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ORIGINAL ARTICLE

Guillain–Barré syndrome following influenza vaccination: A 15-year nationwide population-based case–control study

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Abstract

Background and purpose: Influenza vaccination may increase the risk of developing Guillain–Barré syndrome (GBS) due to an elicited immune response, but the exact magnitude and duration of risk is unclear and hence the aim of this study.

Methods: We conducted a retrospective nationwide population-based case–control study of prospectively collected data on all patients with first-time hospital-diagnosed GBS in Denmark between 2002 and 2016 and 10 age-, sex- and index date-matched population controls per case. The primary exposure was incident influenza vaccination 1 month prior to admission with GBS. We used medical registries to ascertain a complete hospital contact history of pre-existing morbidities. To examine duration of GBS risk, we repeated the analysis for five consecutive 1-month risk periods following vaccination.

Results: Of the 1295 GBS cases and 12,814 controls, 20 cases (1.5%) and 119 controls (0.9%) had received an influenza vaccination within the last month, yielding a comorbidity-adjusted odds ratio of 1.9 (95% confidence interval 1.1–3.2) for GBS. Stratified analyses by calendar time, gender and age showed similar results. The increased risk of GBS was largely confined to 1 month following influenza vaccination. The population-attributable fraction of GBS from influenza vaccination in Denmark was 0.4%.

Conclusions: Influenza vaccination was associated with a slightly elevated risk of GBS occurrence within 1 month after vaccination. However, only 1.5% of GBS cases in Denmark are associated with recent influenza vaccination. Thus, the benefit of influenza vaccines in preventing influenza infections and associated morbidity and mortality needs to be weighed against the small absolute risk of GBS.

KEYWORDS
epidemiology, Guillain–Barré syndrome, neuropathy

INTRODUCTION

Guillain–Barré syndrome (GBS) is a severe immune-mediated neuropathy resulting in an acute or subacute progressive bilateral symmetric weakness [1]. In approximately 25% of GBS cases symptoms are preceded by an infection which may have induced an aberrant immunological response [2]. Similarly, stimulation of the immune system by different vaccines have been investigated (e.g., tetanus toxoid-containing vaccines, polio vaccines, and COVID-19 vaccines) [3–7]. However, apart from the association between influenza vaccine and GBS, evidence for associations between GBS and other vaccines is weak [3–8]. Patone et al. recently undertook a self-controlled

case series study to investigate hospital admissions from neurological complications in the 28 days after a first vaccination against COVID-19 with either ChAdOx1nCoV-19 (n = 20,417,752) or BNT162b2 (n = 12,134,782) and after a SARS-CoV-2-positive test (n = 2,005,280) in England between 1 December 2020 and 31 May 2021. They found an increased risk of GBS after ChAdOx1nCoV-19 vaccination (incidence rate ratio [IRR] 2.0, 95% confidence interval [CI] 1.6–2.6) but not after BNT162b2 vaccination (IRR 0.9, 95% CI 0.5–1.4). A more profoundly increased risk of GBS was observed in the 1–28-day period after a SARS-CoV-2-positive test (IRR 5.3, 95% CI 3.0–9.2) [6]. For influenza vaccines, current evidence suggests a small elevated risk of GBS after influenza vaccination, but long-term data are limited [8, 9]. In 1976, the H1N1 swine influenza vaccine programme was first associated with an estimated relative risk (RR) of GBS of 7–8 in vaccinated individuals [10]. More recently, two meta-analyses showed an increased risk of GBS within 6 weeks following seasonal or 2009 H1N1 monovalent influenza vaccination (odds ratio [OR] 2.4 [95% CI 1.4–4.0] and 2.4 [95% CI 1.6–3.7], respectively) [11, 12]. A meta-analysis of 29 studies conducted between 1981 and 2014 [13] suggested a weaker association between any influenza vaccine, whether seasonal or pandemic, and GBS, with an overall RR of 1.4 (95% CI 1.2–1.7) [13]. Large population-based studies are important to clarify the exact magnitude and duration of GBS risk following influenza vaccination. We determined the risk of GBS following seasonal influenza vaccination from 2002 to 2016 in prospectively collected data using the Danish national healthcare registries.

METHODS

We conducted a nationwide matched case–control study on the risk of GBS in patients exposed to influenza vaccine based on nationwide data from a population of 5.8 million inhabitants. The study received approval from the Danish Data Protection Agency (file number 1-16-02-817-17). No ethical approval or informed consent is required to conduct register-based studies in Denmark [14]. Data were based on Danish national registers, and individual-level data cannot be shared. However, summary statistics and additional results may be provided on request [14]. All Danish citizens are registered in the Danish Civil Registration System (CRS) with a unique personal civil registration number [15]. We used this registration number to link individual-level data across several national registers. The individual-level registration ensured a unique identification across repeated admissions and transferals between hospitals.

We identified all GBS patients in Denmark between March 1, 2002, and December 31, 2016, using inpatient admission dates associated with a first incident primary discharge diagnosis of GBS, as described previously [2]. We used the CRS to randomly select 10 population controls for each case, matched for age and sex. GBS admission date was defined as the index date for the cases. All controls were assigned to an index date identical to that of each corresponding GBS case.

We assessed data on all reimbursed influenza vaccines in the primary care sector, using the National Health Insurance Service Registry (NHSR) [16]. The Danish National Board of Health has recommended annual influenza vaccination to citizens above 65 years and those with chronic disease since 1998, and data on influenza vaccines are available from January 1, 2002 in the NHSR. Population influenza vaccination coverage in these risk groups has been approximately 50% since monitoring started in 2009 [17, 18].

We obtained data for potential confounders, selected a priori from the data sources, including age, gender, and date of first GBS admission (index date), all of which were identified in the CRS. To assess the total burden of comorbidity (which may increase risk of GBS), the Charlson Comorbidity Index (CCI) score was accumulated based on a complete hospital contact history during 10 years prior to the index date, enabled through linkage to the nationwide Danish National Patient Registry (DNPR) [19]. In addition, all preceding treated infections and major surgical procedures were assessed in a subset of GBS cases and controls from 2004 to 2016, where complete data on antibiotic prescriptions and surgical procedures were available [20]. Preceding infections were assessed as hospital-diagnosed infections and/or community antibiotic prescriptions as previously described [2, 21], using the DNPR and the Danish National Health Service Prescription Database [2, 20]. Major surgery was evaluated according to the NOMESCO Classification of Surgical Procedures [22]. Both preceding infections and surgery were assessed in a risk interval within 5 months of the GBS/index date as the impact of these factors on GBS risk is thought to be temporary [2].

We used conditional logistic regression to compute matched odds ratio (ORs) of GBS associated with exposure to recent influenza vaccination in the period from 2002 to 2016. In our primary analyses, we examined the OR for GBS within 1 month of influenza vaccination. Within this risk window, we conducted stratified analyses using predefined subgroups of time periods, level of comorbidity (CCI score of 0, 1, 2, and ≥3), index year, sex, and age subgroups. In cases and controls with an index date from June 1, 2004 to December 31, 2016, we further adjusted for CCI score, acute infections and major surgery to assess if any association of influenza vaccination with GBS was independent of these factors. We calculated the population attributable fraction for influenza vaccination occurring within 30 days before GBS, using the equation: $[P^*(OR-1)]/(1 + OR (OR-1)^*[P])$, where P was the proportion of the comparison cohort with influenza vaccination. To examine the impact of time from influenza vaccination to subsequent GBS occurrence, we extended the risk window to 5 months (150 days) and repeated the analysis for five consecutive 30-day risk periods prior to the GBS index date. Each individual was allowed to contribute with a maximum of one influenza vaccination exposure during each 30-day risk period. To allow comparison with existing literature, we additionally repeated analyses for a narrowed (14-day) and broadened (60-day) risk window. All analyses were performed using STATA software, version 16.

To assess the robustness of the results, we performed a case-crossover analysis of influenza vaccination as a GBS risk factor,

including only GBS cases. Each case contributed to a 1-month risk time window before becoming a GBS case and a 1-month control window beginning 365 days prior to the 1-month GBS case window. This design controls for all time-invariant confounders, including genetic background and other unmeasured covariates [23].

RESULTS

During the study period, we identified 1295 GBS cases and 12,814 matched controls (Table 1). Compared with age-matched controls, GBS cases were slightly more likely to have pre-existing comorbidities (26.6% vs. 19.4%). In the subgroup of cases and controls with complete data on infection and surgery, GBS cases were much more likely to have preceding infection within 5 months (34.4% vs. 17.0%) and recent major surgery (10.6% vs. 5.1%) compared to controls (Table 1).

Among GBS cases, 20 (1.5%) were vaccinated against influenza within 1 month prior to the index date, compared with 119 controls (0.9%) within the same time window. The unadjusted, age-, sex- and index date-matched OR of the association between influenza vaccination and GBS in 2002–2016 was 1.9 (95% CI 1.1–3.4; Table 2). Additional adjustment for comorbidity produced an unchanged OR of 1.9 (95% CI 1.1–3.2). In the group of cases (n = 1086) and controls (n = 10,747) with complete data on infections and surgical procedures, the age-, sex- and index date-matched OR for GBS from influenza vaccination was 1.8 (95% CI 1.0–3.3). In this subset, further adjustment for comorbidities only (OR 1.8, 95% CI 1.0–3.2), infections only (OR 1.8, 95% CI 1.0–3.3) and major surgery only (OR 1.8, 95% CI 1.0–3.1) resulted in unchanged ORs. Adjusting for all covariates simultaneously resulted in an OR of 1.7 (95% CI 1.0–3.1) in 2004 to 2016.

Stratification by calendar time, gender and age showed similar results for the association between influenza vaccination and GBS (Table 2), yet with limited statistical precision. For individuals aged less than 70 years, the association tended to be weaker (OR 1.5, 95% CI 0.6–3.4) than for older individuals (OR 2.5, 95% CI 1.2–5.2; Table 2).

Within the full study period, 723 unique GBS patients received 3888 influenza vaccinations at any time, and 6664 unique controls received 39,452 influenza vaccinations. Thus, only 0.5% (n = 20/3888) of all influenza vaccinations among GBS cases and 0.3% of those in controls (n = 119/39,452) occurred within 1 month of the index date. Assuming a causal association between recent influenza vaccination and GBS, the population attributable fraction was 0.4%. In our additional case-crossover analysis of influenza vaccination, the 1-month GBS risk estimate was higher but more statistically imprecise compared to the main analysis, with an OR of 2.9 (95% CI 1.2–6.8).

The increased GBS risk was confined to 1 month after influenza vaccination only. In the second to fifth months after influenza vaccination, we observed no increased GBS risk (ORs ranged from 0.6 [95% CI 0.3–1.1] to 0.9 [95% CI 0.5–1.8]). In a narrowed 14-day

TABLE 1 Characteristics of Guillain–Barré syndrome cases and matched controls

Characteristics	Cases, *n* (%)	Controls, *n* (%)
2002–2016		
N	1295	12,814
Females	526 (40.6)	5203 (40.6)
Males	769 (59.4)	7611 (59.4)
Year of diagnosis		
2002–2008	665 (51.4)	6587 (51.4)
2009–2016	630 (48.6)	6227 (48.6)
Age groups		
0–19	145 (11.2)	1426 (11.1)
20–39	271 (20.9)	2638 (20.6)
40–59	362 (28.0)	3605 (28.1)
60–79	440 (34.0)	4385 (34.2)
80–99	77 (5.9)	760 (5.9)
CCI score		
0	950 (73.4)	10,332 (80.6)
1	166 (12.8)	1286 (10.0)
2	109 (8.4)	727 (5.7)
≥3	70 (5.4)	469 (3.7)
Myocardial infarction	44 (3.4)	256 (2.0)
Congestive heart failure	37 (2.9)	209 (1.6)
Peripheral vascular disease	27 (2.1)	243 (1.9)
Cerebrovascular disease	63 (4.9)	455 (3.6)
Dementia	3 (0.2)	69 (0.5)
Chronic pulmonary disease	78 (6.0)	589 (4.6)
Connective tissue disease	28 (2.2)	196 (1.5)
Ulcer disease	24 (1.9)	182 (1.4)
Mild liver disease	17 (1.3)	88 (0.7)
Diabetes I and II	68 (5.3)	393 (3.1)
Hemiplegia	8 (0.6)	21 (0.2)
Moderate to severe renal disease	17 (1.3)	107 (0.8)
Diabetes with end organ	34 (2.6)	185 (1.4)
Any tumor	59 (4.6)	525 (4.1)
Leukemia	7 (0.5)	14 (0.1)
Lymphoma	9 (0.7)	40 (0.3)
Moderate to severe liver disease	5 (0.4)	21 (0.2)
Metastatic solid tumor	9 (0.7)	53 (0.4)
AIDS	<5	10 (0.1)
2004–2016		
N, total	1086	10,747
Females	442 (40.7)	4376 (40.7)
Males	644 (59.3)	6371 (59.3)
Year of index		

(Continues)

TABLE 1 (Continued)

Characteristics	Cases, *n* (%)	Controls, *n* (%)
2004–2009	544 (50.1)	5388 (50.1)
2010–2016	542 (49.9)	5359 (49.9)
CCI score		
0	787 (72.5)	8600 (80.0)
1	145 (13.4)	1104 (10.3)
2	91 (8.4)	635 (5.9)
3	63 (5.8)	408 (3.8)
Preceding infection	372 (34.4)	1822 (17.0)
Preceding major surgery	115 (10.6)	552 (5.1)

Abbreviations: Adj., adjusted; CCI, Charlson Comorbidity Index; CI, confidence interval; OR, odds ratio.

TABLE 2 Association between influenza vaccination and Guillain–Barré syndrome

	Number of cases/controls	OR (95% CI)	CCI-adj. OR (95% CI)
Total	20/119	1.94 (1.12–3.36)	1.85 (1.06–3.21)
2002–2009	11/64	2.04 (0.95–4.38)	2.03 (0.94–4.35)
2010–2016	9/55	1.83 (0.82–4.08)	1.67 (0.74–3.74)
Male	13/75	2.05 (1.02–4.11)	1.98 (0.98–3.99)
Female	7/44	1.77 (0.72–4.38)	1.68 (0.68–4.15)
Age < 70	7/50	1.45 (0.62–3.41)	1.32 (0.56–3.11)
Age ≥ 70	13/69	2.47 (1.18–5.19)	2.45 (1.17–5.15)

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; OR, odds ratio.

risk window, we found only five influenza-vaccinated cases and 50 controls, yielding a more imprecise GBS OR of 1.0 (95% CI 0.4–2.6). In a broadened 60-day risk window, the GBS OR was 1.2 (95% CI 0.8–1.9).

DISCUSSION

In this large nationwide epidemiological study, influenza vaccination preceded GBS in only 1.5% of all cases. Vaccination resulted in a 1.9-fold (95% CI 1.1–3.4) temporarily increased risk of GBS occurrence; an increase which was evident for only 1 month after the immunization. The RR of GBS after vaccination was slightly higher (OR 2.5, 95% CI 1.2–5.2) in older patients (>70 years), who may be more prone to various exposures provoking the immune system, for example, vaccines, thus contributing to the overall incidence peak in older patients [24]. In the previous meta-analyses [11, 12], the RR of GBS after pandemic influenza vaccination was slightly higher (OR 2.4) than that found in our nationwide population (OR 1.9). This might be related to pandemic vaccines yielding a higher relative GBS risk (RR 1.8, 95% CI 1.4–2.5) compared to seasonal vaccines (RR 1.2, 95% CI 1.0–1.5), as proposed in another meta-analysis [13]. Another explanation could be the higher relative impact on GBS risk in younger individuals (OR 1.5, 95% CI 0.6–3.4) compared with older individuals (OR 2.5, 95% CI 1.2–5.2) who constitute the majority of seasonal vaccine recipients [18]. Other self-controlled case series studies of the association between GBS and seasonal influenza vaccines after 1976 reported the risk increase to be questionable or minimal, with RRs of 0.6 (95% CI 0.2–1.9) [25] and 1.5 (95% CI 1.2–2.0) [26] assessed within 30 and 42 days, respectively. Our study adds to the literature [13] by providing strong evidence in favor of an increased risk of GBS within 1 month of influenza vaccination. The risk of GBS has previously been reported to peak within the first 2–4 weeks post influenza vaccination [26, 27], consistent with our findings. Importantly, influenza infection itself has been reported to carry a seven- to 16-fold increased risk of GBS [25, 26]. This is in line with our previous findings that either infections treated by community antimicrobial drugs (OR 3.5, 95% CI 3.0–4.1) or in-hospital respiratory tract infections (OR 14.7, 95% CI 8.5–25.6) are strongly associated with a subsequent increased GBS risk [2]. Therefore, any temporary RR increase of GBS following vaccination should be weighed against the potential large benefits of vaccination against developing severe influenza, thus hindering influenza-related complications; not only GBS, but first and foremost pneumonia, hospitalization, possibly cardiovascular events, and death [28].

The strengths of this study include its nationwide population coverage and large sample size. Observational studies may be subjected to selection problems and bias; however, the free and equal access to the Danish tax-financed healthcare system greatly reduces selection bias. Moreover, information bias including investigator or recall bias in our study is unlikely, as data were collected for purposes unrelated to our study. We have previously validated the GBS diagnosis in the DNPR [24, 29] using the GBS criteria from the National Institute of Neurological Disorders and Stroke [30], showing that the GBS diagnosis has a high positive predictive value (84%–86%) [24, 29]. No study has reported on the validity of influenza vaccination in the NHSR. As report of influenza vaccination to the NHSR is mandatory to receive reimbursement we believe coverage is good, and the strengths of this register include completeness, size, and long follow-up period [16]. Our study also has some limitations. First, residual confounding from comorbidities not included in the CCI score and other frailties could influence the probability of being vaccinated and thereby lead to an overestimation of the association between influenza vaccination and GBS. Second, cases of mild GBS without hospitalization, for example, caused by influenza vaccinations, were not included, which may have resulted in an underestimation of the association.

In conclusion, this nationwide case–control study provides robust evidence that influenza vaccination is associated with a modestly increased risk of GBS development 1 month after the vaccine. However, the benefits of influenza vaccines in preventing influenza infection, decreasing mortality and influenza-associated morbidity, including GBS, are likely to greatly outweigh any temporarily increased risk of GBS after influenza vaccination.

AUTHOR CONTRIBUTIONS

Lotte Sahin Levison: Conceptualization (lead); formal analysis (lead); writing – original draft (lead); writing – review and editing (equal). **Reimar Wernich Thomsen:** Conceptualization (equal); methodology (lead); writing – review and editing (equal). **Henning Andersen:** Conceptualization (supporting); writing – original draft (supporting); writing – review and editing (equal).

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CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

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