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Vaccine patterns among patients diagnosed with Guillain-Barré Syndrome and matched counterparts in a Medicare supplemental population, 2000–2020

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Abstract

Some vaccines have a small risk of Guillain-Barré Syndrome (GBS), a rare autoimmune disorder characterized by paralysis if untreated. The CDC's Advisory Committee on Immunization Practices (ACIP) guidelines do not consider GBS a precaution for future vaccines unless GBS developed within six weeks after a tetanus-toxoid-containing vaccine or influenza vaccine. Our goal was to describe vaccine patterns before and after GBS diagnosis. We matched each of 709 patients diagnosed with GBS from 2002–2020 with Medicare supplemental insurance to 10 counterparts without GBS (1:10) on age and sex. Propensity score-based weighting balanced covariates between groups, and we estimated weighted mean cumulative counts (wMCC) of vaccines/person before and after GBS diagnosis. Among patients with GBS, 7% were diagnosed within 42 days after a vaccine. Prior to GBS diagnosis, the wMCC of vaccines per person was similar between GBS cases and matched counterparts, but after two years of follow-up,

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Declaration of interests

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.

GBS patients received 21 fewer vaccines/100 people than counterparts (wMCC difference -0.21 vaccines/person, 95% CI -0.24 to -0.18); GBS patients received 16 vaccines/100 people while matched counterparts received 36/100. Vaccine use was reduced following GBS diagnosis despite no ACIP precaution for most (93%) patients in this study. The observed drop in vaccines after GBS diagnosis indicates a disconnect between clinical practice and current recommendations.

Background

Guillain-Barre Syndrome (GBS) is an autoimmune disorder characterized by polyneuropathy that can lead to paralysis. The world-wide yearly incidence is 1 to 2 cases per 100,000 people, though the risk is slightly higher among males, and the incidence has been shown to increase by 20% with each decade of life.¹ The causes of GBS are still largely unknown, but certain vaccines have been documented as associated with GBS. There is a small risk of GBS following the flu vaccine for some flu seasons, typically between 1–2 cases per 1 million doses of vaccine given.^{2–4}

The CDC's Advisory Committee on Immunization Practices (ACIP) lists GBS onset within 6 weeks after a tetanus-toxoid-containing or influenza vaccine as a precaution against receiving that vaccine in the future.⁵ In these instances, the ACIP states that the risks and benefits of vaccination should be determined on a case-by-case basis. For all other GBS cases, there is no ACIP contraindication for receiving vaccines. Existing literature shows a wide range in the proportion of patients who receive vaccinations after a GBS diagnosis. Excluding SARS-CoV-2 vaccines, the proportion of patients receiving a vaccine after an initial GBS diagnosis ranged from 24%–68%.^{6–10} A study assessing SARS-CoV-2 vaccine use among GBS survivors in Israel found that 82% received at least one vaccine dose.¹¹

Understanding the vaccine patterns of patients prior to diagnosis contextualizes vaccine use after diagnosis. No study to our knowledge has described the vaccine patterns of patients prior to their GBS diagnosis, making it difficult to know whether there was a decline in vaccine use after diagnosis. There is no contraindication for patients whose GBS did not develop within six weeks of a tetanus-toxoid-containing or influenza vaccine, so an observed decrease in vaccine use after diagnosis in this group would indicate that there is a disconnect between current recommendations and clinical practice. Our objective was therefore to describe vaccine patterns of patients with GBS before and after diagnosis.

Methods

We conducted a retrospective cohort study using the Merative MarketScan[®] Medicare Supplemental and Coordination of Benefits Database, which contains data for patients with supplemental Medicare insurance from 2000 to 2020. We included individuals who were age 65 and older with a GBS diagnosis and two years of prior continuous enrollment. We defined an incident case of GBS as an ICD-9-CM or ICD-10-CM diagnosis code for GBS in the primary position for an inpatient claim. The day of hospital admission was defined as the index date. Prior studies that have used this definition in Medicare claims reported a positive predictive value (PPV) ranging from 68% to 82%.^{12–14} We matched each patient with GBS to 10 counterparts without a GBS diagnosis on sex and exact age. The index date

for each set of ten matched counterparts was the GBS patient's diagnosis date. Similar to patients with GBS, matched counterparts were also required to have 2 years of continuous enrollment prior to the index date.

Measures

Vaccines of interest followed the CDC list of recommended adult immunizations for ages ≥ 65 and included: Influenza inactivated, recombinant, high dose, or adjuvanted; Tetanus, diphtheria, and pertussis (Tdap or Td); Pneumococcal conjugate or Pneumococcal polysaccharide; Hepatitis A; Hepatitis B; *Haemophilus influenzae* type b; Zoster; Varicella; Meningococcal B; Meningococcal A, C, W, Y.¹⁵ We also included the measles, mumps, rubella (MMR) vaccine, the human papillomavirus (HPV) vaccine, and the influenza live attenuated vaccine.

We measured vaccine use before and after the index date using the mean cumulative count (MCC), which is a nonparametric extension of the cumulative incidence function that can assess the occurrence of recurrent events in the presence of time-varying hazards and competing events.¹⁶ Whereas Kaplan-Meier and Aalen-Johansen estimators focus on cumulative incidence (i.e., the proportion of a population experiencing an outcome once over a given time period), the MCC adds flexibility by allowing multiple outcome occurrences per person.¹⁷ We estimated weighted mean cumulative counts^{16–18} for vaccines received during the two years before leading up to the index date (day -730 until day 0), and during the two years after the index date (day 1 until day 730). We defined potentially vaccine-associated GBS as any case of GBS that developed within 42 days of receiving any vaccine, which is a common time window to assign causality of GBS related to vaccination.^{2,5}

We measured covariates during a baseline period from two years (730 days) to 90 days before the index date. Because GBS can be difficult to diagnose and patients may receive multiple different diagnoses prior to the GBS diagnosis, we avoided using data for the 90 days prior to diagnosis when defining baseline covariates to ensure that their measurement was not influenced by the diagnostic process for GBS. After matching on exact age at GBS diagnosis and sex, we characterized region, healthcare utilization (number of emergency department visits, inpatient hospital admissions, and outpatient visits), comorbidity (using the Gagne combined comorbidity score¹⁹), and frailty (using an adaptation of the Kim frailty index).²⁰ The Kim frailty index was selected because both ICD-9-CM and ICD-10-CM codes have been validated in Medicare data in conjunction with the Gagne combined comorbidity score.²⁰ To avoid overadjustment, we removed several codes for vaccine administration that are typically part of the Kim frailty index since our outcome of interest before the index date was vaccine use. Finally, we assessed the number of patients with a GBS diagnosis who subsequently had a diagnosis for CIDP in any position on an inpatient or outpatient claim during follow-up (ICD-9-CM 357.81 and ICD-10-CM G61. 81).

Statistical Analysis

We first described disenrollment trends among patients diagnosed with GBS and their matched counterparts using a standardized mortality ratio (SMR) weighted Kaplan-Meier

analysis^{21,22} starting at the index date ($t=0$) until disenrollment, GBS recurrence, or administrative censoring at two years of follow-up. Separately for patients with GBS and their matched counterparts, we estimated the weighted mean cumulative count (wMCC) of the vaccinations received during the two years prior to the index date ($t=-730$ to $t=0$). We also calculated the wMCC post-index date, where we began follow-up for vaccine use at $t=1$ day and continued until $t=730$ days, censoring at disenrollment from the database, and accounting for GBS recurrence as a competing event.

To adjust for potential confounding by covariates that were not incorporated in matching, we weighted the MCC using standardized morbidity ratio (SMR) weighting, which targets the average treatment effect in the treated, asking, “How much would the average number of vaccines per person change among people who were diagnosed with GBS had they not been diagnosed with GBS?”^{17,23} We used logistic regression to calculate the propensity scores at baseline and included: Census region, healthcare utilization variables, combined comorbidity score, adapted Kim frailty index, sex, age, year of index diagnosis, and interaction terms with age and sex for each of these variables except for census region and year of index diagnosis. We assessed covariate balance between the groups using standardized mean differences.²⁴ We then constructed the wMCC, where each count a person contributes at each time is multiplied by the SMR weight calculated at baseline. The weighted number of events are divided by the weighted number of at-risk individuals multiplied by the weighted Kaplan-Meier at each event time¹⁷ to produce the wMCC. The 95% confidence intervals were generated via a non-parametric bootstrap with 1,000 resamples.¹⁷

Sensitivity Analyses

Since the ACIP lists experiencing potentially vaccine-associated GBS (GBS occurring within 42 days following a vaccine) as a precaution for receiving these vaccines in the future, we assessed whether this influenced the wMCC difference prior to the index date. We first reported the wMCC difference in the main sample at $t=-42$ days. As a second sensitivity analysis, we excluded all patients with potentially vaccine-associated GBS (patients with a vaccine from $t=-42$ to $t=0$) and their matched counterparts, and reported the wMCC difference of vaccines per person at $t=-42$ days.

Results

We identified 724 patients with an incident GBS diagnosis. After excluding 5 patients with unknown region and 10 patients who were <65 years at the time of GBS diagnosis, we included 709 patients. All 709 patients were able to be matched to 10 counterparts on exact age and sex. In both exposure groups (patients with GBS and their matched counterparts), median age was 75 years and 59% were men (Table 1). The majority of patients had low comorbidity and frailty scores. After the index date, disenrollment occurred at a similar rate through one year of follow-up for patients with GBS and their matched counterparts (37% vs 38% disenrollment at 1-year post-index), and diverged over the second year of follow-up (54% vs 61% at 2 years post-index). There were three observed GBS recurrences among

patients with GBS. We identified 105 patients (14.8%) with a diagnosis code for CIDP during the two years of follow-up.

Among patients diagnosed with GBS, 33% received at least one vaccine during the two years prior to the index date and 12% received at least one vaccine during the two years of follow-up. Among the matched counterpart group, 28% received at least one vaccine during baseline and 24% received at least one during follow-up. (Table 2). Flu vaccines were the most common; for patients with GBS, flu vaccines were 69% of all vaccines during the two years prior to diagnosis and 57% of all vaccines during the two years after diagnosis. For matched counterparts, flu vaccines were 68% of vaccines prior to the index date and 71% after two years of follow-up. Pneumococcal and Tdap or Td vaccines were the second and third most common vaccines during baseline and follow-up for both groups.

Figure 1 shows the SMR wMCCs of the number of vaccines received per person for patients diagnosed with GBS and matched counterparts. Patients who were diagnosed with GBS had a slightly higher wMCC prior to diagnosis than matched counterparts (0.55 vs. 0.47), but by the end of two years of follow-up, patients with GBS had a lower wMCC of vaccines than matched counterparts (0.16 vs. 0.36). Prior to the index date, the wMCC difference of vaccines per person was 0.08 (95% CI 0.03 to 0.13), and the wMCC ratio was 1.18 (95% CI 1.06 to 1.30). After two years of follow-up, the wMCC difference was -0.21 (95% CI -0.24 to -0.18) and the wMCC ratio was 0.43 (95% CI 0.35 to 0.51). For the first sensitivity analysis assessing the wMCC prior to the index date at $t=-42$ in the main sample, the wMCC difference was 0.06 (95% CI 0.01, 0.11).

There were 47 (7%) cases of GBS that could be considered vaccine-associated GBS, meaning that GBS developed within 42 days following receipt of a vaccine. Among these 47 cases, there were 55 vaccines received during the 42-day risk window; 31 flu vaccines, 12 pneumococcal, 10 TDAP, 1 MMR, and 1 hepatitis A vaccine. Some patients received more than one vaccine during the 42-day risk window from $t=-42$ to $t=0$. Figure 2 shows the wMCCs in the sensitivity analysis that excluded patients diagnosed with GBS who received a vaccine in the 6 weeks prior to index date ($t=-42$ to $t=0$), along with their matched counterparts. We found a wMCC difference before diagnosis from $t=-730$ to $t=-42$ of 0.01 (95% CI -0.03 to 0.06) and a wMCC ratio of 1.03 (95% CI of 0.91 to 1.15). After two years of follow-up, the wMCC difference was -0.20 (95% CI of -0.24 to -0.17) and wMCC ratio was 0.43 (95% CI of 0.34 to 0.53).

Discussion

This is the first study to assess vaccine patterns of patients diagnosed with GBS both before and after diagnosis. Among patients with GBS, the percentage of people receiving vaccines dropped by over half from baseline to the end of follow-up (33% vs. 12%). For matched counterparts, this percentage remained fairly consistent (28% vs. 24%). Prior to the index date, for every 100 people, patients diagnosed with GBS received 8 more vaccines than matched counterparts (wMCC difference of 0.08 vaccines per person). After two years of follow-up, for every 100 people, patients with GBS received 21 fewer vaccines than matched counterparts (wMCC difference of -0.21 vaccines per person). This indicates a

strong effect of a GBS diagnosis on reducing vaccine use after diagnosis, despite no ACIP contraindication for the majority (93%) of patients in this study.

Prior to the index date ($t=0$), the wMCC of patients diagnosed with GBS was slightly higher than the matched counterpart group. This could be due to vaccine-associated GBS (i.e., occurring within 42 days after receiving a vaccine) or some other unmeasured confounding. For both sensitivity analyses, the wMCCs were similar to the main analysis both prior to diagnosis and after two years of follow-up. The exclusion of people with potentially vaccine-associated GBS did not substantially influence the results after two years of follow-up. Because there is no contraindication for vaccines among patients without potentially vaccine-triggered GBS, this indicates a discordance between clinical practice and existing guidance. Patients without potentially vaccine-associated GBS may be unnecessarily avoiding vaccines, and could be a good target group for a public health intervention, particularly in elderly populations, who are more likely to experience flu-related hospitalizations.²⁵

Our results cannot indicate the reasons behind the observed drop in vaccine use after GBS diagnosis. Potential factors could include knowledge status of existing recommendations among both patients and providers and concerns about GBS recurrence. A recent survey study in Germany found that out of 97 people with a history of GBS, 31 did not receive vaccines within five years after diagnosis. Among these 31 patients, 32% did not receive vaccines after diagnosis because of fears related to adverse events and 26% reported being dissuaded by a medical doctor.¹⁰ Future work should assess patient and provider knowledge of existing guidance and the reasons why some patients do not receive vaccines despite no contraindication.

These results should be understood in the context of several limitations. This study was conducted in a patient population 65 years and older with Medicare supplemental insurance, so the results may not directly apply to other patient populations. Additionally, claims for vaccines are only observable if Medicare was billed, which is not always the case for vaccines when received in certain settings, such as when influenza vaccines are given by employers. Since younger populations are more likely to receive vaccines through their employers that are not billed by insurance, we selected a patient population age ≥ 65 to limit this vaccine measurement error. There is limited information on the accuracy of measuring vaccines in Medicare claims, but the literature suggests claims undercount vaccine use compared to self-reported data. One study comparing Medicare influenza vaccine claims to the Medicare Current Beneficiary Survey (MCBS) found that self-reported vaccination was 69% while the claims data was 48%; the sensitivity of the Medicare claims was 68% with 96% specificity.²⁶ A study from 2022 also found MCBS self-reported vaccine use to be higher than the claims, and found that among beneficiaries with no claim for a flu vaccine, 42.6% self-reported a flu vaccine.²⁷

Our study was limited to an examination of vaccine patterns covering two years pre- and two years post-GBS diagnosis. Longer periods would have reduced our sample size, and shorter periods would reduce the potential to accurately capture yearly vaccines like the influenza vaccine. We did not assess other specific contraindications for receiving vaccines. The ACIP

lists developing GBS within 42 days after receiving a vaccine as a precaution for future vaccination. Other contraindications for vaccination, such as severe immunocompromising conditions or previous encephalopathy, are relatively rare and typically temporary, and unlikely to alter the main findings. There may also be limitations in confounding control for race or ethnicity, which is not an available variable in this data source and may be an important confounder. Finally, from the data presented, we cannot elucidate the underlying causes for the decline in vaccine use after GBS diagnosis. However, for patients who did not develop GBS within six weeks of a tetanus-toxoid-containing or influenza vaccine, these results point to opportunities for public health interventions to increase vaccine use among this group.

Conclusion

Patients diagnosed with GBS had slightly higher vaccine use prior to diagnosis compared to matched counterparts, but after diagnosis, GBS cases had much lower vaccine use compared to matched counterparts by the end of follow-up. There was a strong effect of a GBS diagnosis on subsequent vaccine use. To maximize our understanding of vaccines after a GBS diagnosis, future work should investigate the underlying causes for the observed decline in vaccine use after a GBS diagnosis among Medicare beneficiaries and identify key subgroups for targeted public health interventions to increase vaccine use in this population.

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Data Statement:

These data can be obtained through a data use agreement with Merative.

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Weighted mean cumulative count of the number of vaccines received per person before and after the index date

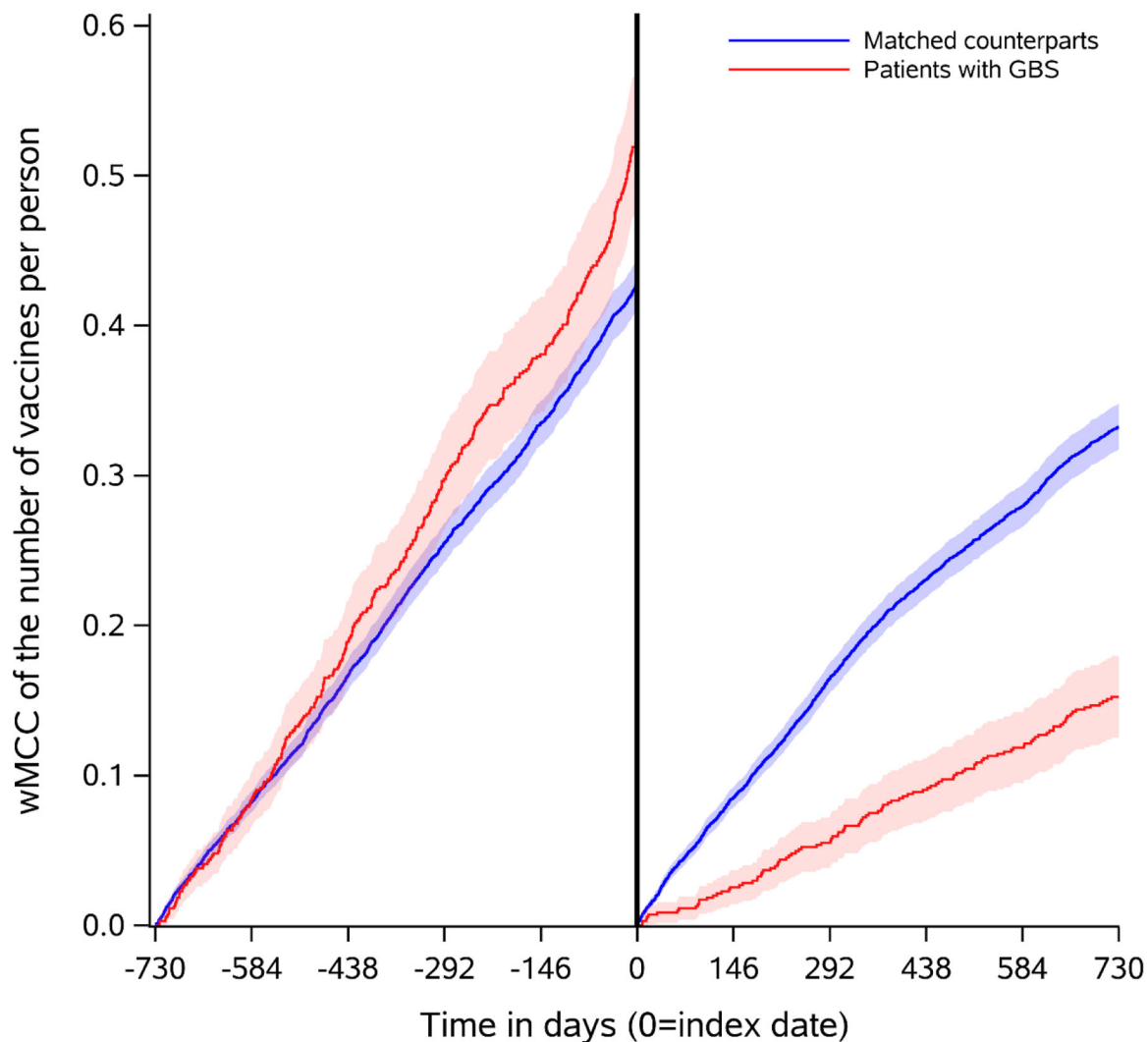


Figure 1: weighted mean cumulative count of vaccines received prior to and after GBS diagnosis among patients with GBS and matched counterparts

Patients with GBS: 0.55 (95% CI 0.50, 0.59)

Patients with GBS: 0.16 (95% CI 0.13, 0.18)

Matched counterparts: 0.47 (95% CI of 0.45, 0.48)

Matched counterparts: 0.36 (95% CI 0.35, 0.37)

wMCC Difference: 0.08 (95% CI of 0.03, 0.13)

wMCC Difference: -0.21 (95% CI of -0.24, -0.18)

wMCC Ratio: 1.18 (95% CI of 1.06, 1.30)

wMCC Ratio: 0.43 (95% CI of 0.35, 0.51)

Weighted mean cumulative count of the number of vaccines received per person before and after the index date

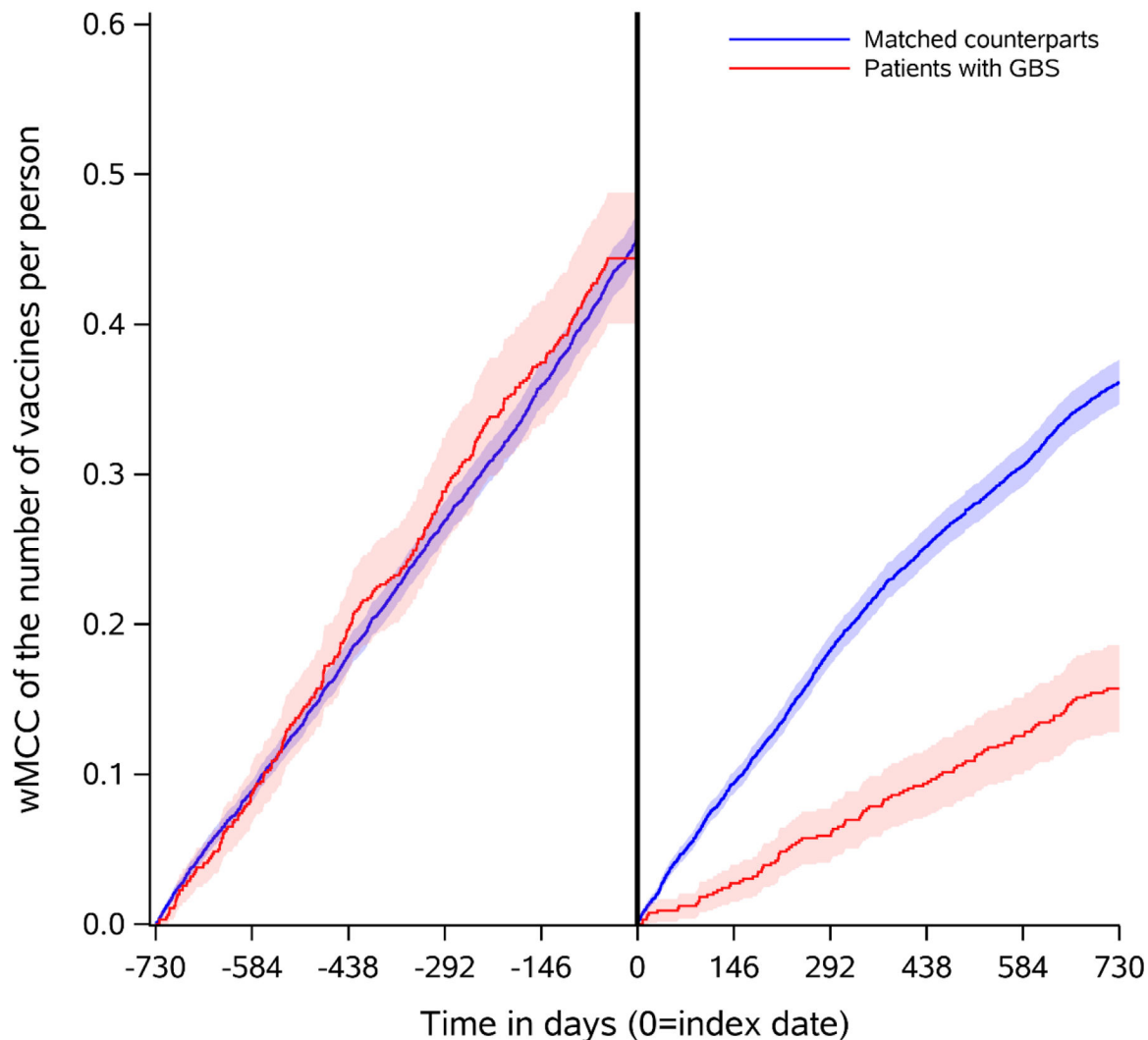


Figure 2: weighted mean cumulative count of vaccines received prior to and after GBS diagnosis among patients with GBS who did not receive a vaccine from $t=-42$ to $t=0$ and their matched counterparts

Patients with GBS: 0.44 (95% CI 0.40, 0.49)

Patients with GBS: 0.16 (95% CI 0.13, 0.19)

Matched counterparts: 0.43 (95% CI of 0.41, 0.45)

Matched counterparts: 0.36 (95% CI 0.35, 0.38)

wMCC Difference: 0.01 (95% CI of -0.03 , -0.06)

wMCC Difference: -0.20 (95% CI of -0.24 , -0.17)

wMCC Ratio: 1.03 (95% CI of 0.91, 1.15)

wMCC Ratio: 0.43 (95% CI of 0.34, 0.53)

Note: wMCCs prior to diagnosis was measured at 42 days prior to index date ($t = -42$)

Table 1.

Baseline Characteristics of Patients Diagnosed with GBS and Matched Counterparts

	1) Patients with GBS N = 709		2) Matched counterparts N = 7090			3) Absolute standardized mean difference	
	N	%	N	%	SMR-weighted	Prior to SMR weighting	After SMR weighting
Age *							
Median (IQR)	75 (70–80)		75 (70–80)		75 (70–80)	0.000	
65–69	134	18.9%	1340	18.9%	18.8%	0.010	
70–74	210	29.6%	2100	29.6%	29.6%		
75–79	172	24.3%	1720	24.3%	24.4%		
80–84	128	18.1%	1280	18.1%	17.9%		
85	65	9.2%	650	9.2%	9.2%		
Sex							
Male	416	58.7%	4160	58.7%	59.0%	0.000	0.005
Female	293	41.3%	2930	41.3%	41.0%		
Emergency Dept. visits							
Mean (std)	0.77	1.56	0.67	1.47	0.79	0.090	0.002
0 visits	456	64.3%	4725	66.6%	64.3%		
1 visit	126	17.8%	1330	18.8%	17.8%		
2 visits	127	17.9%	1035	14.6%	17.9%		
Outpatient visits							
Mean (std)	14.60	12.50	12.36	11.13	14.31	0.196	0.004
0 visits	46	6.5%	615	8.7%	6.5%		
1 visit	14	2.0%	242	3.4%	2.0%		
2–6 visits	131	18.5%	1579	22.3%	18.6%		
7–11 visits	156	22.0%	1641	23.1%	22.0%		
> 11 visits	362	51.1%	3010	42.5%	50.9%		
Inpatient admissions							
Mean (std)	0.45	0.92	0.36	0.75	0.44	0.102	0.002
0 visits	501	70.7%	5307	74.9%	70.5%		
1 visit	142	20.0%	1279	18.0%	20.0%		
2 or more visits	66	9.3%	504	7.1%	9.3%		
US Census Region							
Northeast	128	18.1%	827	11.7%	17.9%	0.373	0.004
Midwest	247	34.8%	3454	48.7%	34.8%		
South	212	29.9%	2211	31.2%	30.0%		
West	122	17.2%	598	8.4%	17.2%		
Combined Comorbidity Score							
Mean (std)	0.90	1.71	0.72	1.52	0.93	0.144	0.008

	1) Patients with GBS N = 709		2) Matched counterparts N = 7090			3) Absolute standardized mean difference	
	N	%	N	%	SMR-weighted	Prior to SMR weighting	After SMR weighting
0	410	57.8%	4574	64.5%	57.5%		
1 or 2	207	29.2%	1821	25.7%	29.5%		
3 to 8	80	11.3%	612	8.6%	11.3%		
9	12	1.7%	83	1.2%	1.7%		
Kim Frailty Index							
Mean (std)	0.16	0.05	0.16	0.05	0.16	0.060	0.003
<0.2	571	80.5%	5806	81.9%	80.4%		
0.2 to < 0.3	120	16.9%	1163	16.4%	17.1%		
0.3	18	2.5%	121	1.7%	2.5%		
Year of GBS diagnosis *							
2002–2005	101	14.2%	1010	14.2%	13.5%	0.000	0.007
2006–2010	207	29.2%	2070	29.2%	29.3%		
2011–2015	261	36.8%	2610	36.8%	38.6%		
2016–2020	140	19.7%	1400	19.7%	18.3%		

* Reported categorically; analyzed as a continuous variable

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Table 2:

Vaccination Patterns of Patients Diagnosed with GBS and Matched Counterparts

	Patients with GBS		Matched Counterparts	
	N	%	N	%
Received at least one vaccine during baseline	231	32.6	1992	28.1
1 flu vaccine	189	26.7	1560	22.0
1 pneumococcal	55	7.8	528	7.4
1 Tdap or Td	48	6.8	331	4.7
Type of vaccination received during baseline ¹				
Total number of vaccines	390	%	3232	%
Flu vaccine	269	69.0	2187	67.7
Tdap or Td	47	12.1	341	10.6
MMR	2	0.5	2	0.1
Zoster	6	1.5	83	2.6
Pneumococcal	61	15.6	556	17.2
Hepatitis A	4	1.0	10	0.3
Hepatitis B	1	0.3	53	1.6
Received at least one vaccine during follow-up	86	12.1	1733	24.4
1 flu vaccine	50	7.1	1356	19.3
1 pneumococcal	24	3.4	390	5.5
1 Tdap or Td	19	2.7	230	3.2
Type of vaccination received during follow-up ²				
Total number of vaccines	109	%	2538	%
Flu vaccine	62	56.9	1793	70.6
Tdap or Td	19	17.4	237	9.3
MMR	0	0.0	1	0.0
MMR/Varicella	0	0.0	1	0.0
Zoster	1	0.9	57	2.2
Pneumococcal	24	22.0	413	16.3
Hepatitis A	0	0.0	2	0.1
Hepatitis B	3	2.8	32	1.3
Haemophilus influenzae b	0	0.0	2	0.1

¹No observations for Human papillomavirus; Meningococcal A, C, W, Y; Meningococcal B; Haemophilus influenzae b; percent based on total number of vaccines

²No observations for Human papillomavirus; Meningococcal A, C, W, Y; Meningococcal B; percent based on total number of vaccines