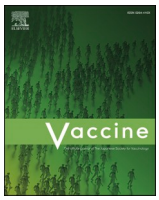
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Risk of Guillain-Barré syndrome after COVID-19 vaccination or SARS-CoV-2 infection: A multinational self-controlled case series study

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ABSTRACT

Background: The association between Guillain-Barré syndrome (GBS) and certain COVID-19 vaccines is inconclusive. We investigated the risk of GBS after COVID-19 vaccination or SARS-CoV-2 infection.
Methods: Using a common protocol, we conducted a self-controlled case series study from 1 December 2020 to 9 August 2023 at 20 global sites within the Global Vaccine Data Network™ (GVDN®). Brighton Collaboration case definition criteria were used to determine the level of certainty (LOC) of medical record-reviewed GBS cases at 15 sites. GBS cases following SARS-CoV-2 infection were identified from electronic data sources (EDS) from 11 sites. We estimated the relative incidence (RI) of GBS within 1–42 days following receipt of adenoviral vector, mRNA, or inactivated COVID-19 vaccines or SARS-CoV-2 infection using conditional Poisson regression models, controlling for seasonality. We used random effects meta-analysis to pool the estimates across sites.
Results: Of 410 medical record-reviewed post-vaccination GBS cases (out of 2086 EDS-identified cases), 49 were LOC 1 or 2, 187 were LOC 3 or 4, and 174 were LOC 5. These cases received a total of 794 doses of COVID-19 vaccines (160 [20 %] adenoviral vector vaccine doses, 556 [70 %] mRNA vaccine doses, 77 [10 %] inactivated vaccine doses, and 1 [0.1 %] protein-based vaccine dose) during the observation period. We observed an increased risk of confirmed (LOC 1–2) GBS after receiving ChAdOx1-S/nCoV-19 (Vaxzevria/Covishield) (RI = 3.10; 95 % confidence interval [CI], 1.12–8.62). Decreased risks of LOC 1–4 GBS were observed after receiving BNT162b2 (Comirnaty/Tozinameran) (RI = 0.48; 95 %CI, 0.27–0.85) and CoronaVac/Sinovac (RI = 0.04; 95 % CI, 0.00–0.61). For 489 EDS-identified GBS cases after SARS-CoV-2 infection, we found GBS risk to be increased (RI = 3.35; 95 %CI, 1.83–6.11).
Conclusion: In this large multinational study, we found increased risks of GBS within 42 days after Vaxzevria/Covishield vaccination or SARS-CoV-2 infection, and decreased risks after receiving Comirnaty/Tozinameran or CoronaVac/Sinovac COVID-19 vaccines.

1. Introduction

Guillain-Barré syndrome (GBS), a condition characterised by progressive ascending limb weakness and reduced or absent reflexes, is the most common cause of acute flaccid paralysis worldwide, with an annual incidence of around 1–4 cases per 100,000 people [1]. Evidence supports an autoantibody-mediated immune process after infection with various pathogens, including *Campylobacter jejuni*, Zika virus, and respiratory viruses such as influenza and SARS-CoV-2 [2].

In the late 1970s, an increased risk of GBS following receipt of the new H1N1 pandemic influenza vaccine was observed (around one case per 100,000 vaccinations) in the United States [3]. Since then, a meta-analysis of epidemiological studies identified a small increase in the risk of GBS after influenza vaccination, with an attributable risk of approximately one case per million seasonal influenza vaccinations [4]. However, studies have also identified a much higher risk of GBS after an episode of influenza-like illness than after influenza vaccination, especially in older adults [5–7].

Rare cases of GBS after receipt of COVID-19 adenoviral vector vaccines ChAdOx1-S (Vaxzevria) [8] and Ad26.COV2·S (Janssen) [9,10] were identified during routine vaccine safety surveillance early in the global vaccine rollout as administration of the vaccines approached and then exceeded millions of doses. Regulatory authorities such as the U.S. Food and Drug Administration and the European Medicines Agency immediately investigated this potential vaccine safety signal [10] [11], product information sheets were amended, and healthcare providers were advised to inform patients of the potential risk of GBS during pre-vaccination informed consent discussions. These responses were endorsed by the World Health Organization Global Advisory Committee on Vaccine Safety COVID-19 Subcommittee [12] while researchers commenced investigations to characterise the risk of vaccine-related GBS. We previously identified the pre-established safety signal for GBS after administration of more than 12 million doses of the first dose of ChAdOx1 using observed versus expected ratios [13].

Several studies have examined the association between COVID-19 vaccines and GBS using self-controlled study designs, which are commonly used to evaluate vaccine safety because they are less prone to time-invariant confounding bias than other study designs [14] (Table 1). These studies used administrative data, without access to source records to confirm the validity of the GBS diagnosis. Four studies found an increased risk of GBS after a first dose of ChAdOx1-S/nCoV-19 [15–18]. There were conflicting findings on the risk of GBS following a single dose of Ad26.COV2·S; one study reported an increased risk [17], while another did not [18]. No association was found between the first, second, or third (first booster) dose of mRNA vaccine BNT162b2 and GBS [15–18]. GBS risk was not increased after receipt of the first, second, or third (first booster) dose of mRNA-1273 vaccine in one study [17], while an increased risk was found after the first and second dose of mRNA-1273 in another study [18]. Thus, further studies are needed, particularly for Ad26.COV2·S and mRNA-1273. Other vaccine platforms, such as inactivated vaccines also became available, but there is a lack of published data regarding their safety related to GBS. Furthermore, any concerns about the potential risk of GBS after COVID-19 vaccine need to be weighed against the risk of GBS after SARS-CoV-2 infection [15,19–22].

We aimed to assess the risk of GBS within 42 days after exposure to adenoviral vector (e.g., ChAdOx1-S/nCoV-19 and Ad26.COV2·S), mRNA (e.g., BNT162b2 and mRNA-1273), inactivated (e.g., BBIBP-CorV, WIBP-CorV, and COVID-19 Vaccine [Vero Cell]), and protein-based (e.g., SARS-CoV-2 rS) COVID-19 vaccines (Table 2) (primary objective) as well as SARS-CoV-2 infection (secondary objective) in a multinational project of the Global Vaccine Data Network™ (GVDN®) [23]. Combining multinational data using a global study protocol increases statistical power to allow a more precise estimation of the risks associated with rare outcomes such as GBS, strengthens the generalizability of findings, and provides a risk assessment with global reach.

2. Methods

2.1. Study design, setting, and population

We used a self-controlled case series (SCCS) design to investigate the associations between GBS and receipt of COVID-19 vaccines or SARS-CoV-2 infection. With SCCS methodology, the relative incidence (RI) of the outcome between a pre-defined period of time hypothesised to be at increased risk due to an exposure ("risk window") and a time window occurring after the risk window ("control window") is calculated [14,24]. As each case serves as their own control, confounding from

Table 1
Results from previous studies investigating the association between COVID-19 vaccines and Guillain-Barré syndrome using the self-controlled case series design.

Country, population covered	Time period	Outcome	Vaccine, dose	Time period, post-vaccination	No. of GBS cases	Incidence rate ratio / relative incidence (95 % confidence interval)
Adenoviral vector vaccine						
England, >32 million [15]	1 December 2020–31 May 2021	Hospital admission or death for GBS in ≥16 years	ChAdOx1nCoV-19, dose 1	1–7 days	17	0.74 (0.44, 1.23)
				8–14 days	23	1.02 (0.65, 1.59)
				15–21 days	65	2.90 (2.15, 3.92)
				22–28 days	48	2.21 (1.59, 3.09)
		GBS in ≥16 years		1–28 days	153	2.04 (1.60, 2.60)
Scotland [15]	1 December 2020–31 May 2021	GBS in ≥16 years	ChAdOx1nCoV-19, dose 1	8–14 days	<5	2.15 (0.63, 7.31)
				15–21 days	8	4.79 (1.72, 13.38)
				22–28 days	5	3.60 (1.11, 11.65)
				1–28 days	17	2.31 (1.02, 5.24)
England, 40 % of England population [16]	8 December 2020–7 July 2021	GBS hospitalisation in ≥18 years	ChAdOx1nCoV-19, dose 1	4–42 days	517 (before and after vaccination; number of post-vaccination cases not available)	2.85 (2.33, 3.47)
France, 58.5 million [17]	27 December 2020–20 May 2022	GBS hospitalisation in ≥12 years	ChAdOx1-S, dose 1	1–42 days	46	2.50 (1.80, 3.60)
			ChAdOx1-S, dose 2	1–42 days	12	0.86 (0.47, 1.60)
			Ad26.COV2·S	1–42 days	10	2.40 (1.20, 5.00)
Italy, 16 million [18]	27 December 2020–20 September 2022	Admitted to emergency care or hospital for GBS in ≥12 years	ChAdOx1-S, dose 1	0–42 days	34	6.52 (2.88, 14.77)
			ChAdOx1-S, dose 2	0–42 days	6	3.56 (0.31, 40.29)
			Ad26.COV2·S	0–42 days	17	1.94 (0.32, 11.69)
mRNA vaccine						
England, >32 million [15]	1 December 2020–31 May 2021	Hospital admission or death for GBS in ≥16 years	BNT162b2, dose 1	1–7 days	9	0.99 (0.49, 2.00)
				8–14 days	7	0.71 (0.32, 1.56)
				15–21 days	9	0.91 (0.45, 1.84)
				22–28 days	9	0.90 (0.45, 1.82)
				1–28 days	34	0.86 (0.54, 1.36)
Scotland [15]	1 December 2020–31 May 2021	GBS in ≥16 years	BNT162b2, dose 1	1–28 days	<5	1.00 (0.02, 41.99)
England, 40 % of England's population [16]	8 December 2020–7 July 2021	GBS hospitalisation in ≥18 years	BNT162b2, dose 1	4–42 days	283 (before and after vaccination)	1.09 (0.75, 1.57)
			BNT162b2, first and second dose as separate exposures, dose 1 post-vaccination	4–42 days		1.12 (0.77, 1.63)
			BNT162b2, first and second dose as separate exposures, dose 2 post-vaccination	4–42 days		1.42 (0.95, 2. 13)
France, 58.5 million [17]	27 December 2020–20 May 2022	GBS hospitalisation in ≥12 years	BNT162b2, dose 1	1–42 days	93	1.10 (0.91, 1.40)
			BNT162b2, dose 2	1–42 days	107	1.00 (0.83, 1.30)
			BNT162b2, dose 3 (first booster)	1–42 days	78	0.92 (0.70, 1.20)
			mRNA-1273, dose 1	1–42 days	14	1.20 (0.68, 2.10)
			mRNA-1273, dose 2	1–42 days	25	1.30 (0.84, 2.00)
			mRNA-1273, dose 3 (first booster)	1–42 days	35	0.98 (0.64, 1.50)
Italy, 16 million [18]	27 December 2020–20 September 2022	Admitted to emergency care or hospital for GBS in ≥12 years	BNT162b2, dose 1	0–42 days	19	0.85 (0.49, 1.48)
			BNT162b2, dose 2	0–42 days	30	1.30 (0.80, 2.10)
			mRNA-1273, dose 1	0–42 days	7	6.83 (2.14, 21.85)
			mRNA-1273, dose 2	0–42 days	5	7.41 (2.35, 23.38)

time-invariant factors is eliminated by the study design.

Healthcare data (whether electronic or paper-based; referred to as electronic data source [EDS]-identified hereafter) from 20 sites within the GVDN were included in this study: seven sites from the African COVID-19 Vaccine Safety Surveillance (ACVaSS) system, Ethiopia, Ghana, Kenya, Malawi, Mali, Mozambique, and Nigeria; Argentina; New South Wales, Australia; Victoria, Australia; British Columbia, Canada; Ontario, Canada; Denmark; Finland; Indonesia; Republic of Korea; South Africa; and three Vaccine monitoring Collaboration for Europe (VAC4EU) [23] sites, Catalonia, Spain, Valencia, Spain, and the United Kingdom. Fifteen sites performed medical record review of all or a sample of their GBS cases: ACVaSS; Argentina; New South Wales, Australia; Victoria, Australia; British Columbia, Canada; Indonesia; South Africa; Catalonia, Spain; and Valencia, Spain. COVID-19 vaccination information was obtained from immunisation registries and medical records. Data on SARS-CoV-2 infection were obtained from: Argentina; New South Wales; British Columbia, Canada; Ontario, Canada; Denmark; Finland; Indonesia; Republic of Korea; Catalonia, Spain; Valencia, Spain; and the United Kingdom. We also obtained information on age, sex, and comorbidities, including immunocompromised status for each case. **Supplementary Table 1** presents detailed information on the data sources for each site.

Participating sites adhered to a common study protocol. To standardize data collection and facilitate case validation, the GVDN Global Coordinating Center (GCC) provided a REDCap electronic data capture tool along with a common data dictionary, ensuring consistent data collection across sites [25,26]. Further implementation details are available in **Supplementary Table 1**.

The study included individuals who were diagnosed with GBS and who received at least one dose of a COVID-19 vaccine (primary objective) and/or tested positive for SARS-CoV-2 (secondary objective) within the prior 364 days (52 weeks). The study period varied by site and study objective, ranging from 1 December 2019 to 9 August 2023 (**Supplementary Table 1**). We excluded cases with GBS diagnosed within one year prior to an initial exposure (i.e., vaccination or SARS-CoV-2 infection), cases enrolled in their healthcare system for less than one year prior to exposure, cases with a diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) at any time during

Table 2
Vaccine platform/type, generic name, and brand.

Vaccine platform/type	Generic name	Vaccine brand(s) [Manufacturer(s)]
Adenoviral vector	ChAdOx1-S/ nCoV-19	Vaxzevria [Oxford-AstraZeneca] or Covishield [Serum Institute of India]
	Ad26.COV2.S	Janssen/Jcovden [Janssen/Johnson & Johnson]
mRNA	BNT162b2	Comirnaty or Riltozinameran or Pfizer/ BioNTech COVID-19 Vaccine Bivalent [Pfizer/BioNTech]
		Comirnaty or Tozinameran [Pfizer/ BioNTech or Fosun-BioNTech][a]
		Comirnaty or Tozinameran Paediatric [Pfizer/BioNTech or Fosun-BioNTech]
	mRNA-1273	Elasomeran or Spikevax Bivalent Original/ Omicron [Moderna]
		Elasomeran or Spikevax or TAK-919 Half Dose [Moderna or Takeda]
		Elasomeran or Spikevax or TAK-919 [Moderna or Takeda][a]
Inactivated (INA)	BBIBP-CorV	Covilo or SARS-CoV-2 Vaccine (Vero Cell) [Sinopharm (Beijing)]
	COVID-19 Vaccine (Vero Cell)	CoronaVac or Sinovac [Sinovac Biotech]
	WIBP-CorV	Inactivated (Vero cell) [Sinopharm (Wuhan)]
Protein-based	SARS-CoV-2 rS	Covovax or Nuvaxovid [Novavax or Serum Institute of India]

[a] Only this was included in the brand-level analysis.

the study period or within one year prior to exposure (as it can be challenging to distinguish GBS from CIDP) [27], cases with incomplete exposure data (e.g., vaccine brand or vaccination date), and cases who died, disenrolled, or were censored prior to reaching the control window.

2.2. GBS case identification

Most of the GBS cases were identified from electronic data sources using the International Classification of Diseases 9th Revision (ICD-9) diagnostic code 357.0, International Statistical Classification of Diseases 10th Revision (ICD-10) or local variations of ICD-10 diagnostic code G61.0, or MedCodeIDs (United Kingdom site only, listed in **Supplementary Table 2**) as the diagnosis for hospitalisation. CIDP cases were identified (for the purposes of exclusion) using the ICD-9 codes 357.8 and 357.9, or ICD-10 codes G61.8, G61.9, G62.8, and G62.9.

Medical record review was performed at a subset of sites to validate the EDS-identified GBS cases using Brighton Collaboration case definition criteria, determining the diagnostic level of certainty (LOC) [28]. Cases with Brighton Collaboration LOC 1 (definite) and 2 (probable), determined based on both clinical and electrophysiologic testing and/or cerebrospinal fluid findings, are considered 'confirmed' GBS cases. LOC 3 (possible) cases are considered GBS but are determined solely based on clinical findings. LOC 4 cases are reported as GBS but without sufficient information to meet any LOC definition, whereas those classified as LOC 5 are not GBS cases.

GBS onset date was the earliest of symptom onset, initial healthcare encounter, or hospital admission.

2.3. Exposures

Detailed information on COVID-19 vaccination (i.e., vaccine platform/generic name/brand [listed in Table 2], date of receipt, and dose number) within 364 days (52 weeks) prior to GBS onset to the end of follow-up (i.e., one year post vaccination), was extracted for all GBS cases.

Information on SARS-CoV-2 infection, either by reverse transcription polymerase chain reaction (RT-PCR) (i.e., laboratory-confirmed) or by rapid antigen test, within 364 days prior to GBS onset was obtained. Positive test results separated by 90 days were considered different episodes of infection based on evidence suggesting reinfection is unlikely within this period, minimizing misclassification of prolonged viral shedding as new infections.

2.4. Case characteristics

Age at study entry or first exposure was categorized as <18, 18–64, or ≥ 65 years. Sex was categorized as male or female. Information was collected on whether cases were immunocompromised due to disease (i.e., immune-mediated inflammatory diseases, organ or stem cell transplant, active cancer, severe disorders of the immune system, human immunodeficiency virus (HIV) infection, and sickle cell anemia) or therapy, or had other comorbidities (i.e., chronic cardiovascular disease, chronic kidney disease, chronic respiratory disease, diabetes, and neurological diseases) using medical records or diagnostic and therapeutic codes (**Supplementary Tables 3 and 4**). Cases were then categorized into three mutually exclusive groups: immunocompromised due to disease or therapy, had other comorbidity, and neither immunocompromised nor had other comorbidity. To account for seasonal effects, four seasons were defined for northern and southern hemispheres separately (**Supplementary Table 5**).

2.5. Statistical analysis

Counts of GBS cases from each site were combined to present descriptive statistics for the total study population and by case characteristics (age group, sex, and immunocompromised or comorbidity status) and by exposure characteristics (number of vaccines received during the study period [i.e., from one year prior to GBS onset to one year post vaccination], vaccine brand, vaccine platform, SARS-CoV-2 infection, and type of SARS-CoV-2 test).

In the SCCS analysis, the associations between the exposures (COVID-19 vaccination or SARS-CoV-2 infection) and GBS were examined by calculating the relative incidence (RI) between the risk and control windows using conditional Poisson regression models, controlling for seasonality. Analyses were conducted at both vaccine brand and platform levels. The pre-specified risk windows were days 1–42 as well as days 1–21 and days 22–42 separately after each exposure. The control window included all non-risk windows in the post-exposure observation period. We excluded pre-exposure observation time because a history of GBS may influence future decisions to receive vaccines.

For the meta-analysis, some sites ($n = 6$) could not share individual-level data and therefore ran SCCS analyses locally by adapting GCC-provided analytic programs and shared summary estimates, whereas other sites ($n = 8$) shared de-identified case-level data. For sites sharing case-level data, individual patient data (IPD) meta-analysis was conducted before combining the estimates with locally analysed site-level results. Random-effects meta-analysis was conducted to estimate the overall RI with 95 % confidence interval (CI) using the method described by Knapp and Hartung [29].

For the primary objective on medical record-reviewed cases using the Brighton Collaboration criteria, we conducted a series of analyses starting with the most stringent case definition (LOC 1–2), which offered the highest diagnostic certainty, but limited statistical power. We then sequentially expanded to broader definitions (LOC 1–3 and LOC 1–4), increasing statistical power at the cost of reduced diagnostic validity. We also considered LOC 5 separately as a negative control outcome (i.e., no association expected). Further, we included all medical record-reviewed cases (i.e., LOC 1–5) in a post-hoc analysis for comparison with all EDS-identified cases (including the sites at which medical record review could not be performed) to evaluate the impact of potential diagnostic misclassification and its impact on risk estimates. Across all analyses, we examined the association between COVID-19 vaccines and GBS using a

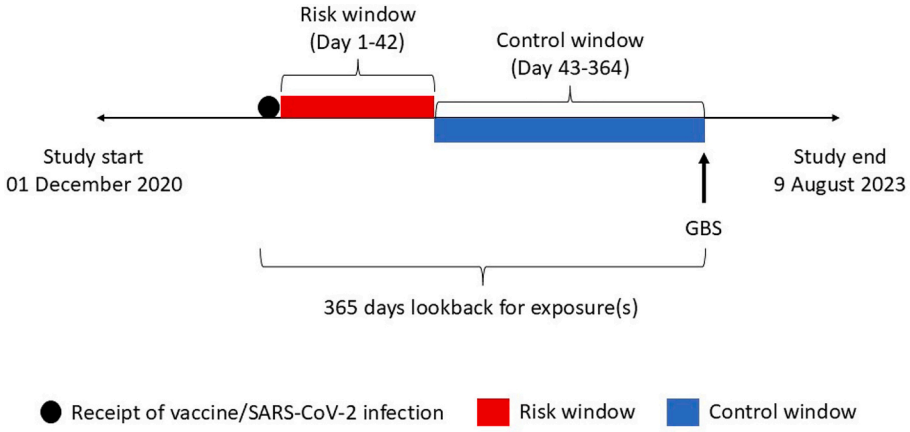


Fig. 1. Observation timeline of GBS cases in the self-controlled case series study.

risk window of 1–42 days post-vaccination (Fig. 1) and did not consider any dose effects due to small sample sizes. COVID-19 vaccines other than the vaccine brand or platform of interest in each model were treated as a time-varying co-exposure regardless of vaccine brand or platform. We did not perform subgroup analysis by case characteristics for the medical record-reviewed cases due to limited statistical power and because these variables were not included in all the submitted de-identified individual-level minimal datasets.

Given the greater statistical power available when using all EDS-identified cases regardless of the level of diagnostic certainty, we conducted further analyses that considered varying risk windows and dose effects. Three models were fitted: model 1 included shorter risk windows (days 1–21 and 22–42) and dose effects (i.e., receiving multiple doses within the one-year observation period); model 2 included the combined risk window (days 1–42) and dose effects; and model 3 included the combined risk window (days 1–42) and did not consider any dose effects. Different COVID-19 vaccines were treated as different exposures in these models, depending on the vaccination history of the cases. Additional analyses were also conducted to include only cases who received homologous schedules (i.e., the same vaccine brand/platform) of interest. Subgroup analyses using a risk window of 1–42 days post-vaccination were conducted based on age group, sex, and immunocompromised/comorbidity status where there were adequate numbers of events in each subgroup category for model convergence.

Due to limited availability of SARS-CoV-2 testing data from many sites, for the secondary objective we used EDS-identified cases only treating SARS-CoV-2 infection as the main exposure of interest. We otherwise used the same approach (i.e., regression models and meta-analyses) as described for the primary objective, and any COVID-19 vaccines received during the observation period were treated as time-varying co-exposures regardless of vaccine brand or platform.

We calculated the number of attributable GBS cases LOC 1–2 (confirmed cases) and LOC 1–4 in the 1–42 days risk window for brands and platforms with an increased RI by multiplying the attributable fraction [AF = (RI-1)/RI] with the number of cases in the risk window. We also calculated the number of attributable GBS cases in the 1–42 days following SARS-CoV-2 infection.

All data analyses were conducted in R (R Project for Statistical Computing), version 4.4.0. The SCCS analyses were conducted using the "SCCS" package, version 1.7 with analytic codes developed centrally by the GCC. Random-effects meta-analyses were conducted using the "metafor" package, version 4.6–0 [30].

2.6. Ethical approval

Approval from the relevant Human Research Ethics Committees was either acquired or an exemption obtained for all participating sites (**Supplementary Table 6**).

3. Results

From EDS, we identified a total of 2086 GBS cases who received 4329 doses of any COVID-19 vaccines during the study period (Table 3, **Supplementary Table 7**). Medical records were reviewed for 410 cases, among which 49 (12 %) were LOC 1–2, a further 187 (46 %) were LOC 3–4, and 174 (42 %) were deemed not to be cases (i.e., LOC 5). We also identified a total of 489 EDS-identified GBS cases after SARS-CoV-2 infection during the study period. The majority of the post-vaccination and post-infection GBS cases were aged 18–64 years (63–69 %), male (57–60 %), and were either immunocompromised due to disease or therapy or had another comorbidity (64–71 %). Among cases following COVID-19 vaccination, the majority received homologous schedules with mRNA vaccines followed by adenoviral vector vaccines (61 % and 19 %, respectively, among medical record-reviewed cases, and 62 % and 13 %, respectively, among EDS-identified cases). An additional 11 % of the medical record-reviewed cases and 23 % of the EDS-identified cases received mixed vaccine schedules.

3.1. Risk of GBS after COVID-19 vaccination in medical record-reviewed cases only

3.1.1. Adenoviral vector vaccines

Most medical record-reviewed cases had the GBS event during the control window (**Supplementary Table 8**). We observed an association between Vaxzevria/Covishield and GBS LOC 1–2 cases 1–42 days post-vaccination (RI = 3.10; 95 %CI, 1.12–8.62) (Fig. 2a), and confidence intervals became narrower when including LOC 3 and 4 cases. No associations were observed between Janssen/Jcovden and GBS (e.g., for LOC 1–2 cases, RI = 2.76; 95 %CI, 0.16–46.30), but the confidence intervals were wide (Fig. 2b). When combining all adenoviral vector vaccines, the estimates were similar to those observed for Vaxzevria/Covishield (Fig. 2c). No associations were observed between receipt of any adenoviral vector vaccine and LOC 5 cases.

Of the nine LOC 1–2 GBS cases that were diagnosed during the 1–42 days risk period after vaccination, an estimated six (9 × [2.05/3.05]) cases were attributable to receiving an adenoviral vector vaccine and five (8 × [2.10/3.10]) were attributable to receiving Vaxzevria/Covishield. Of the 28 LOC 1–4 GBS cases that were diagnosed during the 1–42 days risk period after vaccination, an estimated 17 (28 × [1.60/2.60]) cases were attributable to receiving an adenoviral vector vaccine and 15 (24 × [1.63/2.63]) were attributable to receiving Vaxzevria/Covishield.

Table 3
Characteristics of Guillain-Barré Syndrome cases who received COVID-19 vaccine(s) or had a SARS-CoV-2 infection within the previous 364 days (52 weeks).

	Primary objective		Secondary objective
	Medical record-reviewed post-vaccination cases, n (%)	EDS-identified post-vaccination cases, n (%)	EDS-identified post-infection cases, n (%)
Total number of identified cases, N	410 (100.0)	2086 (100.0)	489 (100.0)
Study sites			
Africa (ACVaSS/South Africa)[*]	11 (2.7)	11 (0.5)	NA
Argentina	7 (1.7)	7 (0.3)	1–5[a]
Victoria, Australia[b]	24 (5.9)	186 (8.9)	NA
New South Wales, Australia[c]	NA	64 (3.1)	1–5[a]
British Columbia, Canada	87 (21.1)	87 (4.2)	13 (2.7)
Ontario, Canada	NA	262 (12.6)	52 (10.6)
Denmark	NA	56 (2.7)	28 (5.7)
Finland	NA	60 (2.9)	1–5[a]
Indonesia	111 (27.1)	111 (5.3)	1–5[a]
Republic of Korea	NA	641 (30.7)	238 (48.7)
Catalonia, Spain (VAC4EU)	125 (30.5)	125 (6.0)	37 (7.6)
Valencia, Spain (VAC4EU)	45 (11.0)	45 (2.2)	11 (2.2)
United Kingdom (VAC4EU)	NA	431 (20.7)	102 (20.9)
Level of Certainty (LOC)			
LOC 1	20 (4.9)	NA	NA
LOC 2	29 (7.1)	NA	NA
LOC 3	15 (3.7)	NA	NA
LOC 4	172 (42.0)	NA	NA
LOC 5	174 (42.4)	NA	NA
Age			
<18 years	20 (4.9)	59–62 (2.8–3.0)	64–70 (13.1–14.3)
18–64 years	284 (69.3)	1306 (62.6)	313 (64.0)
≥ 65 years	105 (25.6)	717–720 (34.4–34.5)	106–112 (21.7–22.9)
Unknown	1 (0.2)[d]	1 (0.0)[d]	0 (0.0)
Sex			
Male	239 (58.3)	1246 (59.7)	278 (56.9)
Female	170 (41.5)	840 (40.3)	211 (43.1)
Unknown	1 (0.2)[d]	0 (0.0)	0 (0.0)
Immunocompromised or had another comorbidity			
Immunocompromised due to disease or therapy	189 (46.1)	777 (37.2)	215 (44.0)
Had another comorbidity	80 (19.5)	557 (26.7)	134 (27.4)
Neither immunocompromised, nor had another comorbidity	130 (31.7)	439 (21.0)	108 (22.1)
Unknown	11 (2.7)	313 (15.0)	32 (6.5)
COVID-19 vaccines (main exposure, primary objective)			
Number of doses the case received during observation period[e]			
0 dose	0 (0.0)	0 (0.0)	88–91 (18.0–18.6)
1 dose	133 (32.4)	584–587 (28.0–28.1)	48–51 (9.8–10.4)
2 doses	170 (41.5)	777–780 (37.2–37.4)	124 (25.4)
3 doses	107 (26.1)	699 (33.5)	83 (17.0)
4 doses	0 (0.0)	23 (1.1)	0 (0.0)
Vaccine schedules by platform			
Adenoviral vector	77 (18.8)	268 (12.8)	NA
mRNA	251 (61.2)	1294 (62.0)	NA
Inactivated	37 (9.0)	37 (1.8)	NA
Protein-based	0 (0.0)	1 (0.0)[e]	NA
Mixed vaccine platform[f]	45 (11.0)	486 (23.3)	NA
SARS-CoV-2 infections (main exposure, secondary objective)			
Number of infections the case had during observation period			
1 infection	NA	NA	456–459 (93.3–93.9)
2 infections	NA	NA	28–31 (5.7–6.3)
3 infections	NA	NA	2 (0.4)[d]
Type of tests			
RT-PCR	NA	NA	447 (91.4)
Rapid antigen test	NA	NA	32 (6.5)
Mixed types	NA	NA	2 (0.4)[d]
Unknown/Other	NA	NA	8 (1.6)

EDS = Electronic health data sources; ACVaSS = African COVID-19 Vaccine Safety Surveillance (Mali, Ghana, Nigeria, Ethiopia, Kenya, Malawi, Mozambique); NA = Not applicable or not available; RT-PCR = Reverse transcription polymerase chain reaction.

[*] ACVaSS and South Africa are presented together because of low numbers of cases.

[a] Count suppressed because of low number (1–5).

[b] Victoria, Australia: Data on chart-reviewed cases were provided by Monash Health.

[c] New South Wales, Australia: Line listed data on 21 chart-reviewed cases were not available and thus were excluded from the analysis.

[d] Includes small cells (1–5) from sites that did not have any ethical restrictions sharing small cells; All small cells from Denmark and United Kingdom (VAC4EU) were suppressed.

[e] Co-exposure if any doses received for the secondary objective.

[f] Received different platform or types of vaccine (heterologous schedule).

3.1.2. mRNA vaccines

No associations were observed between Comirnaty/Tozinameran vaccination and LOC 1–2 (RI = 0.39; 95 %CI, 0.11–1.38) and LOC 1–3 (RI = 0.64; 95 %CI, 0.23–1.76) cases (Fig. 2d). However, a decreased risk of GBS after Comirnaty/Tozinameran vaccination was observed when LOC 4 cases were included (RI = 0.48; 95 %CI, 0.27–0.85). Elasomeran/Spikevax/TAK-919 vaccine was not associated with GBS (e.g., for LOC 1–2 cases, RI = 2.12; 95 %CI, 0.40–11.38) (Fig. 2e). For all mRNA vaccines combined, GBS incidence was decreased for LOC 1–4 cases (RI = 0.62; 95 %CI, 0.41–0.95) (Fig. 2f). mRNA vaccination was not associated with LOC 5 cases.

3.1.3. Inactivated vaccines

No associations were observed between CoronaVac/Sinovac vaccination and LOC 1–2 (RI = 0.16; 95 %CI, 0.00–25.91) and LOC 1–3 (RI = 0.09; 95 %CI, 0.00–4.55) cases, but the confidence intervals were very wide (Fig. 2g). The risk of GBS after CoronaVac/Sinovac vaccination was significantly decreased with the inclusion of LOC 4 cases (RI = 0.04; 95 %CI, 0.00–0.61). Comparable results were observed at the platform level (Fig. 2h). The risk of LOC 5 cases was decreased in both brand (RI = 0.08; 95 %CI, 0.02–0.34) and platform (RI = 0.07; 95 %CI, 0.02–0.31) level analyses.

3.2. Risk of GBS after COVID-19 vaccination in all EDS-identified cases

3.2.1. Adenoviral vector vaccines

Most EDS-identified GBS cases had the event during the control window (**Supplementary Table 9**). No associations were observed between Vaxzevria/Covishield and GBS across the three models **(Supplementary Table 10)**. For Janssen/Jcovden, increased GBS incidence was observed 1–21 days (RI = 61.52; 95 % CI: 8.36–452.71) and 1–42 days (RI = 19.73; 95 % CI: 3.88–100.40) after a first dose, but the confidence intervals were very wide. When combining all adenoviral vector vaccines, GBS incidence was increased 1–21 days after receiving a second dose of an adenoviral vector vaccine (RI = 1.71; 95 %CI, 1.18–2.48) and 1–42 days after receiving any vaccine dose (RI = 2.19;

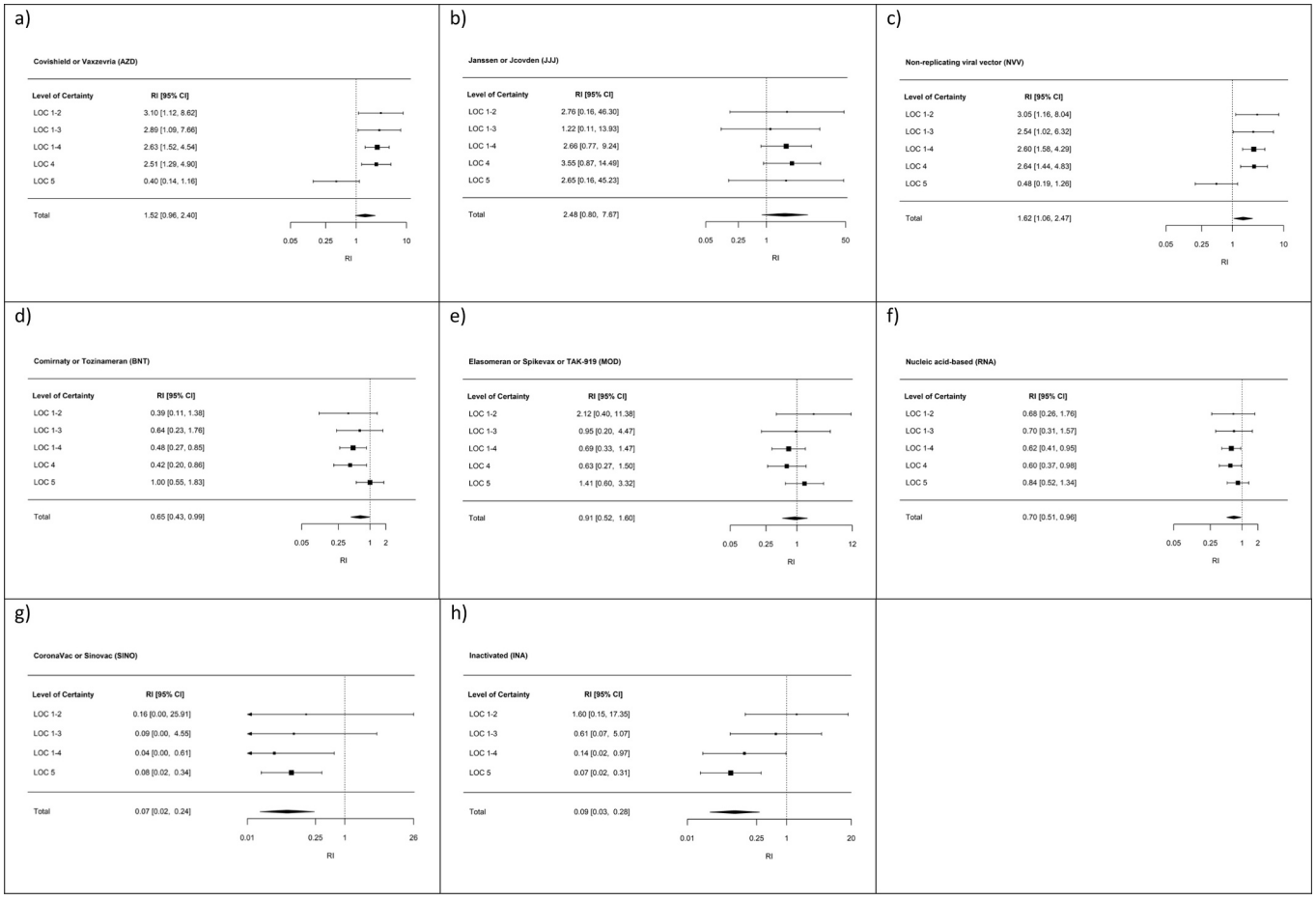


Fig. 2. Relative incidence of Guillain-Barré syndrome in medical record-reviewed cases by level of certainty (LOC) in the 1–42 days after receipt of adenoviral vector vaccines, mRNA vaccines, and inactivated vaccines by vaccine brand and platform.

95 %CI, 1.17–4.07). Although the confidence intervals were very wide, the point estimates for all other RI estimates were > 1.00. The RI estimates were generally consistent across sites, with the point estimate for only one site that was <1.00 (**Supplementary Fig. 1a**).

3.2.2. *mRNA vaccines*

GBS incidence was decreased 1–42 days after a first dose of Comirnaty/Tozinameran (RI = 0.39; 95 %CI, 0.23–0.65) and 1–42 days after any dose (RI = 0.73; 95 %CI, 0.61–0.86) **(Supplementary Table 10)**. There was no association between Elasomeran/Spikevax/TAK-919 and GBS 1–42 days post-vaccination (RI = 0.71; 95 %CI, 0.41–1.24). Combining all mRNA vaccines, GBS incidence was decreased 22–42 days after receiving a first dose (RI = 0.44; 95 %CI, 0.24–0.81), 1–42 days after a first dose (RI = 0.49; 95 %CI, 0.34–0.70), and 1–42 days after any dose (RI = 0.78; 95 %CI, 0.67–0.90). Across sites, GBS incidence was decreased post-mRNA vaccination only for the United Kingdom (RI = 0.64; 95 %CI, 0.47–0.88) and the combined individual-level data (RI = 0.55; 95 %CI, 0.36–0.85); mRNA vaccines were not associated with GBS at any other site (**Supplementary Fig. 1b**).

3.2.3. *Inactivated vaccines*

For Coronavac/Sinovac, GBS incidence was decreased 1–42 days after a first dose (RI = 0.05; 95 %CI, 0.01–0.31) and 1–42 days after any dose (RI = 0.06; 95 %CI, 0.01–0.30) **(Supplementary Table 10)**. We observed similar estimates when combining all inactivated vaccines.

3.2.4. *Subgroup analyses for the risk of GBS after COVID-19 vaccination in EDS-identified cases*

When stratified by various case characteristics, we observed no associations between Vaxzevria/Covishield and GBS 1–42 days post-vaccination **(Supplementary Table 11)**. However, when adenoviral vector vaccines were combined, we observed increased GBS incidence 1–42 days post-vaccination for males (RI = 1.93; 95 %CI, 1.04–3.60) and for those aged 18–64 years (RI = 2.56; 95 %CI, 1.34–4.88). For mRNA vaccines, we noted a decreased incidence of GBS 1–42 days post-vaccination for males (RI = 0.81; 95 %CI, 0.67–0.98) and for those with neither immunocompromise nor another comorbidity (RI = 0.88; 95 % CI, 0.77–0.99). Subgroup analyses could not be performed for those who received inactivated vaccines.

3.3. *Risk of GBS after SARS-CoV-2 infection in EDS-identified cases*

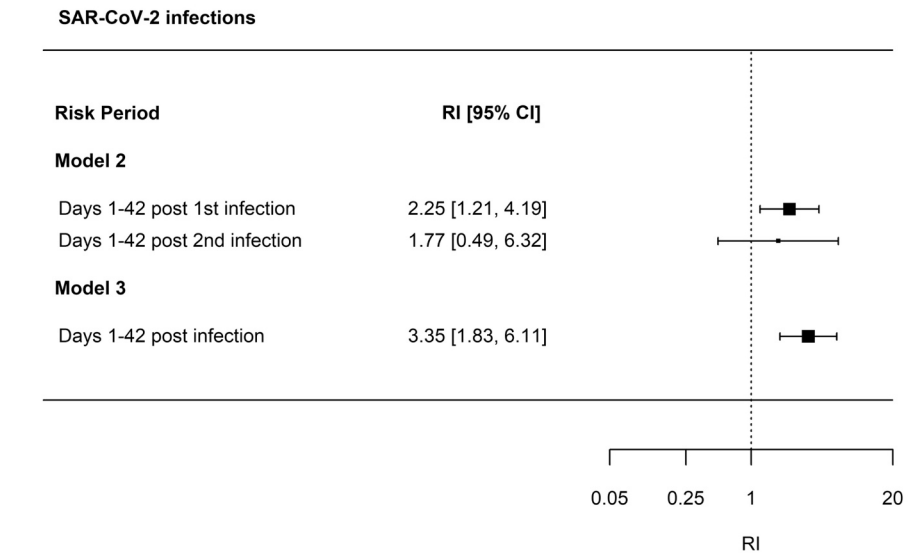
Most of the GBS events after SARS-CoV-2 infection occurred during the control window (**Supplementary Table 12).** GBS incidence was increased 1–42 days after a first infection (RI = 2.25; 95 %CI, 1.21–4.19) and after any infection (RI = 3.35; 95 %CI, 1.83–6.11) (Fig. 3, **Supplementary Table 13**).

Of the 136 GBS cases that were diagnosed during the 1–42 days risk period after SARS-CoV-2 infection, an estimated 95 (136 x [2.35/3.35]) cases were attributable to SARS-CoV-2 infection.

3.3.1. *Subgroup analyses for the risk of GBS after SARS-CoV-2 infection in EDS-identified cases*

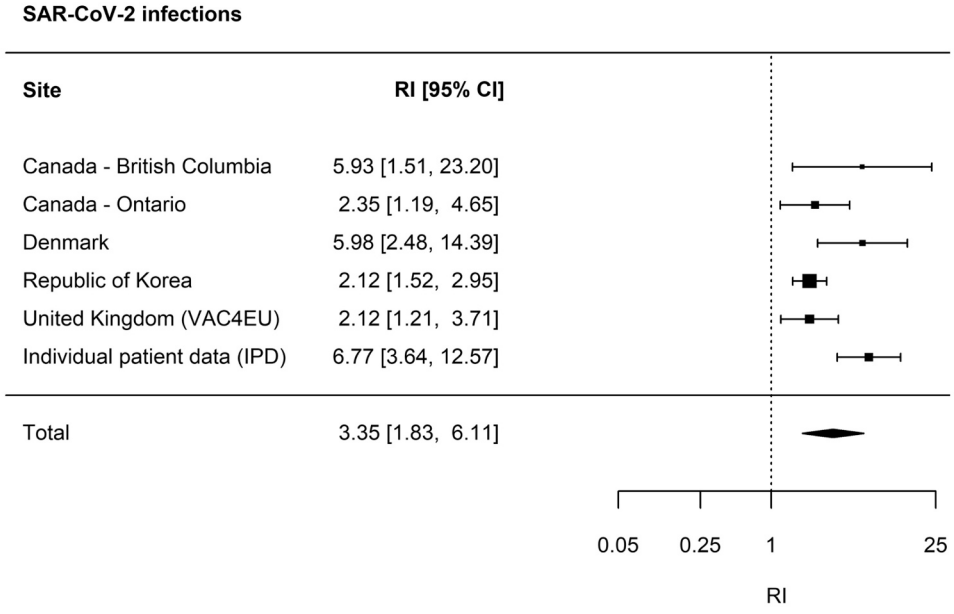
In subgroup analyses, GBS incidence was increased for:

(a)



Footnote: Model 1 yielded very imprecise confidence intervals and thus was excluded from the figure.

(b)



Footnote: IPD are aggregated from available sites including: Argentina, ACVaSS, South Africa, Indonesia, Spain – Valencia (VAC4EU), Spain – Catalonia (VAC4EU).

Fig. 3. Relative incidence of Guillain-Barré syndrome identified from electronic data sources after SARS-CoV-2 infection: (a) models 2 and 3; (b) model 3 only, by study site. Model 2 included a risk window of days 1–42 and dose effects, and model 3 included a risk window of days 1–42 and no dose effects.
Footnote: Model 1 yielded very wide confidence intervals and thus was excluded from the figure.
Footnote: IPD are aggregated from available sites including: Argentina, ACVaSS, South Africa, Indonesia, Valencia, Spain (VAC4EU), Catalonia, Spain (VAC4EU).

immunocompromised cases 1–21 days and 22–42 days after a first infection, and 1–21 days after a second infection (**Supplementary Table 14**). Using a risk window of 1–42 days, GBS incidence after a first infection was increased for males, females, and immunocompromised cases. Similarly, GBS incidence 1–42 days after any infection was increased for males, females, cases aged 18–64 years, cases aged ≥65 years, immunocompromised cases, and cases with another comorbidity.

4. Discussion

In this large, multinational study covering more than 230 million people observed from 1 December 2019 to 9 August 2023, we found that receipt of adenoviral vector vaccines, particularly Vaxzevria/Covishield, and SARS-CoV-2 infection were both associated with an approximately three-fold increased risk of confirmed GBS during the 1–42 days post exposure, whereas receipt of mRNA vaccines (specifically Comirnaty/Tozinameran) was associated with an approximately 30–50 % decreased risk of GBS. By starting with the most valid outcome measure (i.e., GBS cases classified as LOC 1–2 based on manual review of medical records) and sequentially incorporating additional cases with lower diagnostic certainty (i.e., LOC 3 and 4), and subsequently also considering all EDS-identified cases, we observed that increasing statistical precision in risk estimates by including cases with lower diagnostic certainty tended toward a slight shift to the null, indicating a trade-off between improved precision and the potential introduction of measurement bias. As anticipated, the negative control outcome of LOC 5 cases (i.e., those deemed not to be GBS after medical record review) revealed no association with COVID-19 vaccines (with the exception of inactivated vaccines showing a decreased incidence), supporting the specificity of the observed associations. Finally, risk estimates using EDS-identified cases were generally similar across study sites and subgroups defined by case characteristics. Receipt of inactivated vaccines also appeared to be associated with reduced risk of LOC 1–4 GBS cases, but the confidence intervals were wide, and an accompanying reduction in the risk of LOC 5 cases makes interpretation of this finding challenging.

Previous studies (Table 1) [15–18] reported a 2.0- to 6.5-fold increased risk of GBS during the 42 days after a first dose of Vaxzevria/Covishield; our estimates for LOC 1–4 cases fall within this range. We were unable to examine the dose effect for medical record-reviewed cases because of the small number of cases during the risk interval. However, for the EDS-identified cases, we observed a higher risk of GBS after the first dose than the second dose of Vaxzevria/Covishield, although the confidence intervals were wide and overlapped, and both RI estimates were not statistically significant. We did not observe any statistically significant increased risk of GBS after receipt of Janssen/Jcovden, which contrasts with a previous study using administrative and medical data without LOC ascertainment [17]. Previous studies did not find any increased or decreased risk of GBS 1–42 days after a first, second, or third (first booster) dose of BNT162b2 [15–18], and one study found an increased risk of GBS 1–42 days after a first or second dose of mRNA-1273 [18]. In our study, we observed a decreased risk of GBS 1–42 days after receiving Comirnaty/Tozinameran for LOC 1–4 cases, which might be due to decreased risk of SARS-CoV-2 infection after vaccination or due to some residual bias (given the effect was observed mainly in LOC 4 cases), and we did not observe any association between Elasomeran/Spikevax/TAK-919 and GBS cases.

There are some limitations to our study. First, we only considered exposures within 364 days before the GBS diagnosis, thus the first COVID-19 vaccine dose or SARS-CoV-2 infection recorded in our study may not have been the actual first vaccine dose received, or infection experienced. Consequently, we were unable to estimate the attributable risk of each vaccine dose or infection episode number. Nevertheless, we estimated the number of attributable cases using the attributable fraction calculated from the RI. Second, we identified relatively low numbers of confirmed (i.e., LOC 1–2) GBS cases, likely due to unavailability of electrophysiologic testing and/or cerebrospinal fluid results in medical records, and it is uncertain whether these tests were not performed, or the information was unavailable. Furthermore, 42 % of reviewed cases were deemed not to be GBS (i.e., LOC 5), which was higher than anticipated since previous studies conducted in Italy, USA, and Denmark assessing the validity of diagnostic codes for GBS hospitalisations reported positive predictive values of 61.8–83.8 % [31–33]. Third, we were unable to adjust for the history of SARS-CoV-2 infection in our primary objective analyses due to incomplete or unavailable SARS-CoV-2 testing data. Fourth, there were insufficient numbers of GBS cases who had received inactivated and protein-based vaccines to provide precise RI estimates for those vaccines. Fifth, the meta-analysis results using site-estimated RIs may be biased because they did not account for site-specific contextual information that would ideally be incorporated in a meta-regression. Meanwhile, strengths of our study include the use of the SCCS design, which mitigates the impact of time-invariant confounders, the application of Brighton Collaboration case definition criteria to medical records to validate GBS cases, use of LOC 5 cases as a negative control outcome to explore the specificity of our observed associations, and the comparison of the risks of GBS associated with COVID-19 vaccination and with SARS-CoV-2 infection to make risk comparisons and inform decision-making around benefit compared with risk.

5. Conclusion

In this large multinational study, we found comparably increased risks of GBS after Vaxzevria/Covishield vaccination or SARS-CoV-2 infection, and decreased risks after receiving Comirnaty/Tozinameran or CoronaVac/Sinovac, suggesting that mRNA or inactivated vaccines may be preferable to adenoviral vector vaccines to minimize the risk of GBS. Since new vaccines continue to be developed using the non-replicating viral vector platform, continued safety monitoring and evaluation of both existing and emerging vaccine platforms are essential to inform vaccine policy decisions.

Disclaimers

All analyses, inferences drawn, opinions, conclusions, and statements are those of the authors and do not necessarily represent the official views of, nor an endorsement by, CDC/HHS, or the U.S. Government.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jeffrey C. Kwong reports financial support was provided by Centers for Disease Control and Prevention. Eero Poukka reports a relationship with AstraZeneca Pharmaceuticals LP that includes: equity or stocks. Helen Petousis-Harris reports a relationship with Pfizer Inc that includes: board membership and speaking and lecture fees. Helen Petousis-Harris reports a relationship with GSK plc that includes: board membership and speaking and lecture fees. Karina A Top reports a relationship with Coalition for Epidemic Preparedness Innovations UK Limited that includes: funding grants. If there are other authors, they 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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2025.127291.

Data availability

The authors do not have permission to share data.

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