Window	8–21 Day Window
Total (%)	158 (100)	111 (100)	95 (100)	69 (100)	112.9 (100)	81.7 (100)	148 (100)	110 (100)	105.3 (100)	78.3 (100)
Sex										
Male (%)	88 (55.7)	60 (54.1)	55 (57.9)	38 (50.8)	65.0 (57.6)	44.4 (54.3)	78 (52.7)	58 (52.7)	55.5 (52.7)	41.3 (52.7)
Female (%)	70 (44.3)	51 (46.0)	40 (42.1)	31 (49.3)	47.9 (42.4)	37.4 (45.7)	70 (47.3)	52 (47.3)	49.8 (47.3)	37.0 (47.3)
Age (years)										
65–74 years (%)	76 (48.1)	52 (46.9)	47 (49.5)	34 (47.8)	52.7 (46.7)	38.3 (46.8)	78 (52.7)	62 (56.4)	55.7 (52.9)	44.2 (56.4)
75–84 years (%)	73 (46.2)	52 (46.9)	40 (42.1)	29 (47.8)	52.2 (46.2)	37.5 (45.9)	60 (40.5)	42 (38.2)	42.5 (40.4)	29.9 (38.2)
≥85 years (%)	9 (5.7)	7 (6.3)	8 (8.42)	6 (4.5)	8 (7.1)	6 (7.3)	10 (6.8)	6 (5.5)	7.1 (6.8)	4.3 (5.5)
Race										
White (%)	138 (87.3)	96 (86.5)	82 (86.3)	59 (86.6)	97.0 (86.0)	70.3 (86.0)	132 (89.2)	96 (87.3)	94.0 (89.2)	68.4 (87.4)
Black (%)	9 (5.7)	8 (7.2)	4 (4.2)	4 (9.0)	6.1 (5.4)	5.4 (6.6)	7 (4.7)	6 (5.5)	5 (4.8)	4.3 (5.4)
Other (%)	11 (7.0)	7 (6.3)	9 (9.5)	6 (4.5)	9.7 (8.6)	6 (7.3)	9 (6.1)	8 (7.3)	6.4 (6.1)	5.7 (7.2)
Region										
Midwest (%)	34 (21.5)	21 (18.9)	20 (21.1)	12 (20.9)	24.3 (21.6)	14.8 (18.1)	35 (23.7)	27 (24.6)	24.9 (23.7)	19.2 (24.6)
Northeast (%)	33 (20.9)	19 (17.1)	18 (19.0)	10 (16.4)	22.3 (19.7)	12.1 (14.9)	21 (14.2)	15 (13.64)	14.9 (14.2)	10.7 (13.6)
South (%)	65 (41.1)	52 (46.9)	42 (44.2)	35 (44.8)	48.4 (42.9)	41.4 (50.6)	59 (39.9)	43 (39.1)	42.1 (40.0)	30.6 (39.1)
West (%)	26 (16.5)	19 (17.1)	15 (15.8)	12 (17.9)	17.9 (15.9)	13.4 (16.4)	33 (22.3)	25 (22.7)	23.4 (22.2)	17.8 (22.7)
Concomitant Vaccines										
Combined* (%)	25 (15.8)	15 (13.5)	13 (13.7)	8 (4.5)	10.1 (9.0)	10.1 (12.4)	18 (12.5)	12 (10.9)	12.8 (12.1)	8.6 (11.0)
Pneumococcal (%)	23 (14.6)	13 (11.7)	11 (11.6)	6 (4.5)	14.6 (12.9)	8.1 (10.0)	18 (12.5)	12 (10.9)	12.8 (12.1)	8.6 (11.0)
Hepatitis B (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Tetanus (%)	3 (1.9)	3 (2.7)	2 (2.1)	2 (1.5)	2 (1.8)	2 (2.5)	0 (0)	0 (0)	0 (0)	0 (0)

* Presence of any concomitant vaccine.

a statistically significant GBS risk for females or beneficiaries aged <75 years. We also found a statistically significant elevated GBS risk for males who received seasonal vaccines (OR: 2.18; 95% CI: 1.15, 4.15) and HD vaccine (OR: 3.33; 95% CI: 1.35, 8.20) in the 8–21 day window.

Of the 95 chart-confirmed GBS cases, we noted a history of antecedent respiratory or gastrointestinal illness within six weeks prior to onset of GBS symptoms in 47 (49.5%) charts, one of which had a documented history of *Campylobacter jejuni*. Our SCRI analysis with the remaining 48 cases showed 30 GBS cases in the 1–42 day risk window including 17 in the 8–21 day risk window, and 18 GBS cases in the control window. For the 1–42 day window, we did not find any statistically significant SCRI results. For the 8–21 day window, we found a statistically significant increased GBS risk for all seasonal vaccines (OR: 2.83; 91% CI: 1.46, 5.50). We did not have adequate power to analyze by vaccine type, i.e., HD and SD.

3.2. 2016–2017 season

In the 2016–2017 season our claims-based near real-time surveillance using USPRT first revealed a GBS signal in week 14 of surveillance (as of November 18, 2016) in the 8–21 day window among beneficiaries aged ≥ 65 years who received all seasonal vaccines, as a risk of 2.23 GBS cases per million vaccinees. Subsequently, we also received a GBS signal in week 16 (as of December 2, 2016) in the 1–42 day window among beneficiaries aged ≥ 65 years who received all seasonal vaccines, as a risk of 4.32 GBS cases per million vaccinees. Full USPRT results are not shown.

A total of 13,645,659 Medicare FFS influenza-vaccinated beneficiaries were observed for our SCRI analysis. Of these, 8,100,846 (59%) beneficiaries received the HD vaccine, 5,298,835 (39%) received a SD vaccine, and the remaining received other influenza vaccines (adjuvanted, recombinant, intradermal, and cell-culture based) or did not have specific codes for a vaccine type. We found 148 claims-based GBS cases in the 84 days post-vaccination. The demographic characteristics of the influenza-vaccinated beneficiaries and the GBS cases in the two risk windows are shown in Tables 1 and 2, respectively.

The results of our SCRI analyses are shown in Table 3. We did not find an excess GBS risk in the 1–42 day risk window for any vaccine type or subgroup for claims-based or attributed cases. However, in the secondary risk window (8–21 day), we found a statistically significant increased GBS risk in both claims-based and attributed-case SCRI analyses for all seasonal vaccines. After influenza infection adjustment, we found a statistically significant increased GBS risk for claims-based and attributed cases (OR: 1.97; 95% CI: 1.20, 3.23 and OR: 1.97; 95% CI: 1.01, 3.84, respectively) after HD vaccine.

Our attributed-case SCRI analyses showed that, in the 8–21 day window, the attributable risk of GBS was 0.87 (95% CI: 0.03, 1.61) excess cases of GBS per million vaccinees after all seasonal vaccines and 1.11 (95% CI: 0, 2.01) excess cases of GBS per million vaccinees after the HD vaccine. Stacked strip plots of the GBS cases are shown in eFig. 1 (Supplement E).

Our claims-based analyses also showed that in the 8–21 day risk window, GBS risk was statistically significantly higher for males following all seasonal vaccines (OR: 2.20; 95% CI: 1.27, 3.81) and HD vaccine (OR: 2.67; 95% CI: 1.36, 5.23). Attributed-case analyses mirrored these results. We found that GBS risk for claims-based cases was statistically significantly higher in the 8–21 day window for beneficiaries aged ≥75 years following all seasonal vaccines (OR: 1.80; 95% CI: 1.00, 3.23) and for beneficiaries aged 65–74 years following the HD vaccine (OR: 2.57; 95% CI: 1.37, 4.83). We did not find a statistically significant GBS risk for females.

Table 3
Results of SCRI analyses in 2015–2016 and 2016–2017 seasons.

Population	Primary Risk Window (1–42 days), Control Window (43–84 days)						Secondary Risk Window (8–21 days), Control Window (43–84 days)					
	Risk Window GBS Cases	Control Window GBS Cases	OR	OR 95% CI	AR	AR 95% CI	Risk Window GBS Cases	Control Window GBS Cases	OR	OR 95% CI	AR	AR 95% CI
2015–2016 Season												
Seasonal Influenza Vaccines												
Claims-Identified	87	71	1.23	(0.90, 1.68)	1.20	(−0.65, 2.99)	40	71	1.69**	(1.15, 2.49)	1.22	(0.33, 2.03)
Chart-Confirmed	52	43	1.21	(0.81, 1.81)	0.67	(−0.76, 2.05)	26	43	1.81*	(1.11, 2.95)	0.87	(0.16, 1.49)
Chart-Confirmed + Imputed	62.09	50.79	1.22	(0.84, 1.78)	0.85	(−0.75, 2.38)	30.95	50.78	1.83**	(1.16, 2.89)	1.05	(0.26, 1.74)
HD Influenza Vaccine												
Claims-Identified	47	32	1.47	(0.94, 2.30)	2.16	(−0.37, 4.49)	26	32	2.44***	(1.45, 4.09)	2.21	(0.98, 3.21)
Chart-Confirmed	31	19	1.63	(0.92, 2.89)	1.73	(−0.29, 3.50)	18	19	2.84**	(1.49, 5.42)	1.68	(0.69, 2.41)
Chart-Confirmed + Imputed	36.78	21.86	1.68	(0.98, 2.89)	2.15	(−0.08, 4.10)	22.24	21.84	3.05***	(1.67, 5.59)	2.16	(1.06, 2.96)
SD Influenza Vaccines												
Claims-Identified	39	38	1.03	(0.66, 1.60)	0.16	(−2.57, 2.87)	14	38	1.11	(0.60, 2.04)	0.21	(−1.08, 1.47)
Chart-Confirmed	20	24	0.83	(0.46, 1.51)	−0.64	(−2.61, 1.43)	8	24	1.00	(0.45, 2.23)	0.00	(−0.98, 0.98)
Chart-Confirmed + Imputed	24.31	28.93	0.84	(0.48, 1.46)	−0.74	(−2.98, 1.60)	8.71	28.95	0.90	(0.42, 1.95)	−0.15	(−1.21, 0.95)
Seasonal Influenza Vaccines Without Concomitant Vaccines												
Claims-Identified	70	63	1.11	(0.79, 1.56)	0.60	(−1.34, 2.52)	33	63	1.57*	(1.03, 2.39)	1.04	(0.07, 1.91)
Chart-Confirmed	43	39	1.10	(0.71, 1.70)	0.35	(−1.18, 1.84)	22	39	1.69*	(1.00, 2.85)	0.78	(0.01, 1.45)
Chart-Confirmed + Imputed	50.93	45.36	1.12	(0.75, 1.69)	0.48	(−1.21, 2.13)	26.25	45.35	1.74*	(1.06, 2.84)	0.96	(0.10, 1.71)
Seasonal Influenza Vaccines With Concomitant Vaccines												
Claims-Identified	17	8	2.12	(0.92, 4.92)	5.07	(−0.61, 9.34)	7	8	2.63	(0.95, 7.24)	2.44	(−0.13, 4.13)
Chart-Confirmed	9	4	2.25	(0.69, 7.31)	2.82	(−1.33, 5.56)	4	4	3.00	(0.75, 12.00)	1.50	(−0.43, 2.54)
Chart-Confirmed + Imputed	11.15	5.43	2.07	(0.71, 6.04)	3.25	(−1.60, 6.69)	4.7	5.43	2.60	(0.72, 9.35)	1.63	(−0.59, 2.96)
Seasonal Influenza, Vaccine, Influenza Infection-Adjusted												
Claims-Identified	87	71	1.26	(0.92, 1.72)	1.35	(−0.50, 3.13)	40	71	1.74**	(1.18, 2.56)	1.28	(0.39, 2.09)
Chart-Confirmed	52	43	1.25	(0.84, 1.88)	0.80	(−0.63, 2.17)	26	43	1.89*	(1.16, 3.07)	0.93	(0.22, 1.54)
Chart-Confirmed + Imputed	62.09	50.79	1.26	(0.86, 1.84)	0.98	(−0.62, 2.50)	30.95	50.78	1.89**	(1.20, 2.99)	1.11	(0.32, 1.79)
HD Influenza Vaccine, Influenza Infection-Adjusted												
Claims-Identified	47	32	1.50	(0.96, 2.35)	2.28	(−0.25, 4.59)	26	32	2.48***	(1.48, 4.16)	2.25	(1.02, 3.24)
Chart-Confirmed	31	19	1.67	(0.94, 2.96)	1.81	(−0.21, 3.57)	18	19	2.91**	(1.53, 5.54)	1.71	(0.73, 2.44)
Chart-Confirmed + Imputed	36.78	21.86	1.72*	(1.00, 2.96)	2.24	(0.02, 4.18)	22.24	21.84	3.12***	(1.70, 5.72)	2.19	(1.11, 2.99)
SD Influenza Vaccine, Influenza Infection-Adjusted												
Claims-Identified	39	38	1.06	(0.68, 1.65)	0.35	(−2.39, 3.05)	14	38	1.15	(0.62, 2.12)	0.29	(−1.00, 1.54)
Chart-Confirmed	20	24	0.88	(0.48, 1.59)	−0.47	(−2.46, 1.61)	8	24	1.06	(0.48, 2.36)	0.08	(−0.91, 1.04)
Chart-Confirmed + Imputed	24.31	28.93	0.87	(0.50, 1.52)	−0.57	(−2.83, 1.77)	8.71	28.95	0.95	(0.44, 2.05)	−0.08	(−1.15, 1.02)
2016–2017 Season												
Seasonal Influenza Vaccines												
Claims-Identified	78	70	1.11	(0.81, 1.54)	0.59	(−1.16, 2.30)	40	70	1.71**	(1.16, 2.53)	1.22	(0.35, 2.01)
Chart-Confirmed + Attributed	55.57	49.76	1.12	(0.72, 1.73)	0.43	(−1.24, 2.06)	28.51	49.80	1.71*	(1.02, 2.89)	0.87	(0.03, 1.61)
HD Influenza Vaccine												
Claims-Identified	48	40	1.20	(0.79, 1.83)	0.99	(−1.28, 3.17)	26	40	1.95**	(1.19, 3.19)	1.56	(0.42, 2.54)
Chart-Confirmed + Attributed	34.13	28.44	1.20	(0.68, 2.13)	0.71	(−1.50, 2.80)	18.51	28.43	1.95	(1.00, 3.80)	1.11	(0.00, 2.01)
SD Influenza Vaccines												
Claims-Identified	29	30	0.97	(0.58, 1.61)	−0.19	(−2.96, 2.60)	13	30	1.30	(0.68, 2.49)	0.57	(−0.83, 1.85)
Chart-Confirmed + Attributed	20.73	21.32	0.97	(0.49, 1.94)	−0.12	(−2.75, 2.55)	9.27	21.37	1.29	(0.52, 3.17)	0.39	(−0.96, 1.61)

*Significant at $p < 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$.
Abbreviations: OR = Odds Ratio; AR = Attributable Risk (per million vaccinations); CI = Confidence Interval; HD = High Dose; SD = Standard Dose.

4. Conclusions

In our chart-confirmed SCRI analyses after influenza vaccination of Medicare FFS beneficiaries in the 2015–2016 season, we did not find an elevated GBS risk within 42 days following influenza vaccination. However, in the secondary 8–21 day window we found a slightly elevated but statistically significant risk of GBS after all seasonal influenza vaccines and after the HD vaccine. Findings for the SD vaccines were not statistically significant. Similarly, for attributed cases in the 2016–2017 season, we did not find an elevated GBS risk for the primary (1–42 day) risk window but found a slightly elevated risk of GBS after all seasonal influenza vaccines and the HD vaccine in the secondary (8–21 day) risk window.

Our chart-confirmed analysis showed that the attributable risk in the secondary (8–21 day) risk window for all seasonal vaccines was slightly less than one excess GBS case per million vaccinees, and that for the HD vaccine was slightly less than two excess cases of GBS per million vaccinees. These findings are consistent with the risks noted on the package insert of influenza vaccines distributed in the U.S. [22], the statement from the Advisory Committee on Immunization Practices [23], and other studies [15,24,25]. We found no excess risk of GBS after SD vaccines. These results should also be viewed in context of some studies showing greater effectiveness of the HD vaccine in preventing influenza infections and hospitalizations, and possibly mortality, depending on the circulating influenza virus, as compared to the SD vaccines [26–28].

Our secondary analysis finding of a higher GBS risk among males and individuals aged $\geq$ 75 years who received seasonal vaccines is consistent with existing literature [6–8,11,12]. A difference in GBS risk between SD and HD vaccines is a new finding. We considered the possibility that the difference may be related to egg-based versus recombinant influenza vaccine, which was included in our SD vaccine group. However, we observed only 8,609 and 9,196 recombinant vaccine recipients in the 2015–2016 and 2016–2017 seasons, respectively, and no GBS cases after the recombinant vaccine. This precluded any comparative analysis with HD vaccine.

In the 2015–2016 season, almost half of the chart-confirmed GBS cases had a history of antecedent respiratory or gastrointestinal illness within six weeks prior to the onset of GBS symptoms. SCRI analyses after exclusion of these cases mirrored our overall claims-based and chart-confirmed analyses, showing increased risk of GBS following all seasonal influenza vaccines in that season.

Our study had several strengths. We had access to a very large database (approximately 16 million Medicare FFS beneficiaries have received influenza vaccination each season for the past several seasons). A claims-based analysis has the potential for non-differential misclassification, biasing the association between vaccination and GBS towards the null. However, for the 2015–16 season, we performed chart confirmation and found a high (71.2%) PPV for our claims-based GBS diagnosis. Moreover, we had an excellent return on the requested charts and did not find any relevant differences between facilities that provided and did not provide the charts. Results of our imputation analysis for missing charts mirrored those for chart-confirmed cases.

Our study had some limitations. We used a 42-day primary risk window and a 42-day control window, with no wash-out period between them. Earlier analyses of the 1976 swine flu vaccine have suggested that the risk of GBS after vaccination may be elevated for up to eight or even 10 weeks [1,29]. Although it is possible that some risk may extend beyond six weeks, thus biasing our results towards the null, it is reassuring that several other studies have not shown the excess risk extending beyond six weeks post-vaccination [30,31]. Since a chart-review based GBS investigation for the 2009–2010 season [4] found that GBS discharge diagnosis in the secondary positions had a PPV of only 7.8%, we decided to use only the first discharge diagnosis position. Because we do not have any evidence to suggest that GBS cases associated with influenza vaccination could have a different likelihood than others to be coded in the second diagnosis position, we believe this restriction did not affect our results.

We excluded beneficiaries with a prior GBS diagnosis in any setting and any diagnosis position during the 183 days prior to and on the day of influenza vaccination. For the analyses in the 8–21 day window, we also excluded beneficiaries who had a discharge diagnosis of GBS in any position and setting in the 1–7 day window (Supplement A2). This could potentially lead to the loss of some GBS cases who were seen by providers in the outpatient setting prior to hospitalization. Some variation in where the GBS cases access the health care system is expected; however, all cases of GBS will need to be hospitalized for clinical evaluation and treatment. To provide uniformity, we chose the date of hospitalization rather than date of symptom onset as the date of GBS. This could lead to some GBS cases with symptom onset in the risk window but hospitalization in the control window, and some GBS cases with symptom onset in the control window but hospitalization after the control window. However, these numbers would be small because GBS symptoms progress rapidly [10] and would affect both 42-day windows similarly.

We conducted a claims-based analysis of the age, sex, geographic distribution, and comorbidities of the populations vaccinated with HD and SD vaccines, which did not reveal any obvious differences. However, it is possible that the populations who received HD and SD vaccines may have differences not captured by these analyses. Also, an SCRI design is not optimal for direct comparison between groups.

The reason for our secondary analysis finding of differences in the risk of GBS after HD vaccine and SD vaccines is unclear. One possible explanation is chance. Another explanation may be the presence of four times the amount of influenza antigen in HD versus the SD vaccines, which could, at least hypothetically, contribute to an increased risk of GBS. The hypothesis of a dose response in the association of GBS and influenza vaccination was proposed during the 2009–2010 influenza pandemic [19]. It is interesting to note that even though the uptake of the HD vaccine is steadily increasing in the Medicare FFS population, we did not observe a statistically increased GBS risk in either the 8–21 or 1–42 day risk windows for all seasonal influenza vaccines, HD vaccine, or SD vaccines in the 2017–2018 season [32]. However, if our findings regarding HD vaccine are confirmed, they should be considered when evaluating the risk–benefit ratio of using HD vaccine. Host factors for the development of an autoimmune disease after vaccination are also important. Additional research is needed to identify biomarkers and predisposed individuals [10,11,33–35].

In conclusion, we did not find an excess GBS risk in our primary analysis. The excess risk in some of our secondary analyses was close to what was expected; however, the slightly elevated GBS risk after all seasonal and HD vaccines, but not after standard dose vaccines is hypothesis-generating. This difference between HD and SD vaccines may be related to vaccine factors such as the amount of antigen or the antigen strains in various seasons or related to host factors. The risk of GBS after influenza disease is estimated to be much greater than the potential risk following influenza vaccine, ranging from four [11] to almost 16 times [24] higher, and the benefits of influenza vaccines in preventing morbidity and mortality heavily outweigh this risk [9,36]. Influenza vaccines continue to be our best defense against influenza disease and the morbidity and mortality associated with it [33,37].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authorship attestation

All authors attest they met the ICMJE criteria for authorship.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.08.045.

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