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ORIGINAL ARTICLE

Incidence of Guillain–Barré syndrome following SARS-CoV-2 immunization: Analysis of a nationwide registry of recipients of 81 million doses of seven vaccines

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Abstract

Background and purpose: Information on Guillain–Barré syndrome (GBS) as an adverse event following immunization (AEFI) against SARS-CoV-2 remains scarce. We aimed to report GBS incidence as an AEFI among adult (≥18 years) recipients of 81,842,426 doses of seven anti-SARS-CoV-2 vaccines between December 24, 2020, and October 29, 2021, in Mexico.

Methods: Cases were retrospectively collected through passive epidemiological surveillance. The overall observed incidence was calculated according to the total number of administered doses. Vaccines were analyzed individually and by vector as mRNA-based (mRNA-1273 and BNT162b2), adenovirus-vectored (ChAdOx1 nCov-19, rAd26-rAd5,

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Ad5-nCoV, and Ad26.COV2-S), and inactivated whole-virion-vectored (CoronaVac) vaccines.

Results: We identified 97 patients (52 males [53.6%]; median [interquartile range] age 44 [33–60] years), for an overall observed incidence of 1.19/1,000,000 doses (95% confidence interval [CI] 0.97–1.45), with incidence higher among Ad26.COV2-S (3.86/1,000,000 doses, 95% CI 1.50–9.93) and BNT162b2 recipients (1.92/1,00,000 doses, 95% CI 1.36–2.71). The interval (interquartile range) from vaccination to GBS symptom onset was 10 (3–17) days. Preceding diarrhea was reported in 21 patients (21.6%) and mild COVID-19 in four more (4.1%). Only 18 patients were tested for *Campylobacter jejuni* (positive in 16 [88.9%]). Electrophysiological examinations were performed in 76 patients (78.4%; axonal in 46 [60.5%] and demyelinating in 25 [32.8%]); variants were similar across the platforms. On admission, 91.8% had a GBS disability score ≥3. Seventy-five patients (77.3%) received intravenous immunoglobulin, received seven plasma exchange (7.2%), and 15 (15.5%) were treated conservatively. Ten patients (10.3%) died, and 79.1% of survivors were unable to walk independently.

Conclusions: Guillain–Barré syndrome was an extremely infrequent AEFI against SARS-CoV-2. The protection provided by these vaccines outweighs the risk of developing GBS.

KEYWORDS
adverse events, COVID-19, Guillain–Barré syndrome, SARS-CoV-2, Vaccines

INTRODUCTION

The outbreak of Guillain–Barré syndrome (GBS) among recipients of seasonal influenza A vaccines in 1976 linked vaccines to its development as an adverse event following immunization (AEFI) [1]. GBS is the most frequent cause of acute flaccid weakness, with an incidence of 1.1–1.8 cases per 100,000 person-years worldwide [2, 3]. The epidemiology of adverse events that occur after immunization against severe acute respiratory coronavirus 2 (SARS-CoV-2), including GBS, remains incompletely understood, particularly in underdeveloped countries and underserved regions, and data on neurological AEFIs originate from only a few countries and involve only a handful of vaccines [4–6].

According to the Mexican Health Ministry, in 2019 (i.e., pre-COVID-19), the nationwide reported GBS incidence was 0.71 cases per 100,000 person-years [7, 8]. Between December 2020 and September 2021, the Mexican Ministry of Health granted emergency approval for the use of seven different vaccines against SARS-CoV-2, using three different platforms: mRNA (mRNA-1273 and BNT162b2), adenovirus (ChAdOx1 nCov-19, rAd26-rAd5, Ad5-nCoV, and Ad26.COV2-S), and inactivated whole-virion (CoronaVac) [9], thus, it was in a unique position to evaluate the differences among several of the currently available anti-SARS-CoV-2 vaccines and not only those commonly used in developed nations, for which ample safety information has already been reported. Epidemiological data from the United States and the United Kingdom indicate that two adenovirus-vectored vaccines (Ad26.COV2.S [1 case per 100,000 doses administered] and ChAdOx1 nCov-19 [0.87 per 100,000 first-doses administered]) have associations with GBS [10–12]. We previously reported a preliminary incidence of GBS ranging from 0.18 to 0.43 cases per 100,000 doses administered among 3.9 million first-dose recipients of BNT162b2—the only vaccine in use at that time—which fell within the expected (pre-COVID-19 and pre-SARS-CoV-2 vaccine) incidence [13, 14].

At the time of writing, there are no epidemiological data on GBS among recipients of rAd26-rAd5, Ad5-nCoV or CoronaVac, vaccines that are used in low-income and middle-income countries [6, 15]. Moreover, information on vaccine-associated GBS among a Latinx/Hispanic population, a heterogeneous group that is underrepresented in clinical trials, is scarce. Here, we report GBS incidence occurring within 42 days after receiving any vaccine against SARS-CoV-2 from a nationwide registry of AEFIs. In addition, we report the presence of concomitant GBS potential triggers (where these were reported or prospectively traceable at the local level), clinical presentation, and functional outcomes among recipients of seven different vaccines who sought hospital attention during a 10-month period in Mexico.

METHODS

Study design and population

We performed a retrospective study of a nationwide registry of GBS among recipients of 81,842,426 doses of seven anti-SARS-CoV-2 vaccines in Mexico between December 24, 2020, and October 29, 2021. We included hospitalized patients fulfilling the National Institute of Neurological and Communicative Disorders and Stroke

clinical features for GBS (Asbury criteria) who were officially reported to the Mexican Ministry of Health through a passive epidemiological surveillance system [16], and presented during the first 42 days after receiving the most recent vaccine according to the time window reported by other authors for recipients of anti-SARS-CoV-2 vaccines [11, 12, 17]. Patients with missing clinical data and those with alternative diagnoses explaining the neurological deficits were excluded.

We identified cases using the Mexican epidemiological surveillance system, which collects and processes data on all reported AEFIs from ~23,300 public and private medical units distributed across the country [13]. By law, cases identified as potential AEFIs must be reported to the local or national authority as soon as they are identified. Event severity was initially classified at the local level by the attending medical teams according to the World Health Organization operational case definition as either serious (e.g., those that put life in danger, require hospitalization, cause disability, or death) or non-serious (e.g., injection-site pain, swelling, rash, headache, fever, malaise, muscle and/or joint pain) [18]. Hence, all patients with suspected GBS were hospitalized and classified as having potentially serious AEFIs nationwide.

Aiming to establish causality, an ad hoc committee appointed by the Mexican Ministry of Health, consisting of five experienced neurologists and a neuroradiologist, performed a detailed case-by-case analysis of all potentially serious neurological adverse events occurring after SARS-CoV-2 vaccination through single or multiple virtual sessions with the individual attending physicians. Operational details of the Mexican epidemiological surveillance system, AEFI definitions, ad hoc committee case evaluation, and data collection protocols have been previously reported [19, 20].

Standard protocol approvals, registrations, and patient consent

The study was reviewed and approved by the *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán* (ID: NER-3903-21-23-1) Ethics and Research Committees who waived the need for signed informed consent due to its observational nature and usage of an anonymized database. This report was elaborated according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist [21].

Assessment of potential triggers, clinical, and electrophysiological features of GBS

Clinical diagnosis was made according to the Asbury criteria [16]. Clinical variants were determined by the local medical teams and, if necessary, adjusted by the ad hoc committee. Disease severity upon admission and at hospital discharge were determined using the GBS disability scale [22]. Severe disease was defined as a GBS disability score ≥3 [2, 23]. Detection and testing for potential triggers such as respiratory tract infections, preceding diarrhea, detection of *Campylobacter jejuni* (by culture or stool real-time reverse transcription-polymerase chain reaction [RT-PCR]), or other well-known triggers relied on local medical teams. Due to limited countrywide access, testing for anti-ganglioside antibodies was not routinely performed.

The probability of walking independently at 6 months was estimated using the modified Erasmus GBS outcome score (mEGOS) on the seventh day after admission [24]. The risk of developing respiratory failure during the first week of admission was evaluated using the Erasmus GBS respiratory insufficiency score (EGRIS) [25]. When available, electrophysiological subtypes were determined locally and confirmed retrospectively by an experienced neurophysiologist using the raw data from the first nerve conduction studies according to the Hadden criteria [26]. Diagnostic certainty was graded according to Brighton Collaboration GBS Working Group criteria [23, 27].

Data collection

De-identified data were collected in a secure online database using a standardized case report form that was filled and reviewed by at least four members of the ad hoc committee during virtual sessions; by consensus, two researchers adjudicated any differences between the primary reviewers (M.G.-G and S.I.V.-F). Data collection included: demographics (age and sex); potential triggers, including preceding infections; history of or concurrent confirmed SARS-CoV-2 infection by either RT-PCR or antigen testing; type of administered vaccine and, in the case of two-dose schemes, the number of doses received; the interval in days between last vaccine administration and GBS symptom onset; GBS clinical severity on admission, as well as nerve conduction studies and cerebrospinal fluid (CSF) analysis results; immunomodulatory treatments (plasma exchange or intravenous immunoglobulin); requirement for invasive mechanical ventilation; length of hospital stay; and functional outcome at discharge. The total number of doses administered and reported AEFIs nationwide were obtained from the Mexican Ministry of Health.

Statistical analysis

For the purpose of analyzing the differences among platforms, we evaluated vaccines individually and according to the used vector as either mRNA-based (mRNA-1273 and BNT162b2), adenovirus-vectored (ChAdOx1 nCov-19, rAd26-rAd5, Ad5-nCoV, and Ad26.COV2-S), or inactivated whole-virion-vectored (CoronaVac). Age was stratified according to the mEGOS cut-off values. A statistical power calculation was not required because this was a registry-based analysis. Categorical variables are presented as frequencies with proportions, while continuous variables, after testing for normality with the Shapiro–Wilk test, are reported as median with interquartile range (IQR) or as mean with standard deviation (SD),

as appropriate. Some percentages may not add up to 100% due to rounding. We calculated the unadjusted overall observed incidence per 1,000,000 administered doses according to the total number of administered doses, as well as incidences for each vaccine subtype and platform; 95% confidence intervals (CIs) for these incidences were obtained using the Wilson interval method [28]. To evaluate differences in incidence among vaccine subtypes and platforms, we calculated incidence ratios with 95% CIs using the lowest observed incidence for each vaccine and platform as the reference value [29, 30]. Analyses were performed using IBM SPSS Statistics version 26 (IBM Corp.) and figures were created using GraphPad Prism, version 9 (GraphPad Software).

RESULTS

During the study period, the Mexican Epidemiological Surveillance System processed 31,095 AEFI reports, of which 30,279 (98%) were categorized as non-serious and 816 (2%) as serious. Among the latter, we identified 111 patients with potential GBS; after evaluation by the ad hoc committee, an alternative diagnosis was detected in 11 patients (five with functional neurological disorders, three with compressive radiculopathy, two with acute transverse myelitis, and one with an acute ischemic stroke), and were excluded from this report. Due to missing data to establish a clinical diagnosis of GBS, three more were excluded from the analysis altogether (Figure 1).

Ninety-seven patients with confirmed GBS were included, representing 11.9% of all serious AEFIs. Fifty-two (53.6%) were male, and the median (IQR) age was 44 (33–60) years (Table 1). Most cases occurred among patients aged 18–40 years, with similar proportions across the platforms; however, inactivated virus vaccine recipients were older than those immunized via other platforms (median [IQR] age 59 [30–63] years). GBS symptoms developed after the first dose in 73 patients (75.3%) and during the first 14 days after the most recent dose in 64 (66%). Figure 2 shows the time from the last administered dose to GBS symptom onset according to vaccine platform.

Guillain–Barré syndrome incidence

The overall observed GBS incidence was 1.19 (95% CI 0.97–1.45) cases per 1,000,000 administered doses (Table 2), with higher observed incidences among recipients of two vaccines: Ad26.COV2-S (3.86/1,000,000 administered doses; 95% CI 1.50–9.93) and BNT162b2 (1.92/1,00,000 administered doses; 95% CI 1.36–2.71). Regarding vaccine platforms, the observed incidence was higher among recipients of mRNA-based vaccines (1.85/1,000,000 administered doses; 95% CI 1.33–2.57). We then calculated incidence ratios using the CoronaVac (inactivated virus vaccine) as the reference value due to its lower observed incidence. In comparison to CoronaVac, Ad26.COV2-S (5.61/1,00,000; 95% CI 1.76–17.89), BNT162b2 (2.79/1,00,000; 95% CI 1.37–5.68), and the combined mRNA-based vaccines (2.68/1,00,000; 95% CI 1.33–5.42) also had significantly higher incidence ratios (Figure 3 and Table S1). Three cases (3.1%) occurred in pregnant women: two in the first trimester (one of them an anembryonic pregnancy) and one in the second trimester, all among first-dose recipients immunized–one each–with BNT162b2, ChAdOx1 nCov-19, or Ad5-nCoV.

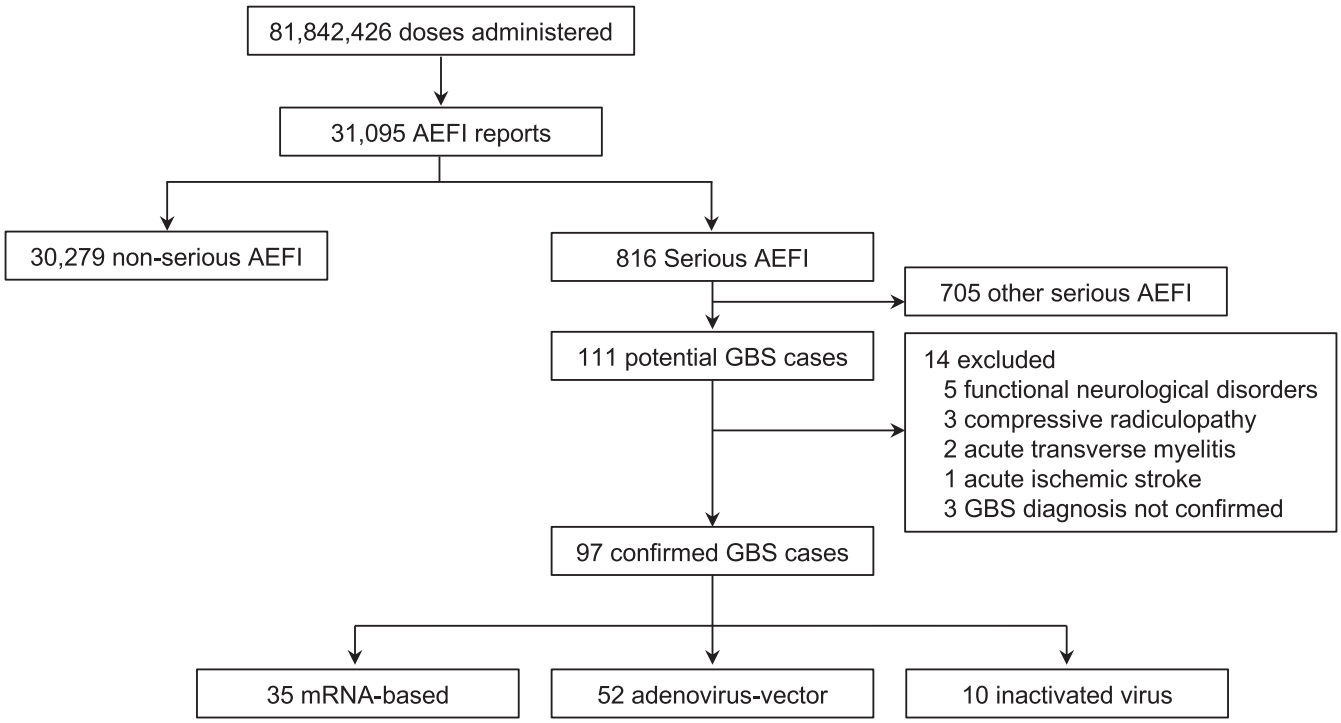

FIGURE 1 Patient selection flowchart. AEFI, adverse event following immunization; GBS, Guillain–Barré syndrome

TABLE 1 Baseline characteristics, potential triggers, and clinical presentation according to vaccine platform

	All patients (*n* = 97)	mRNA-based (*n* = 35)	Adeno-vector (*n* = 52)	Inactivated virus (*n* = 10)
Sex, *n* (%)				
Male	52 (53.6)	21 (60)	25 (48.1)	6 (60)
Female	45 (46.4)	14 (40)	27 (51.9)	4 (40)
Age, median (IQR), years	44 (33–60)	41 (31–63)	45 (37–57)	59 (30–63)
Age group, *n* (%)				
18–40 years	41 (42.3)	15 (42.9)	22 (42.3)	4 (40)
41–60 years	32 (33)	10 (28.6)	21 (40.4)	1 (10)
>60 years	24 (24.7)	10 (28.6)	9 (17.3)	5 (50)
Potential triggers, (%)				
Past SARS-CoV-2 infection	7 (7.2)	3 (8.6)	2 (3.8)	2 (20)
Active SARS-CoV-2 infection	4 (4.1)	0 (0)	2 (3.8)	2 (20)
Diarrhea, ≤4 weeks	21 (21.6)	6 (17.1)	11 (21.2)	4 (40)
Campylobacter jejuni RT-PCR testing	18 (18.6)	3 (8.6)	13 (25)	2 (20)
Positive RT-PCR result[a]	16/18 (88.9)	3/3 (100)	11/13 (84.6)	2/2 (100)
Most recent vaccine dose, (%)				
First	73 (75.3)	23 (65.7)	43 (82.7)	7 (70)
Second	24 (24.7)	12 (34.3)	9 (17.3)	3 (30)
Days from most recent immunization to GBS symptoms, median (IQR)	10 (3–17)	10 (3–21)	11 (4–19)	3 (1–15)
≤14 days, *n* (%)	64 (66)	24 (68.6)	32 (61.5)	8 (80)
Neurological symptoms, (%)				
Facial nerve involvement	24 (24.7)	8 (22.9)	16 (30.8)	0 (0)
Bulbar cranial nerves involvement	30 (30.9)	11 (31.4)	18 (34.6)	1 (10)
Weakness in legs only	20 (20.6)	7 (20)	11 (21.2)	2 (20)
Weakness in arms and legs	74 (76.3)	28 (80)	38 (73.1)	8 (80)
Sensory deficits	46 (47.4)	15 (42.9)	29 (55.8)	2 (20)
Clinical variant, *n* (%)				
Pure motor	48 (49.5)	20 (57.1)	22 (42.3)	6 (60)
Pure sensory	2 (2.1)	0 (0)	2 (3.8)	0 (0)
Sensorimotor	43 (44.3)	14 (40)	27 (51.9)	2 (20)
Miller Fisher syndrome	4 (4.1)	1 (2.9)	1 (1.9)	2 (20)
GBS disability score at admission, *n* (%)				
0, 1, or 2	8 (8.3)	3 (8.6)	5 (9.6)	0 (0)
3	18 (18.6)	5 (14.3)	11 (21.2)	2 (20)
4	55 (56.7)	19 (54.3)	28 (53.8)	8 (80)
5	16 (16.5)	8 (22.9)	8 (15.4)	0 (0)
Erasmus GBS respiratory insufficiency score, median (IQR), points	4 (3–5)	4 (3–6)	4 (3–5)	4 (3–5)

Abbreviations: CI, confidence interval; GBS, Guillain-Barré syndrome; IQR, interquartile range; RT-PCR, real-time reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory coronavirus 2.

[a]Proportions for patients tested for *Campylobacter jejuni* by stool RT-PCR.

Potential triggers

Twenty-one patients (21.6%) had preceding (≤4 weeks) diarrhea (in one of these, norovirus was detected). All patients were tested for active SARS-CoV-2 infection, and only four tested positive for SARS-CoV-2; three tested positive at the time of GBS symptom onset, and one 4 days after. Seven more had a history of COVID-19 (Table 1); in those patients, the time from COVID-19 to GBS symptoms could not be accurately determined. Only 18 patients were tested for *Campylobacter jejuni* infection by stool culture or RT-PCR,

of whom 16 (88.9%) tested positive. Two patients immunized with the first dose of BNT162b2 had sub-acute (<30 days) hepatitis A infection. One patient had received influenza immunization 40 days before GBS onset, developing the symptoms 3 days after receiving the first dose of BNT162b2. None had reports of recent respiratory tract infections. There were no differences in the aforementioned proportions among platforms.

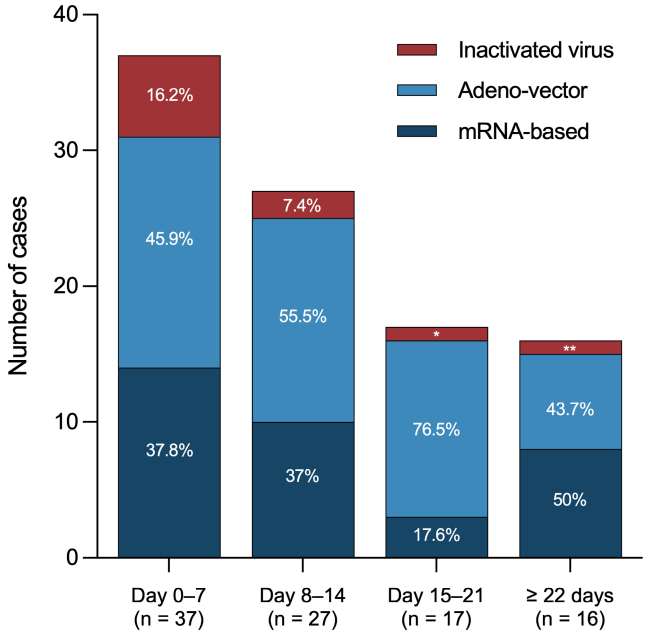

FIGURE 2 Time from the last administered dose to Guillain–Barré symptom onset according to vaccine platform. The figure shows that when cases were analyzed according to the time from the last administered dose, Guillain–Barré symptoms occurred most commonly within the first week after vaccination. Inactivated virus includes CoronaVac; adeno-vector includes ChAdOx1 nCov-19, rAd26-rAd5, Ad5-nCoV, and Ad26.COV2-S; mRNA-based includes mRNA-1273 and BNT162b2. *Represents 5.9% of cases occurring during Days 15 to 21 after immunization. **Represents 6.3% of cases occurring during ≥22 days after immunization

Clinical and electrophysiological features

The most frequent presenting signs/symptoms were limb weakness in 74 patients (76.3%), sensory deficits in 46 (47.4%), cranial (excluding facial) nerve involvement in 30 (30.9%), and facial palsy in 24 (24.7%). On admission, 89 patients (91.8%) had severe GBS. The most common clinical variants observed were pure motor (49.5%) and sensorimotor (44.3%; Table 1). In four patients (4.1%), Miller Fisher syndrome was diagnosed: two cases after inactivated virus vaccines and one case each after mRNA-based or adenovirus-vectored vaccines.

Electrophysiological studies were performed on 76 patients (78.4%; Table 3). Among these, 46 (60.5%) had an axonal pattern: 32 (42.1%) had acute motor axonal neuropathy, and 14 (18.4%) had acute motor and sensory axonal neuropathy. Twenty-five patients (32.8%) were classified as having acute inflammatory demyelinating polyradiculoneuropathy and five (6.6%) as equivocal; none was classified as inexcitable. CSF analysis was performed in 65 patients (67%); albuminocytological dissociation was detected in 57 (87.7%). Clinical and electrophysiological features were similar among vaccine platforms. Fifty patients (51.5%) fulfilled the Brighton level of certainty 1, 34 (35.1%) level 2, and 13 (13.4%) level 3. Electrophysiological variants and diagnostic certainty were similar among the groups.

Treatment and outcomes

Treatment and outcomes among vaccine platforms were similar. Eighty-two patients (84.5%) received immunomodulatory treatment: 75 (77.3%) intravenous immunoglobulin and seven (7.2%) plasma exchange; 15 patients (15.5%) were treated conservatively (Table 3). None received concomitant steroids, including those four patients (4.1%) with concomitant mild SARS-CoV-2 infection. Thirty (30.9%) required invasive mechanical ventilation; the median (IQR) length of stay was 10 (7–16) days. At discharge, 79.1% of patients (61/87) were unable to walk independently (GBS disability

TABLE 2 Observed incidence according to vaccine subtype and platform

Vaccine	Total doses	Number of cases	Unadjusted incidence (95% CI)*	Vector	Total doses	Number of cases	Unadjusted incidence (95% CI)[a]
BNT162b2	16,646,623	32	1.92 (1.36–2.71)	mRNA-based	18,964,680	35	1.85 (1.33–2.57)
mRNA-1273	2,318,057	3	1.29 (0.44–3.81)				
ChAdOx1 nCov-19	38,516,372	37	0.96 (0.70–1.32)	Adeno-vectored	48,344,792	52	1.08 (0.82–1.41)
Ad5-nCoV	2,979,697	5	1.68 (0.72–3.93)				
rAd26-rAd5	5,812,864	6	1.03 (0.47–2.25)				
Ad26.COV2-S	1,035,859	4	3.86 (1.50–9.93)				
CoronaVac	14,532,954	10	0.69 (0.37–1.27)	Inactivated virus	14,532,954	10	0.69 (0.37–1.27)
				All vaccines	81,842,426	97	1.19 (0.97–1.45)

Abbreviations: CI, confidence interval.

[a]Incidence per 1,000,000 doses administered.

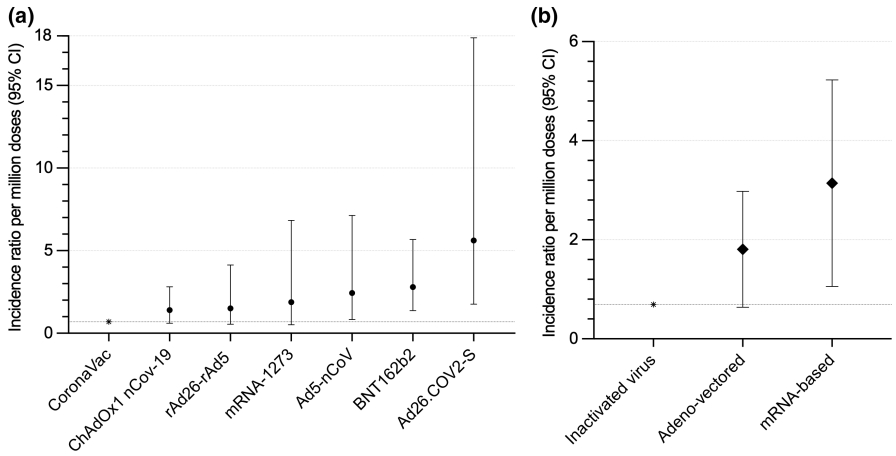

FIGURE 3 Incidence ratio of Guillain–Barré syndrome according to vaccine subtype and platform. This figure shows that when using CoronaVac (inactivated virus vaccine) as a reference value, incidences were higher for Ad26.COV2-S, BNT162b2, and mRNA-based vaccine recipients. (a) Incidence ratio according to vaccine subtype. (b) Incidence ratio according to vaccine platform. All calculations were made using CoronaVac, an inactivated virus single-dose regimen vaccine as the reference. *Reference vaccine and platform value

score ≥3). There were 10 deaths (10.3%): the cause was septic shock in six patients and dysautonomia in three patients, and one patient (a pregnant woman) died from respiratory failure due to ventilator-associated pneumonia. There were no reports of pulmonary embolism-related deaths.

DISCUSSION

This analysis of passive epidemiological surveillance monitoring of more than 81.8 million doses of seven anti-SARS-CoV-2 vaccines in Mexico suggests that GBS is an exceedingly rare AEFI, independently of the vaccine used. Real-world, population-wide analysis is crucial to identify AEFIs that may not have been detected in randomized clinical trials. While GBS incidence has been reported for some vaccines, the number of approved and used vaccines in Mexico allowed us to evaluate the safety of individual vaccines and vaccine platforms.

The 1976 swine influenza vaccination campaign in the United States prompted the first formal GBS diagnostic criteria [16, 31]. However, since then and until the worldwide vaccination against SARS-CoV-2, no clear risk associations had been observed between vaccines and GBS [1, 32–34]. GBS during pregnancy is considered a rare event, occurring at a rate of 2.8 (95% CI 0.5–9.3) cases per million person-years, and little is known about pregnancy-related immunological changes being a trigger [35]. Interestingly, 3.1% of our cases occurred during pregnancy. Hence, further surveillance is needed to assess the risk of such an infrequent AEFI.

The overall incidence that we observed of 1.19/1,000,000 doses (95% CI 0.97–1.45) was much lower than the incidence in 2019 (pre-COVID-19) officially reported by the Mexican ministry of health of 0.71 cases per 100,000 persons-years (7.1 cases 1,000,000 persons-years) [7, 8]; however, as we did not have information on GBS occurring among unvaccinated persons or during 2020, our results should be interpreted with caution. Regarding mRNA-based vaccines, previous reports suggest a lack of association between these vaccines and GBS [13, 14, 17, 36, 37]. The unadjusted GBS incidence that we observed for mRNA-based vaccines was similar to that of a previous report including recipients of 13,952,901 doses of either mRNA-1273 or BNT162b2 [17]. In the United States, a lower but similar unadjusted incidence for these two vaccines was observed (0.68 and 0.69 cases per 1,000,000 doses, respectively) [38]. Interestingly, we observed that BNT162b2 individually–and mRNA-based vaccines as a group–resulted in a slight increase in GBS risk compared to other vaccines and vectors.

Concerning adeno-vectored vaccines, our results support previous reports suggesting an increased risk among Ad26.COV2.S recipients, when compared with other vaccines [11]. We also observed an increased risk of GBS among Ad26.COV2.S recipients (3.86 per 1,000,000 doses administered); however, this frequency was much lower than that reported in the United States (7.8 per 1,000,000 doses administered) [12]. Among ChAdOx1 nCoV-19 recipients, we observed an incidence of 0.96 cases per 1,000,000 doses administered, which was lower than the incidence reported in the United Kingdom National Immunoglobulin Database (0.87 cases per 100,000 first-doses administered or 8.7 per 1,000,000 first-doses administered) [10]. We hypothesize that these differences may result from differences in epidemiological surveillance systems or the number of administered doses of each vaccine subtype per country. At the time of writing this manuscript, little to no information exists on GBS among recipients of Ad5-nCoV, rAd26-rAd5, and CoronaVac. That may be explained in part because those vaccines are only being used in a few low-income and middle-income countries, where vaccine numbers are still small, and cases may be potentially underreported [6, 39].

In line with previous studies and independently of vaccine type, in this cohort, GBS symptoms generally started within the first 14 days after immunization and occurred mostly among first-dose

TABLE 3 Diagnostic assessment, treatments, and outcomes according to vaccine platform

	All patients (*n* = 97)	mRNA-based (*n* = 35)	Adeno-vector (*n* = 52)	Inactivated virus (*n* = 10)
Nerve conduction studies performed, (%)	76 (78.4)	29 (82.9)	41 (78.8)	6 (60)
Neurophysiological variant, *n* (%)[a]				
Acute inflammatory demyelinating polyneuropathy	25 (32.9)	10 (34.5)	13 (31.7)	2 (33.3)
Acute motor axonal neuropathy	32 (42.1)	14 (48.3)	17 (41.5)	1 (16.7)
Acute motor sensory axonal neuropathy	14 (18.4)	3 (10.3)	8 (19.5)	3 (50)
Equivocal	5 (6.6)	2 (6.9)	3 (7.3)	0 (0)
Lumbar puncture performed, (%)	65 (67)	22 (62.9)	35 (67.3)	8 (80)
Cytoalbuminologic dissociation, *n* (%)[b]	59/65 (87.7)	19/22 (86.4)	32/35 (91.4)	8/8 (100)
Brighton Collaboration level of certainty, (%)				
1	50 (51.5)	17 (48.6)	29 (55.8)	4 (40)
2	34 (35.1)	14 (40)	14 (26.9)	6 (60)
3	13 (13.4)	4 (11.4)	9 (17.3)	0 (0)
Treatment, *n* (%)				
Intravenous immunoglobulin	75 (77.3)	32 (91.4)	36 (69.2)	7 (70)
Plasma exchange	7 (7.2)	1 (2.9)	6 (11.5)	0 (0)
Conservative	15 (15.5)	2 (5.7)	10 (19.2)	3 (30)
Invasive mechanical ventilation, *n* (%)	30 (30.9)	10 (28.6)	18 (34.6)	2 (20)
mEGOS at Day 7, median (IQR), points	6 (4–10)	6 (4–10)	6 (4–10)	7 (5–8)
GBS disability score at discharge, *n* (%)				
0, 1, or 2	26 (27)	10 (25.7)	13 (25)	4 (40)
3	23 (23.7)	7 (20)	12 (23.1)	4 (40)
4	23 (23.7)	8 (22.9)	14 (26.9)	1 (10)
5	15 (15.5)	7 (20)	8 (15.4)	0 (0)
6	10 (10.3)	4 (11.4)	5 (9.6)	1 (10)
Length of hospital stay, median (IQR), days	10 (7–16)	9 (6–12)	13 (7–21)	13 (8–22)

Abbreviations: GBS, Guillain–Barré syndrome; IQR, interquartile range; mEGOS, modified Erasmus GBS outcome score.

[a]Proportions for patients in which nerve conduction studies were performed.

[b]Proportions for patients in which a lumbar puncture was performed.

recipients [10, 11, 17, 38]. Regarding disease severity, 91.8% of our patients had severe GBS compared to 58.5% reported in ChAdOx1 nCoV-19 and mRNA-1273 recipients in the United Kingdom [10]. This may be attributable to differences in electrophysiological variants, as patients with axonal variants, known to develop a more severe disease course with worse functional outcomes [40, 41], accounted for 60.5% of our cases, whereas demyelinating variants accounted for 79.5% of theirs. This may be the result of genetic and environmental differences, as demyelinating variants are more frequent in white populations, while axonal variants are more frequent in Latin American and Asian populations [41]. The proportion of axonal variants and mortality rate we observed are consistent with pre-COVID-19 rates, where axonal subtypes accounted for up to 60% of cases, with an overall mortality rate as high as 12% [42–44].

Interestingly, when comparing mRNA-based versus adeno-vectored vaccines, we observed a significantly higher incidence ratio for the former. These variations in an unusually large sample suggest that genetic and environmental factors may result in increased susceptibility to GBS among recipients of specific SARS-CoV-2 vaccines. However, our data, and that of others, indicate that all seven vaccines evaluated in this report are safe concerning GBS, and their benefits clearly outweigh the risk of GBS.

Mechanism of disease is beyond the scope of our manuscript. A causal association between SARS-CoV-2 and GBS is still debatable. Some authors have demonstrated a potential epidemiological link between these entities [45]. It has been suggested that the hyperinflammatory state associated with COVID-19 that promotes an excessive release of cytokines may trigger additional autoimmune mechanisms that could cross-react with neural proteins resulting in GBS [46]; however, large-scale epidemiological studies have failed to demonstrate a clear association between COVID-19 and GBS [47].

Hypothetically, immunization-elicited antibodies against SARS-CoV-2 may cross-react with self-antigens expressed in the peripheral nervous system, including Schwann cells and nodes of Ranvier [48, 49]. In the case of mRNA-vectored vaccines, it is also possible that

the lipid nanoparticles required to prevent enzymatic degradation of mRNA particles may be a trigger for GBS in genetically or environmentally susceptible individuals [50, 51]. Also, other neuroimmunological syndromes such as fulminant encephalomyelitis (overlapping with GBS), optic neuritis, and acute disseminated encephalomyelitis as AEFIs have been reported among recipients of SARS-CoV-2 vaccines [52–54]. Still, a causal relationship between anti-SARS-CoV-2 vaccines and GBS is unknown.

While only 18.6% of our cases were evaluated for *Campylobacter jejuni*, more than 90% of those tested positive, and 20% of all patients had preceding diarrhea, suggesting that other well-known GBS triggers may be the cause and that these cases were coincident with, but unrelated to, SARS-CoV-2 vaccination. Although a trigger cannot be identified in up to one-third of patients with GBS [41, 55]. a comprehensive approach for known triggers must be performed to establish causality accurately, something that should improve on a nationwide scale in light of our findings.

This study has strengths and limitations. One of its strengths is that we relied on an unusually large population of vaccine recipients and included vaccines for which no safety data related to GBS have been reported, including Ad5-nCoV, rAd26-rAd5, and CoronaVac. The study has the following limitations. First, interpretation of the study is limited by its descriptive nature. Second, we were unable to estimate incidence rate ratios or adjust incidences by age and sex, or calculate an incidence during pregnancy because we could not obtain the number of administered doses per month, sex, or age group. Third, as AEFI reports rely on local healthcare providers, we could not establish causality or accurately determine other relevant clinical data, such as the development of dysautonomia, due to a lack of standardized diagnostic protocols. Fourth, due to the passive nature of the Mexican epidemiological surveillance system, which is less likely to detect cases than active surveillance systems, our data were susceptible to selection bias as some cases may have not been reported to the sanitary authorities. Finally, in line with the last statement, mildly symptomatic patients (GBS disability score <2) presenting with non-disabling symptoms or sequelae may be underdiagnosed or underreported, as well as cases occurring in rural settings where there is limited access to medical services.

In conclusion, we show that GBS is extremely infrequent among recipients of all vaccines against SARS-CoV-2. We observed higher frequency among recipients of Ad26.COV2.S and BNT162b2 individually, and in mRNA-vectored vaccines as a group. However, the magnitude of the increased risk was minuscule in comparison to the magnitude of protection against severe and lethal forms of COVID-19.

AUTHOR CONTRIBUTIONS

Miguel García-Grimshaw: Conceptualization (lead); data curation (lead); formal analysis (lead); project administration (lead); visualization (lead); writing – original draft (lead); writing – review and editing (lead). **Javier Andrés Galnares-Olalde:** Conceptualization (lead); data curation (lead); formal analysis (lead); methodology (lead); writing – original draft (lead). **Omar Yaxmehen Bello-Chavolla:** Data curation (equal); formal analysis (equal); writing – original draft (equal). **Anaclara Michel-Chavez:** Data curation (equal); formal analysis (equal); writing – original draft (equal). **Arturo Cadena-Fernández:** Data curation (equal); formal analysis (equal); writing – original draft (equal). **María Eugenia Briseño-Godínez:** Data curation (equal); formal analysis (equal); writing – original draft (equal). **Neftali Eduardo Antonio-Villa:** Data curation (equal); formal analysis (equal); writing – original draft (equal). **Isaac Núñez:** Conceptualization (equal); data curation (equal); formal analysis (equal); writing – original draft (equal); writing – review and editing (equal). **Alonso Gutiérrez-Romero:** Data curation (equal); resources (equal); writing – original draft (equal). **Laura Hernández-Vanegas:** Conceptualization (equal); data curation (equal); formal analysis (equal); writing – original draft (equal). **María del Mar Saniger-Alba:** Conceptualization (equal); data curation (equal); writing – original draft (equal). **Roger Carrillo-Mezo:** Conceptualization (equal); data curation (equal); writing – original draft (equal). **Santa Elizabeth Ceballos-Liceaga:** Conceptualization (equal); data curation (equal); formal analysis (equal); supervision (equal); writing – original draft (equal). **Guillermo Carbajal-Sandoval:** Conceptualization (equal); data curation (equal); formal analysis (equal); writing – original draft (equal). **Fernando D Flores-Silva:** Conceptualization (equal); data curation (equal); formal analysis (equal); validation (equal); writing – original draft (equal). **Jose Luis Diaz-Ortega:** Formal analysis (equal); investigation (equal); supervision (equal); writing – original draft (equal). **Ricardo Cortes-Alcala:** Conceptualization (equal); supervision (equal); writing – original draft (equal). **José Rogelio Pérez-Padilla:** Conceptualization (equal); formal analysis (equal); validation (equal); writing – original draft (equal). **Hugo López-Gatell:** Conceptualization (equal); supervision (equal); validation (equal); writing – original draft (equal). **Erwin Chiquete:** Conceptualization (equal); data curation (equal); writing – original draft (equal). **Gustavo Reyes-Terán:** Supervision (equal); validation (equal); writing – original draft (equal); writing – review and editing (equal). **Antonio Arauz:** Conceptualization (equal); formal analysis (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Sergio Iván Valdés-Ferrer:** Conceptualization (lead); data curation (equal); formal analysis (equal); supervision (equal); validation (equal); writing – original draft (equal); writing – review and editing (lead).

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CONFLICT OF INTEREST

Authors declare no competing conflicts of interest.

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DATA AVAILABILITY STATEMENT

The manuscript provides all the collected data. After approval by the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán Ethics and Research Committees, de-identified data to replicate our results will be available to qualified researchers upon written request to the corresponding author.

ETHICAL APPROVAL

The study was reviewed and approved by the Ethics and Research Committees of the *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán* (NER-3903-21-23-1); due to the observational nature of the study, informed consent was waived.

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SUPPORTING INFORMATION

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