



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Full Length Article



Neurologic adverse events among 704,003 first-dose recipients of the BNT162b2 mRNA COVID-19 vaccine in Mexico: A nationwide descriptive study

Miguel García-Grimshaw^{a,1}, Santa Elizabeth Ceballos-Liceaga^{b,1},
 Laura E. Hernández-Vanegas^c, Isaac Núñez^d, Noé Hernández-Valdivia^b,
 Daniel Amado Carrillo-García^b, Anaclara Michel-Chávez^a, Javier Andrés Galnares-Olalde^c,
 Guillermo Carbajal-Sandoval^b, María del Mar Saniger-Alba^a, Roger A. Carrillo-Mezo^e,
 Sergio Frago-Saavedra^{a,f}, Alba Espino-Ojeda^g, Carlos Blaisdell-Vidal^g,
 Juan Luis Mosqueda-Gómez^h, Juan Sierra-Maderoⁱ, Rogelio Pérez-Padilla^j,
 José Luis Alomía-Zegarra^b, Hugo López-Gatell^b, José Luis Díaz-Ortega^k,
 Gustavo Reyes-Terán^{l,2}, Antonio Arauz^{b,b}, Sergio Iván Valdés-Ferrer^{a,i,m,b,*}

^a Department of Neurology and Psychiatry, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

^b Secretaría de Salud, Gobierno de México, Mexico

^c Department of Neurology, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City, Mexico

^d Department of Internal Medicine, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

^e Department of Neuroradiology, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City, Mexico

^f Programa de Estudios Combinados en Medicina (MD/PhD program), Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico City, Mexico

^g Instituto Mexicano del Seguro Social, Mexico City, Mexico

^h Hospital Regional de Alta Especialidad del Bajío, León, Mexico

ⁱ Department of Infectious Diseases, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

^j Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico

^k Centro Nacional para la Salud de la Infancia y la Adolescencia, Mexico City, Mexico

^l Comisión Coordinadora de Institutos Nacionales de Salud y Hospitales de Alta Especialidad, Mexico City, Mexico

^m Feinstein Institutes for Medical Research, Manhasset, NY, USA

ARTICLE INFO

Keywords:

Adverse event
 COVID-19
 SARS-CoV-2
 Vaccine
 BNT162b2

ABSTRACT

mRNA vaccines against SARS-CoV-2 are remarkably effective. Limited information exists about the incidence of adverse events following immunization (AEFI) with their use. We conducted a prospective observational study including data from 704,003 first-doses recipients; 6536 AEFI were reported, of whom 65.1% had at least one neurologic AEFI (*non-serious* 99.6%). Thirty-three *serious* events were reported; 17 (51.5%) were neurologic (observed frequency, 2.4/100,000 doses). At the time of writing this report, 16/17 cases had been discharged without deaths. Our data suggest that the BNT162b2 mRNA COVID-19 vaccine is safe; its individual and societal benefits outweigh the low percentage of *serious* neurologic AEFI. This information should help to dissipate hesitancy towards this new vaccine platform.

1. Introduction

Since the coronavirus disease 2019 (COVID-19) pandemic began,

>127 million infections and > 2.7 million deaths have been reported worldwide [1]. To reduce the burden on healthcare systems, massive vaccination is, therefore, a top global priority. Shortly after

* Corresponding author at: Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Vasco de Quiroga 15, Tlalpan, 14080 Ciudad de México, México.
 E-mail address: sergio.valdesf@incmnsz.mx (S.I. Valdés-Ferrer).

¹ Contributed equally to this work.

² Senior co-authors.

demonstrations of the BNT162b2 mRNA COVID-19 vaccine safety and efficacy, Mexico granted emergency approval for its use and started widespread vaccination (mainly among healthcare workers) on December 24, 2020 [2]. Mexico has an ongoing passive surveillance system assessing adverse events potentially related to immunizations, including COVID-19 vaccines [3]. Within days, the surveillance system identified a suspicious cluster of *serious* neurologic adverse events following immunization (AEFI) among first-dose recipients, prompting a thorough analysis of every potentially *serious* AEFI by a multidisciplinary group of physicians.

To this day, there are only two published papers describing at least one neurologic adverse following vaccination with the BNT162b2 mRNA vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A worldwide randomized clinical trial (RCT) evaluating its safety and efficacy reported a headache frequency > 30% [4], and a descriptive study from the United States conducted by the Centers for Disease Control and Prevention (CDC) using data obtained from their Vaccine Adverse Event Reporting System describes a lower frequency of 21.8% [5], both among first-dose recipients. However, none of those studies described other *serious* or *non-serious* neurologic AEFI.

This report on first-dose recipients of the BNT162b2 mRNA COVID-19 vaccine from December 24, 2020, to February 12, 2021, in Mexico, aims to describe the systemic, and potential neurologic AEFI, focusing on *serious* neurologic events. This information has potential implications for increasing awareness of vaccine safety among Latinx, an underrepresented group in RCTs that has historically shown skepticism for novel vaccines [6,7].

2. Methods

2.1. Study design and population

This prospective observational cohort study on all adverse events following the first dose of the BNT162b2 mRNA COVID-19 vaccine from December 24, 2020, to February 12, 2021, in Mexico, was performed using a dataset comprising daily updated information on AEFI, obtained from the General Board of Epidemiology (in Spanish, *Dirección General de Epidemiología*) of the Mexican Ministry of Health. The cut-off date for this data and follow-up of hospitalized cases was February 18, 2021. The Mexican Epidemiological Surveillance System monitors AEFI throughout >23,300 medical units, distributed across the country, including public, social security-managed, and private units. This is a passive surveillance system where events are reported either by the health institution or directly by the recipient. Surveillance is carried out for 30 days after vaccine administration; vaccine-specific, clinical, and epidemiological data are recorded. A printed and web-based operational manual guides on the definition, reporting, and follow-up of AEFI. When AEFI are identified, evaluation and follow-up are performed at the local level, where they are characterized as either *non-serious* or *serious* [3]. All potentially *serious* AEFI were evaluated by an ad-hoc committee. The study was revised and approved by the Ethics and Research Committees of the *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán* (Ref. NER-3667-20-21-1) and the Mexican Ministry of Health. Due to the nature of the study, both Committees waived the need for signed informed consent.

2.2. Definitions of adverse events following immunization

Following the World Health Organization (WHO) operational definition [8], in Mexico, *non-serious* AEFI are events attributable to and occurring in the first 30 days after vaccination and immunization that a) do not pose an imminent risk of death; b) disappear without treatment or only require symptomatic treatment; c) do not require hospitalization; and, d) do not cause long-term disability, including local (e.g., rash, swelling, injection-site pain or infection that is treated on an outpatient basis), or systemic (e.g., fever, headache, malaise, muscle and/or joint

pain or Diarrhea) events. In contrast, *serious* AEFI are those occurring in the first 30 days after vaccination, presenting with any clinical manifestation that meets one or more of the following criteria: a) lead to death; b) put life in imminent danger; c) lead to persistent or significant disability; d) in the case of pregnant women, cause in-utero malformations; or, e) require or prolong in-hospital treatment [3].

2.3. Definitions of neurologic adverse events following immunization

For this analysis, we defined neurologic AEFI as those presenting with any sign or symptom potentially related to central or peripheral nervous system dysfunction; we, therefore, considered AEFI as neurologic whenever they included at least one of the following: headache, motor symptoms, sensory symptoms, focalizing signs, and altered mental status (including syncope). From the clinical notes, we defined *weakness* as a construct using the following search terms taken from the clinical notes: paresis, weakness, diminished strength, lack of strength, paralysis, or a combination thereof. Similarly, a construct of *sensory* symptoms included the following: paresthesia, dysesthesia, numbness, pinprick, tingling, or a combination thereof. Headache, sensory symptoms, weakness, and syncope were considered *non-serious* neurologic adverse events unless otherwise defined by the medical personnel or if fulfilling the definition of *serious* AEFI. Guillain-Barré syndrome (GBS), acute transverse myelitis, seizures, and acute palsy or paralysis were confirmed by a neurologist and considered *serious* neurologic adverse events.

2.4. Data collection

We obtained de-identified data for all AEFI, including age, sex, pregnancy (self-reported), history and type of allergies (drugs, food, or other); history of confirmed SARS-CoV-2 infection by either real-time reverse transcription-polymerase chain reaction (RT-PCR), or antigen tests; the history of non-SARS-CoV-2 infection ≤ 15 days before vaccination; occupation; vaccine-related symptoms (assessed by the attending physician of the event); interval in minutes from vaccine receipt to first symptom onset; AEFI-related relevant clinical notes by the medical personnel; type of AEFI; as well as hospitalization requirement, including clinical outcome and hospital length of stay (LOS). At least two researchers (MG-G, AA, LH-V, AE-O, MMS-A, SIV-F.) independently reviewed all data for the constructed and non-constructed variables, and a third researcher adjudicated any difference in interpretation between the primary reviewers.

2.5. Statistical analysis

We compared the characteristics between vaccine recipients who developed neurologic AEFI and those who did not. Continuous variables are reported as median with interquartile range (IQR), and categorical variables are presented as frequencies and proportions. Analyses of differences between categorical variables were performed with the χ^2 or Fisher's exact tests as appropriate. Differences in non-parametric continuous variables were assessed with the Mann-Whitney *U* test. We calculated the incidence proportion of neurologic adverse events per 100,000 administered doses. Variables with missing data were analyzed and presented separately. All values were two-tailed and considered significant when the *P*-value was <0.05. Statistical analyses were performed using IBM SPSS Statistics, version 26 (IBM Corp., Armonk, NY, USA).

3. Results

From December 24, 2020, to February 12, 2021, 704,003 first doses of the BNT162b2 mRNA COVID-19 vaccine were administered in Mexico; 188,349 (26.8%) to women and 515,654 (74.2%) to men. During that period, the Mexican Epidemiological Surveillance System

received and processed 6536 (0.5%) reports of AEFI. Among all reported AEFI, 6503 (99.5%) were classified as *non-serious*, and 33 (0.005%) as *serious* (4.7/100,000 doses). The median age of the vaccine recipients who reported AEFI was 36 (IQR, 30–44) years; 4984 (76.3%) were women (Table 1); six of them were pregnant, but none develop *serious* AEFI. Information on allergy history was available from 5847 cases; among these, 5825 (99.6%) of those developing AEFI had a positive history of allergy. Information on the history of SARS-CoV-2 infection was available to form 6411 recipients; of those, 1763 (27.5%) had a known history of COVID-19.

Of all AEFI, 4258 (65.1%) were neurologic (604.8/100,000 doses); 3242 (76.1%) occurred in women, and 1016 (23.9%) in men (Table 1); patients with neurologic AEFI were younger ($P < 0.001$). Neurologic events were more frequent among nurses and other healthcare workers ($P < 0.001$). The proportion of recent (≤ 15 days) history of non-SARS-CoV-2 infection and allergies was similar between groups. The rate of confirmed SARS-CoV-2 infection any time before receiving the vaccine was higher among those who developed neurologic AEFI (29.8% vs 23.2%; $P < 0.001$). Except for bronchospasm ($P < 0.870$) and anaphylaxis/anaphylactic shock ($P < 0.252$), other non-neurologic AEFI were significantly ($P < 0.001$) more common among patients with neurologic AEFI (Table 2). The interval in minutes from vaccination to the first symptom was significantly longer in patients with neurologic AEFI (62.5% of them presented ≥ 60 min after receiving the vaccine) versus those with non-neurologic AEFI ($P < 0.001$).

The overall incidence of *non-serious* neurologic AEFI was 600.7 cases per 100,000 administered doses, with headache (62.2%; 577.7/100,000 doses), transient sensory symptoms (3.5%; 32.9/100,000 doses), and weakness (1%; 9.1/100,000 doses) being the most frequent complaints. Table 3 shows frequent neurologic adverse events per sex and age group. Interestingly, seizures not requiring hospitalization were reported in eight recipients (1.1/100,000 doses); those occurred in patients with pre-existing epilepsy or in patients who missed doses of anti-epileptic drugs and were deemed unrelated to the vaccine by the evaluating medical team.

Among 33 *serious* AEFI, 17 (51.7%) were neurologic (2.4/100,000

Table 1
Baseline characteristics.

	All AEFI (<i>n</i> = 6536)	Non- neurologic (<i>n</i> = 2278)	Neurologic (<i>n</i> = 4258)
Age, median (IQR), years	36 (30–44)	37 (30–45)	36 (29–44)
Sex, <i>n</i> (%)			
Male	1552 (23.7)	536 (23.5)	1016 (23.9)
Female	4984 (76.3)	1742 (76.5)	3242 (76.1)
Occupation, <i>n</i> (%)			
Nurses	3332 (51)	1065 (46.8)	2267 (53.2)
Physicians	1460 (22.3)	523 (23)	937 (22)
Other HCWs	806 (12.3)	335 (14.7)	471 (11.1)
Hospital administrative staff	526 (8)	187 (8.2)	339 (8)
Other	412 (6.3)	168 (7.4)	244 (5.7)
History of allergic reactions, <i>n</i> (%) ^a	5825/5847 (99.7)	2002/2013 (99.5)	3823/3834 (99.7)
Drugs	1133 (19.4)	380 (18.9)	753 (19.6)
Food	4682 (80.1)	1621 (80.5)	3061 (79.8)
Other	10 (0.17)	1 (0.05)	9 (0.23)
Non-SARS-CoV-2 infection \leq 15 days, <i>n</i> (%) ^a	113/5943 (1.9)	38/2072 (1.8)	75/3871 (1.9)
History of confirmed SARS-CoV-2 infection ^c	1763/6411 (27.5)	513/2210 (23.2)	1250/4201 (29.8)

Differences between categorical variables were analyzed with the X^2 or Fisher's exact test and continuous variables with the Mann-Whitney U test; P values for those variables with statistical differences are reported in the text.

Abbreviations: AEFI, adverse event following immunization; IQR, interquartile range; HCWs, Health care worker. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. ^aData were available for 5847 cases (missing: 689 [10.5%]). ^bData were available for 5943 cases (missing: 593 [9.1%]). ^cData were available for 6411 cases (missing: 125 [1.9%]).

Table 2

Systemic adverse events observed in the whole cohort and those with neurologic adverse events following immunization.

	All AEFI (<i>n</i> = 6536)	Non- neurologic (<i>n</i> = 2278)	Neurologic (<i>n</i> = 4258)
Systemic AEFI, <i>n</i> (%)			
Injection site pain	3147 (48.1)	890 (39.1)	2257 (53)
Fatigue	2382 (36.4)	399 (17.5)	1983 (46.6)
Muscle pain	2300 (35.2)	423 (18.6)	1877 (44.1)
Joint pain	1874 (28.7)	330 (14.5)	1544 (36.3)
Chills	1745 (26.7)	286 (12.6)	1459 (34.3)
Nausea	1709 (26.1)	429 (18.8)	1280 (30.1)
Fever, $\geq 38^\circ\text{C}$	1607 (24.6)	278 (12.2)	1329 (31.2)
Tachycardia	963 (14.7)	284 (12.5)	679 (15.9)
Rhinorrhea	889 (13.6)	171 (7.5)	718 (16.9)
Diarrhea	584 (8.9)	109 (4.8)	475 (11.2)
Vomiting	469 (7.2)	113 (5)	356 (8.4)
Irritability	187 (2.9)	26 (1.1)	161 (3.8)
Bronchospasm	62 (0.95)	21 (0.94)	41 (1)
Anaphylaxis/anaphylactic shock	19 (0.3)	9 (0.4)	10 (0.2)
Time to AEFI onset, median (IQR), minutes ^a	180 (15–900)	30 (10–600)	300 (20–1020)

Differences between categorical variables were analyzed with the X^2 or Fisher's exact test and continuous variables with the Mann-Whitney U test; P values for those variables with statistical differences are reported in the text.

Abbreviations: AEFI, adverse event following immunization; IQR, interquartile range. ^aTime to AEFI onset, $n = 6053$ (missing: 486 [7.4%]) for the whole cohort, $n = 2134$ (93.7%) for non-neurologic, and $n = 3919$ (92%) for neurologic.

doses); of those, seven corresponded to seizures (0.99/100,000 doses); four, to functional syndromes (0.56/100,000 doses); three, to GBS (0.43/100,000 doses); two, to acute transverse myelitis (0.28/100,000 doses); and one, to lumbar radiculopathy exacerbation (0.14/100,000 doses). Table 4 details the characteristics of patients who required hospitalization due to a neurologic AEFI. At the time of this report, 16/17 cases of *serious* neurologic AEFI had been discharged with no observed deaths.

4. Discussion

To this day, this cohort represents the largest study describing the potential neurologic AEFI among first-dose recipients of the BNT162b2 mRNA COVID-19 vaccine. Less than a year after identifying SARS-CoV-2, at least two mRNA vaccines had been proven effective to prevent and reduce the severity and mortality of COVID-19 [4,9,10], but the full spectrum of adverse events is incompletely understood, particularly among Latinx, an underrepresented population in RCTs. Furthermore, as those who had recovered from COVID-19 were excluded from RCTs, the type and rate of adverse events were unknown in this group. On December 11, 2020, Mexico granted emergency approval for the use of the BNT162b2 mRNA COVID-19 vaccine [3], and the first doses were administered on December 24, 2020. During the first 50 days, 704,003 first doses of the vaccine were administered across the country.

Recent post-RCT vaccine experiences from Israel [10], and the United States [9], have confirmed real-world effectiveness. However, limited information exists on adverse events. Here, we show that *non-serious* events occurred in less than 1% of recipients, while *serious* ones occurred in only 33 (0.005%) recipients, suggesting that the vaccine is not only effective but also safe. Most potentially systemic neurologic manifestations (e.g., headache) were *non-serious* and may have occurred as part of the so-called *sickness behavior* [11], or secondary to vaccine reactogenicity [12], both related to systemic inflammation, hence unrelated to sustained nervous system dysfunction.

Among *serious* AEFI, 52% were neurologic. Interestingly 9 (53%) of these presented in those with concomitant allergic, anaphylactic or infectious conditions, suggesting that a double hit (e.g., vaccine-infection,

Table 3
Most frequent neurologic adverse events per sex and age group.

Age group, n (%)	Female (n = 3242)				Male (n = 1016)			
	Headache (n = 3089)	Sensory symptoms (n = 196)	Weakness (n = 42)	Syncope (n = 19)	Headache (n = 978)	Sensory symptoms (n = 36)	Weakness (n = 22)	Syncope (n = 7)
18 to 29 years	776 (25.1)	46 (23.5)	15 (35.7)	5 (26.3)	285 (29.1)	9 (25)	10 (45.5)	3 (42.9)
30 to 39 years	1128 (36.5)	71 (36.2)	14 (33.3)	5 (26.3)	400 (40.9)	15 (41.7)	4 (18.2)	2 (28.6)
40 to 49 years	828 (26.8)	60 (30.6)	7 (16.7)	5 (26.3)	198 (20.2)	8 (22.2)	5 (22.7)	2 (28.6)
50 to 59 years	333 (10.8)	18 (9.2)	6 (14.3)	3 (15.8)	76 (7.8)	2 (5.6)	2 (9.1)	0
≥60 years	24 (0.8)	1 (0.5)	0	1 (5.3)	19 (1.9)	2 (5.6)	1 (4.5)	0

Table 4
Characteristics of patients with *serious* neurologic adverse events after the first dose of the BNT162b2 mRNA COVID-19 vaccine.

Baseline characteristics			Concomitant factors			Neurologic AEFI characteristics			
Sex / Age, years	Medical history	History of COVID-19	Non-neurologic AEFI	Infectious	Pre-existing neurologic condition	Time to neurologic AEFI onset	Diagnosis	LOS	Current status
M / 25	Food allergy	No	Fever	GI	No	12 days	GBS	7 days	Discharged home
F / 53	Drug allergy	Yes	No	GI	No	6 days	GBS	NA	Hospitalized (IMV)
M / 33	Food allergy	No	No	GI	No	28 days	GBS	10 days	Discharged home
F / 33	None	Unknown	Anaphylactic shock	No	No	25 min	Transverse myelitis	8 days	Discharged home
F / 33	Drug allergy	No	No	No	No	10 min	Transverse myelitis	8 days	Discharged home
M / 26	Food allergy	No	Allergic reaction	COVID-19	No	24 h	Seizures and pseudo-seizures (organic/functional)	6 days	Discharged home
M / 32	Food allergy	No	Allergic reaction	COVID-19 (hyponatremia and AKI)	No	10 h	Generalized seizures	10 days	Discharged home
F / 31	Food allergy	No	No	No	No	4 days	Generalized seizures	4 days	Discharged home
F / 32	Food allergy	No	Anaphylactic reaction	No	No	20 min	Generalized seizures	12 days	Discharged home
F / 44	Epilepsy (poor AED compliance) Drug allergy	No	Acute anxiety	No	Yes	19 min	Generalized seizures	4 days	Discharged home
M / 64	Epilepsy (poor AED compliance) Cerebral cavernous malformation Drug allergy	No	Fever	No	Yes	5 h	Generalized seizures	2 days	Discharged home
F / 39	Epilepsy (poor AED compliance) Drug allergy	No	Acute anxiety	No	Yes	3 min	Generalized seizures	2 days	Discharged home
F / 29	Drug allergy	No	No	No	No	8 h	Functional (weakness)	4 days	Discharged home
F / 18	Drug allergy	No	No	No	No	30 min	Functional (weakness)	1 days	Discharged home
F / 22	Drug allergy	No	No	No	No	13 h	Functional (weakness)	5 days	Discharged home
F / 42	Epilepsy (poor AED compliance)	Unknown	No	No	No	20 min	Functional (seizures)	1 days	Discharged home
F / 52	Lumbar radiculopathy Food allergy	Yes	No	No	Yes	14 days	Lumbar radiculopathy exacerbation	5 days	Discharged home

Abbreviations: F, female; M, male; AED, antiepileptic drugs; COVID-19, coronavirus disease 2019; AEFI, adverse event following immunization; GI, gastrointestinal; AKI, acute kidney injury; LOS, hospital length of stay; GBS, Guillain-Barré syndrome; NA, not applicable; IMV, invasive mechanical ventilation.

vaccine-anaphylaxis) is likelier to breach the immuno-privileged nervous system and lead to neurologic manifestations [13]. Most patients experienced complete recovery within days to weeks without long-term sequelae, suggesting that an acute and transient inflammatory trigger may lead to nervous system dysfunction.

Seizures were the most frequent (35%) *serious* neurologic AEFI. SARS-CoV-2 has the potential to gain access to the central nervous system [14] and induce the production of proinflammatory cytokines by

microglia and astrocytes [15], leading to hyperexcitability and epileptic seizures [16]. In our cohort, at least two cases of seizures occurred in patients with concomitant COVID-19. A change in seizure threshold among recipients of mRNA vaccines has not been observed in RCTs, and, according to our data, this is unlikely; it is possible that structural (e.g., pre-existing epilepsy) or pathological conditions (e.g., concomitant COVID-19) may explain most of the reported seizures. While vaccines may increase the frequency of febrile seizures in children, in most cases,

the coexistence of structural or genetic causes explains epileptic seizures [17–19]. The temporal association of seizures with inactivated and live attenuated viral vaccines is well known but infrequent [17]. The calculated lifetime prevalence of epilepsy in Latin America is 14.9/1000 inhabitants [19]. A similar prevalence is expected in our cohort, where only a handful of epileptic seizures occurred, suggesting that mRNA vaccines are not associated with a higher frequency of new-onset seizures, and are safe even among those with a history of seizures/epilepsy (~1.5% of those immunized).

GBS is an acquired, rapidly progressive autoimmune disorder of the peripheral nerve roots involving myelin, axons, or both, resulting in an acute, monophasic paralyzing illness. [20] Systemic viral infections, including COVID-19 [20–22], have been associated with the loss of immune tolerance leading to GBS. While vaccines have also been empirically linked to GBS, epidemiological evidence from different vaccine types and genetic backgrounds suggests that a causal association is spurious [23,24]. In our cohort, we identified only three cases of GBS, all with clinical, laboratory, and electrophysiological confirmation. Interestingly, although COVID-19 has been epidemiologically linked to GBS [20–22], none of the three cases tested positive for SARS-CoV-2 during the presentation of GBS. Interestingly, all three had suspected or confirmed acute gastrointestinal infections with clinical onset after receiving the vaccine, suggesting that concomitant infections may result in increased susceptibility (if not entirely responsible) for peripheral nerve damage. However, an observed incidence of 0.43/100,000 doses falls within the expected all-cause incidence of GBS (1.1–1.8/100,000 persons/year) [20,25], suggesting that mRNA vaccines are not linked mechanistically to GBS.

Functional neurologic disorders are relatively common in the general neurology practice. Clusters of functional neurologic events can occur in response to novel vaccines' mass administration, as recently observed in Colombian teenagers after human papillomavirus immunization [26]. Unsurprisingly, fear and hopelessness surrounding COVID-19 mix well with skepticism towards a novel vaccine platform [6,27], leading to increased awareness and anxiety towards the vaccine [28], which may also explain the frequency of other events such as transient sensory symptoms, weakness, and syncope (vasovagal response) as part of an immunization stress-related response [29,30]. At least two functional paralysis cases coincided in time and place, both in healthcare workers, where the index case was treated by the person developing the neurologic symptoms within hours. Statistics of COVID-19 vaccine hesitancy in Mexico are unknown, but a scenario similar to the one in the United States is likely, where about one in four adults admits that probably or definitely will not get the vaccine [31]. We fear that news of adverse events -organic or functional- taken out of context can harm public confidence in all COVID-19 vaccines, creating further hesitance resulting in suboptimal vaccination.

Finally, we observed a disproportionate effect of adverse events among female recipients. While only 26.8% of vaccines in the present report were administered to women, 76.3% of adverse events occurred in them; putting this in perspective, there was a 10-fold increase in AEFI among women (1.7% vs 0.19%). This trend has been observed with other vaccines and, while probably multifactorial, is likely the effect of sexual dimorphism of the immune system [32]. Genetic and hormonal differences influence response to self and exogenous antigens. Women are more susceptible to autoimmune disease but have lower infection rates and better antibody response to vaccines than men [33,34]. Alas, women consistently report more vaccine-related adverse events [35]. Furthermore, it is also possible beyond biological factors, external pressures including social (e.g., communal perception of symptoms as a manifestation of weakness), psychological, and cultural factors (e.g., societal perceptions of toughness and resilience) may lead to reduce self-reporting by Latinx male [36].

Our study has limitations, including the passive nature of the reporting system, where some *non-serious* events may be underreported. We relied on limited data, and other relevant data such as comorbidities,

duration of symptoms, and data on those recipients without adverse events to investigate other possible associations for the development of neurologic AEFI were not included in the dataset. Also, healthcare workers constitute a large majority of this cohort, a population that is more aware of potential adverse events but more prone to self-medicate and probably underreport them. In line with that, this manuscript represents an early analysis of vaccine recipients consisting mainly of first-line healthcare workers, a population that in Mexico is currently over-represented by young and healthy males. When we planned the present study, Mexico had only started the vaccination campaign focusing on frontline healthcare workers and using only the BNT162b2 mRNA. However, as of June 10, 2021, at least 35.2 million people are at least partially vaccinated with six different options, including both, mRNA and adenovirus-based ones. Shortly, we plan to perform a new analysis of a larger sample size that will include not only healthcare workers but the general public as well. Moreover, that analysis will compare mRNA vaccines with adenovirus-vectored ones.

5. Conclusions

Our data suggest that the BNT162b2 mRNA COVID-19 vaccine is safe and effective. The potential reduction in disease severity and mortality (that is, the benefits at individual and societal levels) outweigh the observed local, systemic, and neurological adverse events. We hope this data will help to reduce hesitancy towards mRNA COVID-19 vaccines.

Funding

This work was supported by Consejo Nacional de Ciencia y Tecnología, Mexico (COVID-19 Fund [F0005-2020-01]; grant 311790), to SIV-F]. The funder had no role in the study design, data collection, data analysis, data interpretation, writing, or revision of the report.

Author contributions

MG-G, and SEC-L., contributed to study conceptualization and design, data collection, data analysis, and manuscript writing. LEH-V, NH-V, and SF-S. contributed to study design, data collection, and data analysis. IN contributed to study design, data collection, data analysis, and manuscript writing. DAC-G, AM-C, JAG-O., GC-S, AE-O, and CB-V contributed to study design, and data collection. MMS-A, and RAC-M. contributed to study design, data collection, and conceptualization. JLM-G, JS-M, and JLD-O contributed to study design, data collection, and data interpretation RP-P, JLA-Z, and HL-G contributed to study design and data interpretation. SIV-F, GR-T, and AA contributed to study design, data collection, manuscript writing, and data interpretation. SIV-F contributed to study conceptualization, study design, study supervision, data interpretation, data collection, manuscript writing (original drafts and final version), and funding acquisition. Approval of final version: all authors. Accountability for all aspects of the work, accuracy, and integrity of all and any part of the work: all authors.

Data sharing

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

Declaration of Competing Interest

All authors declare no competing interests. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Acknowledgments

None.

References

- [1] Johns Hopkins University, Johns Hopkins Coronavirus Resource Center. <https://coronavirus.jhu.edu/map.html>, 2021 (accessed March 29, 2021).
- [2] Gobierno de México, Secretaría de Salud, Guía técnica para la aplicación de la vacuna BNT162b2 Pfizer/BioNTech contra el virus SARS-CoV-2. https://coronavirus.gob.mx/wp-content/uploads/2021/01/GuiaAplicacionVx_BNT162b_08En_e2021.pdf, 2021 (accessed March 2, 2021).
- [3] Gobierno de México, Dirección General de Epidemiología, Manual de procedimientos estandarizados para la vigilancia epidemiológica de eventos supuestamente atribuibles a la vacunación o inmunización (ESAVI). https://epidemiologia.salud.gob.mx/gobmx/salud/documentos/manuales/42_Manual_ESAVI.pdf, 2021 (accessed March 2, 2021).
- [4] F.P. Polack, S.J. Thomas, N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart, J. L. Perez, G. Pérez Marc, E.D. Moreira, C. Zerbini, R. Bailey, K.A. Swanson, S. Roychoudhury, K. Koury, P. Li, W.V. Kalina, D. Cooper, R.W. Frenck, L. L. Hammit, Ö. Türeci, H. Nell, A. Schaefer, S. Ünal, D.B. Tresnan, S. Mather, P. R. Dormitzer, U. Şahin, K.U. Jansen, W.C. Gruber, C4591001 Clinical Trial Group, Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine, *N. Engl. J. Med.* 383 (2020) 2603–2615, <https://doi.org/10.1056/NEJMoa2034577>.
- [5] J. Gee, P. Marquez, J. Su, G.M. Calvert, R. Liu, T. Myers, N. Nair, S. Martin, T. Clark, L. Markowitz, N. Lindsey, B. Zhang, C. Licata, A. Jazwa, M. Sotir, T. Shimabukuro, First Month of COVID-19 Vaccine Safety Monitoring - United States, December 14, 2020-January 13, 2021, *MMWR Morb. Mortal. Wkly Rep.* 70 (2021) 283–288, <https://doi.org/10.15585/mmwr.mm7008e3>.
- [6] M.B. Moran, L.B. Frank, J.S. Chatterjee, S.T. Murphy, L. Baezconde-Garbanati, Information scanning and vaccine safety concerns among African American, Mexican American, and non-Hispanic white women, *Patient Educ. Couns.* 99 (2021) 147–153, <https://doi.org/10.1016/j.pec.2015.08.016>.
- [7] M.B. Moran, J.S. Chatterjee, L.B. Frank, S.T. Murphy, N. Zhao, N. Chen, S. Ball-Rokeach, Individual, cultural and structural predictors of vaccine safety confidence and influenza vaccination among Hispanic female subgroups, *J. Immigr. Minor. Health* 19 (2017) 790–800, <https://doi.org/10.1007/s10903-016-0428-9>.
- [8] World Health Organization, Global Manual on Surveillance of Adverse Events following Immunization. https://apps.who.int/iris/bitstream/handle/10665/206144/9789241507769_eng.pdf, 2016.
- [9] M.G. Thompson, J.L. Burgess, A.L. Naleway, H.L. Tyner, S.K. Yoon, J. Meece, L.E. W. Olsho, A.J. Caban-Martinez, A. Fowlkes, K. Lutrick, J.L. Kuntz, K. Dunnigan, M. J. Odean, K.T. Hegmann, E. Stefanski, L.J. Edwards, N. Schaefer-Solle, L. Grant, K. Ellingson, H.C. Groom, T. Zunie, M.S. Thiese, L. Ivacic, M.G. Wesley, J. M. Lambert, X. Sun, M.E. Smith, A.L. Phillips, K.D. Groover, Y.M. Yoo, J. Gerald, R.T. Brown, M.K. Herring, G. Joseph, S. Beitel, T.C. Morrill, J. Mak, P. Rivers, K. M. Harris, D.R. Hunt, M.L. Arvay, P. Kutty, A.M. Fry, M. Gaglani, Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers — Eight U.S. Locations, December 2020–March 2021, *MMWR Morb. Mortal. Wkly Rep.* 70 (2021), <https://doi.org/10.15585/mmwr.mm7013e3>.
- [10] N. Dagan, N. Barda, E. Kepten, O. Miron, S. Perchik, M.A. Katz, M.A. Hernán, M. Lipsitch, B. Reis, R.D. Balicer, BNT162b2 mRNA Covid-19 vaccine in a Nationwide mass vaccination setting, *N. Engl. J. Med.* (2021), <https://doi.org/10.1056/NEJMoa2101765>.
- [11] S.I. Valdés-Ferrer, A. Benkendorf, R. Sankowski, Persistent inflammatory states and their implications in brain disease, *Curr. Opin. Neurol.* 33 (2020) 341–346, <https://doi.org/10.1097/WCO.0000000000000809>.
- [12] C. Hervé, B. Laupèze, G. Del Giudice, A.M. Didierlaurent, F. Tavares Da Silva, The how's and what's of vaccine reactivity, *NPJ Vaccines.* 4 (2019) 39, <https://doi.org/10.1038/s41541-019-0132-6>.
- [13] R. Sankowski, S. Mader, S.I. Valdés-Ferrer, Systemic inflammation and the brain: novel roles of genetic, molecular, and environmental cues as drivers of neurodegeneration, *Front. Cell. Neurosci.* 9 (2015) 28, <https://doi.org/10.3389/fncel.2015.00028>.
- [14] J. Matschke, M. Lütgehetmann, C. Hagel, J.P. Sperhake, A.S. Schröder, C. Edler, H. Mushumba, A. Fitzek, L. Allweiss, M. Dandri, M. Dottermusch, A. Heinemann, S. Pfeifferle, M. Schwabenland, D. Sumner Magruder, S. Bonn, M. Prinz, C. Gerloff, K. Püschel, S. Krasemann, M. Aepfelbacher, M. Glatzel, Neuropathology of patients with COVID-19 in Germany: a post-mortem case series, *Lancet Neurol.* 19 (2020) 919–929, [https://doi.org/10.1016/S1474-4422\(20\)30308-2](https://doi.org/10.1016/S1474-4422(20)30308-2).
- [15] I.H. Solomon, E. Normandin, S. Bhattacharyya, S.S. Mukerji, K. Keller, A.S. Ali, G. Adams, J.L. Hornick, R.F. Padera, P. Sabeti, Neuropathological features of COVID-19, *N. Engl. J. Med.* 383 (2020) 989–992, <https://doi.org/10.1056/NEJMc2019373>.
- [16] M. Hepburn, N. Mullaguri, P. George, S. Hantus, V. Punia, A. Bhimraj, C.R. Newey, Acute symptomatic seizures in critically ill patients with COVID-19: is there an association? *Neurocrit. Care.* 34 (2021) 139–143, <https://doi.org/10.1007/s12028-020-01006-1>.
- [17] N.E. Verbeek, F.E. Jansen, P.E. Vermeer-de Bondt, C.G. de Kovel, M.J.A. van Kempen, D. Lindhout, N.V.A.M. Knoers, N.A.T. van der Maas, E.H. Brilstra, Etiologies for seizures around the time of vaccination, *Pediatrics.* 134 (2014) 658–666, <https://doi.org/10.1542/peds.2014-0690>.
- [18] A.T. Kawai, L. Li, M. Kulldorff, C. Vellozzi, E. Weintraub, R. Baxter, E.A. Belongia, M.F. Daley, S.J. Jacobsen, A. Naleway, J.D. Nordin, G.M. Lee, Absence of associations between influenza vaccines and increased risks of seizures, Guillain-Barré syndrome, encephalitis, or anaphylaxis in the 2012–2013 season, *Pharmacoepidemiol. Drug Saf.* 23 (2014) 548–553, <https://doi.org/10.1002/pds.3575>.
- [19] C. Alva-Díaz, A. Navarro-Flores, O. Rivera-Torres, A. Huerta-Rosario, R. A. Molina, V. Velásquez-Rimachi, C. Morán-Mariños, C. Farroñay, J. Pacheco-Mendoza, T. Metcalfe, J.G. Burneo, K. Pacheco-Barrios, Prevalence and incidence of epilepsy in Latin America and the Caribbean: A systematic review and meta-analysis of population-based studies, *Epilepsia* (2021), <https://doi.org/10.1111/epi.16850>.
- [20] N. Shahrizaia, H.C. Lehmann, S. Kuwabara, Guillain-Barré syndrome, *Lancet* 397 (2021) 1214–1228, [https://doi.org/10.1016/S0140-6736\(21\)00517-1](https://doi.org/10.1016/S0140-6736(21)00517-1).
- [21] M. Fragieli, Ö. Miró, P. Llorens, S. Jiménez, P. Piñera, G. Burillo, A. Martín, F. J. Martín-Sánchez, E.J. García-Lamberechts, J. Jacob, A. Alquézar-Arbé, R. Juárez, B. Jiménez, R. Del Río, M. Mateo Roca, A.H. García, N. López Laguna, M.P. Lopez Diez, J. Pedraza García, A. Fernández de Simón Almela, J.J. Lopez Diaz, P. Eiroa Hernández, N. Ruiz de Lobera, J. Porta-Etessam, C. Fernández Pérez, E. Calvo, J. González Del Castillo, SIESTA (Spanish Investigators in Emergency Situations Team) network, Incidence, clinical, risk factors and outcomes of Guillain-Barré in Covid-19, *Ann. Neurol.* 89 (2021) 598–603, <https://doi.org/10.1002/ana.25987>.
- [22] G. Toscano, F. Palmerini, S. Ravaglia, L. Ruiz, P. Invernizzi, M.G. Cuzzoni, D. Franciotta, F. Baldanti, R. Daturi, P. Postorino, A. Cavallini, G. Micieli, Guillain-Barré syndrome associated with SARS-CoV-2, *N. Engl. J. Med.* 382 (2020) 2574–2576, <https://doi.org/10.1056/NEJMc2009191>.
- [23] R. Baxter, N. Bakshi, B. Fireman, E. Lewis, P. Ray, C. Vellozzi, N.P. Klein, Lack of association of Guillain-Barré syndrome with vaccinations, *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* 57 (2013) 197–204, <https://doi.org/10.1093/cid/cit222>.
- [24] Y. Chen, J. Zhang, X. Chu, Y. Xu, F. Ma, Vaccines and the risk of Guillain-Barré syndrome, *Eur. J. Epidemiol.* 35 (2020) 363–370, <https://doi.org/10.1007/s10654-019-00596-1>.
- [25] A. McGrogan, G.C. Madle, H.E. Seaman, C.S. de Vries, The epidemiology of Guillain-Barré syndrome worldwide, . A systematic literature review, *Neuroepidemiology* 32 (2009) 150–163, <https://doi.org/10.1159/000184748>.
- [26] C. Simas, N. Munoz, L. Arregoces, H.J. Larson, HPV vaccine confidence and cases of mass psychogenic illness following immunization in Carmen de bolivar, Colombia, *Hum. Vaccines Immunother.* 15 (2019) 163–166, <https://doi.org/10.1080/21645515.2018.1511667>.
- [27] F. Momplaisir, N. Haynes, H. Nkwihoreze, M. Nelson, R.M. Werner, J. Jemmett, Understanding drivers of COVID-19 vaccine hesitancy among blacks, *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* (2021), <https://doi.org/10.1093/cid/ciab102>.
- [28] A.A. Dror, N. Eisenbach, S. Taiber, N.G. Morozov, M. Mizrahi, A. Zigran, S. Strouji, E. Sela, Vaccine hesitancy: the next challenge in the fight against COVID-19, *Eur. J. Epidemiol.* 35 (2020) 775–779, <https://doi.org/10.1007/s10654-020-00671-y>.
- [29] M.S. Gold, N.E. MacDonald, C.M. McMurtry, M.R. Balakrishnan, U. Heining, L. Menning, O. Benes, R. Pless, P.L.F. Zuber, Immunization stress-related response - redefining immunization anxiety-related reaction as an adverse event following immunization, *Vaccine.* 38 (2020) 3015–3020, <https://doi.org/10.1016/j.vaccine.2020.02.046>.
- [30] C.M. McMurtry, Managing immunization stress-related response: a contributor to sustaining trust in vaccines, *Can. Commun. Dis. Rep. Relevé Mal. Transm. Au Can.* 46 (2020) 210–218, <https://doi.org/10.4745/ccdr.v46i06a10>.
- [31] KFF COVID-19 Vaccine Monitor, December 2020, <https://www.kff.org/coronavirus-covid-19/report/kff-covid-19-vaccine-monitor-december-2020/>, 2021 (accessed February 27, 2021).
- [32] I.F. Cook, Sexual dimorphism of humoral immunity with human vaccines, *Vaccine.* 26 (2008) 3551–3555, <https://doi.org/10.1016/j.vaccine.2008.04.054>.
- [33] R. Shepherd, A.S. Cheung, K. Pang, R. Saffery, B. Novakovic, Sexual dimorphism in innate immunity: the role of sex hormones and epigenetics, *Front. Immunol.* 11 (2020) 604000, <https://doi.org/10.3389/fimmu.2020.604000>.
- [34] S.L. Klein, K.L. Flanagan, Sex differences in immune responses, *Nat. Rev. Immunol.* 16 (2016) 626–638, <https://doi.org/10.1038/nri.2016.90>.
- [35] S. Fischinger, C.M. Boudreau, A.L. Butler, H. Streeck, G. Alter, Sex differences in vaccine-induced humoral immunity, *Semin. Immunopathol.* 41 (2019) 239–249, <https://doi.org/10.1007/s00281-018-0726-5>.
- [36] L.S. Morales, M. Lara, R.S. Kington, R.O. Valdez, J.J. Escarce, Socioeconomic, cultural, and behavioral factors affecting Hispanic health outcomes, *J. Health Care Poor Underserved* 13 (2002) 477–503, <https://doi.org/10.1177/104920802237532>.