





BRIEF COMMUNICATION

Seizures following COVID-19 vaccination in Mexico: A nationwide observational study

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Abstract

The COVID-19 pandemic led to the development and emergency approval of an array of effective vaccines against SARS-CoV-2. Given the relatively small number of patients included in vaccine trials, postapproval epidemiological surveillance is crucial to detect infrequent vaccine-related adverse events. We conducted a nationwide retrospective descriptive study evaluating the incidence of seizures among recipients of SARS-CoV-2 vaccines in Mexico from December 24, 2020 (date of administration of first doses nationwide) to October 29, 2021. Among 81 916 351 doses of any vaccine that were administered, we documented seizures in 53 patients, of which 31 (60%) were new onset seizures. The incidence rate of seizures per million doses was highest for mRNA-1273 (Moderna) with 2.73 per million, followed by BNT162b2 (Pfizer-BioNTech) with 1.02 per million, and Ad5-nCoV (CanSino) with 1.01 per million. Thus, we found that seizures following SARS-CoV-2 vaccination are exceedingly rare events.

Isaac Núñez and Miguel García-Grimshaw contributed equally to this work as first authors

Antonio Arauz, Sergio Iván Valdés-Ferrer, and Laura E. Hernández-Vanegas contributed equally to this work as senior authors.

KEYWORDS

COVID-19, epilepsy, SARS-CoV-2 vaccines, seizures

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic triggered multinational collaborative research efforts to develop effective vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), its etiological agent.¹ Due to the global burden of COVID-19, several countries and regulatory agencies granted emergency approval for their use with preliminary data (e.g., a single randomized trial, preprint data, or even data based on the preliminary results presented at a press conference).¹⁻³ Although efficacy can undoubtedly be assessed with a single randomized trial, serious or unsolicited adverse events following immunization (AEFI) cannot be thoroughly documented due to the small number of patients included in these trials compared to the number of persons who will be vaccinated.⁴⁻⁶ As the number of people needing vaccination includes every human being on earth, postapproval epidemiological surveillance remains critical to detect potential AEFI. Health agencies constantly monitor AEFI occurring among recipients of these novel vaccines to promptly identify events not detected during clinical trials.⁵ The General Board of Epidemiology, part of the Mexican Health Ministry, monitors AEFI among recipients of SARS-CoV-2 vaccines. During the study period, seven vaccines (BNT162b2, mRNA-1273, ChAdOx1 nCov-19, rAd26-rAd5, Ad5-nCoV, Ad26.COV2-S, CoronaVac) were utilized after being granted emergency approval by the Mexican Ministry of Health.

Neurologic AEFI have been reported with most of the available SARS-CoV-2 vaccines.^{7,8} Perhaps the most representative example is cerebral venous sinus thrombosis due to vaccine-induced thrombotic thrombocytopenia among ChAdOx1 nCov-19 recipients, which caused some countries to pause its use.⁹ Our group previously reported a low risk for serious neurologic AEFI among recipients of six different vaccines.¹⁰⁻¹² Seizure reports have been mostly anecdotal, and seizure risk has not been thoroughly examined. The International League Against Epilepsy recommends that persons with epilepsy should be routinely vaccinated, as no conclusive evidence exists suggesting that these vaccines may increase the risk of seizure.¹³ Here, we report the incidence of seizures among COVID-19 vaccine recipients in Mexico, as well as their clinical characteristics and outcomes.

2 | MATERIALS AND METHODS

We conducted a nationwide retrospective descriptive study evaluating the incidence of seizures among recipients of any COVID-19 vaccine dose in Mexico from December 24, 2020 (when vaccines were rolled out nationwide) to October 29, 2021. We used official databases provided by the Mexican Ministry of Health of all reported AEFI during the study period. The study protocol was reviewed and approved by the ethics and research committees of the Salvador Zubirán National Institute of Medical Sciences and Nutrition (NER-3903-21-23-1). As the study was observational, relied on an anonymized database, and involved no contact between investigators and patients, no informed consent was required.

The Mexican Ministry of Health documents AEFI through a passive epidemiological surveillance system in which local health authorities, private or public hospitals, and physicians submit reports of possible adverse events. According to the World Health Organization, AEFI are considered *serious* if they put life in imminent danger, require or prolong in-hospital treatment, lead to persistent or significant disability or death, or cause in utero malformations; otherwise, they are considered *nonserious*.⁵

Operational details on the Mexican Epidemiological System and ad hoc committee evaluation protocols have been described elsewhere.^{10,11} In this report, we included patients who developed new onset or recurrent seizures within the first 30 days following immunization.

2.1 | Data collection and definitions

The total number of administered doses nationwide of each vaccine was obtained from the Mexican Ministry of Health. Seizures were reported on a continuous basis to the Mexican Epidemiological System as AEFI. The medical team evaluating each patient at the local level discussed individual details with the ad hoc committee via videoconference. Each case was assessed by four neurologists and a neuroradiologist (henceforth referred to as "neurology team") to determine whether data supported an epileptic seizure or an alternative diagnosis. The neuroradiologist aided in evaluating central nervous system (CNS) images, when available. Seizures were classified as acute symptomatic if they occurred at the time of a systemic insult or in close temporal association

(within 7 days) with a documented brain insult. Seizures were considered recurrent if the patient had a previous diagnosis of epilepsy. Status epilepticus was defined as a seizure with duration of ≥ 5 min or two seizures with no recovery of consciousness between them.¹⁴ Stroke and CNS infections were diagnosed and reported by the team that reported the AEFI and subsequently confirmed or refuted by the neurology team. Whenever available, additional data (i.e., ambulance files, eyewitness narratives, etc.) were incorporated into the individual analysis.

2.2 | Statistical analysis

Categorical variables are presented as frequencies with proportions, and continuous variables are reported as median with interquartile range (IQR) or as minimum–maximum range as deemed appropriate. We calculated the incidence rate for seizures following each vaccine per 1 000 000 administered doses. For patients with multiple seizures after vaccination, we only counted the first one for incidence calculations. We calculated 95% confidence intervals for these proportions using the Wilson score interval method. All statistical analyses were performed with R version 4.1.2.

3 | RESULTS

During the study period, 81 916 351 vaccine doses were administered; in this cohort, 53 patients with seizures were reported to the federal authorities, and therefore evaluated by the ad hoc committee. Of these, 31 (60%) were new onset seizures. Clinical and sociodemographic characteristics among seizure cases classified by history of epilepsy are shown in Table 1. Median age was 36 years (IQR = 25 to 49 years), and most seizures occurred in women ($n = 29$, 54.7%). Median time to seizure was 19 h, and 75% occurred in the first day after vaccination. Additionally, median time to seizure was 18 h (IQR = 30 min to 24 h) in those with no underlying trigger and 24 h (IQR = 24 h to 8 days) in those with a potential cause. Status epilepticus occurred in 10 cases (18.9%), and the median number of seizures was one. The most common triggers were stroke and CNS infections, each documented in seven (13.2%) cases. Among those with CNS infections, the microorganism could not be determined for any of them, and the diagnoses were made based on cerebrospinal fluid with inflammatory characteristics in the appropriate clinical context. Of these patients, in only two did the neurology team have reasonable suspicion of an autoimmune cause. However, the treating hospitals did not have the capability to perform antibody testing. Additionally, two patients

TABLE 1 Clinical and sociodemographic characteristics of patients with post-COVID-19 vaccine seizures

Variable	New onset seizures	History of epilepsy	All patients
Number of patients, <i>n</i> (%)	31 (60)	22 (40)	53 (100)
Age, years, median (IQR)	34 (25–47)	38.5 (30–51)	36 (25–49)
Female sex, <i>n</i> (%)	15 (48.4)	14 (63.6)	29 (54.7)
Vaccine, <i>n</i> (%)	-	-	-
ChAdOx1 nCov-19	12 (38.7)	9 (40.9)	21 (39.6)
Ad5-nCoV	2 (6.5)	1 (4.5)	3 (5.7)
mRNA-1273	2 (6.5)	2 (9.1)	4 (7.5)
BNT162b2	10 (32.3)	7 (31.8)	17 (32.1)
CoronaVac	2 (6.5)	2 (9.1)	4 (7.5)
rAd26-rAd5	3 (9.7)	1 (4.5)	4 (7.5)
Previous diagnosis of COVID-19, <i>n</i> (%)	1 (3.2)	1 (4.5)	2 (3.8)
Number of seizures, median (IQR)	1 (1–2)	3 (1–5)	2 (1–3)
Time to first seizure, h, median (IQR)	24 (6.3–60)	0.3 (0.08–24)	19 (0.16–24)
Status epilepticus, <i>n</i> (%)	4 (12.9)	6 (27.3)	10 (18.9)
Stroke, <i>n</i> (%)	7 (22.6)	0 (0)	7 (13.2)
CNS infection, <i>n</i> (%)	7 (22.6)	0 (0)	7 (13.2)
Length of hospital stay, median (IQR), days	5 (1–14)	1 (1–1)	1 (1–11)
Deaths	4 (12.9)	0 (0)	4 (7.5%)

Abbreviations: CNS, central nervous system; IQR, interquartile range. Ad26.COV2-S is not included as no seizures were reported with this vaccine.

TABLE 2 Incidence rate of seizures following a COVID-19 vaccine per million doses

Vaccine	Total applied doses	Total reported events	Seizures per million doses	Total reported events [only patients with no other explanation] ^a	Seizures per million doses [only patients with no other explanation] ^a
All vaccines	81 916 351	53	0.64 (0.49–0.85)	18	0.22 (0.14–0.35)
mRNA-1273 (Moderna)	2 318 057	4	1.73 (0.67–4.44)	2	0.86 (0.24–3.15)
BNT162b2 (Pfizer-BioNTech)	16 646 623	17	1.02 (0.64–1.64)	6	0.36 (0.17–0.79)
Ad5-nCoV (CanSino)	2 979 697	3	1.01 (0.34–2.96)	0	0
rAd26-rAd5 (Sputnik V)	5 812 864	4	0.69 (0.27–1.77)	2	0.34 (0.09–1.25)
ChAdOx1 nCov-19 (AstraZeneca-Oxford)	38 516 372	21	0.55 (0.36–0.83)	7	0.18 (0.09–0.38)
CoronaVac (Sinovac)	14 532 954	4	0.28 (0.11–0.71)	1	0.07 (0–0.39)

Note: Shown in parentheses are 95% confidence intervals.

^aThis excludes patients with previous seizures, documented stroke, or central nervous system infection as competing causes for the seizures. Ad26.COVID-S is not included as no seizures were reported with this vaccine.

with CNS infections received new diagnoses of human immunodeficiency virus infection during the index hospitalization.

By October 2021, the total applied doses by vaccine type were as follows: 16 646 623 of BNT162b2, 38 516 372 of ChAdOx1 nCov-19, 5 812 864 of rAd26-rAd5, 14 532 954 of CoronaVac, 2 979 697 of Ad5-nCoV, 1 035 859 of Ad26.COVID-S, and 2 318 057 of mRNA-1273. ChAdOx1 nCov-19 was the most commonly implicated vaccine with 21 cases (39.6%), followed by BNT162b2 with 17 cases (32.1%), and mRNA-1273, CoronaVac, and rAd26-rAd5 with four cases each (7.5%). The observed incidence rate for all vaccines was 0.64 seizures per million doses. The incidence rate was highest for mRNA-1273 with 2.73 per million doses, followed by BNT162b2 with 1.02 per million doses, and Ad5-nCoV with 1.01 per million doses (Table 2). There were only 31 events of new onset seizures, which were associated with ChAdOx1 nCov-19, the vaccine with the highest incidence rate of 0.55 per million doses. No seizures were reported for Ad26.COVID-S.

4 | DISCUSSION

After approval of vaccines and other interventions is granted by regulatory agencies, large-scale epidemiological surveillance of adverse events is crucial to understand their effectiveness and safety.⁵ The emergency approval of vaccines makes this especially important, given that infrequent AEFI may be underestimated due to the relatively small number of administered doses in clinical trials.⁵ Although numerous studies exist in which neurological complications such as stroke, transverse myelitis, and Guillain-Barré syndrome are described in the context of

COVID-19 vaccination, seizures among anti-SARS-CoV-2 vaccine recipients had been only documented in a few case reports.^{10–12,15,16}

In this study, analyzing >80 million administered doses, we found that seizures as a potential AEFI are extremely infrequent after administration of any COVID-19-directed vaccine. When excluding patients with history of epilepsy and with a competing cause for seizures, the events are even rarer, with fewer than two cases per million doses for any given vaccine. Seizure prevalence in Latin America varies according to geographic area and ranges from 3.9 to 42.2 per 1000 persons.¹⁷ Meanwhile, incidence of unprovoked seizures has been reported to be of 23–61 per 100 000 person-years.^{18,19} Although not directly comparable with these estimates, the extremely low incidence observed in our study does not suggest causality between COVID-19 vaccination and seizures. Additionally, although the mRNA-1273 vaccine had the highest point estimate of incidence rate, considerable overlap occurred in the confidence intervals of all vaccines. Thus, we cannot conclusively determine which vaccine had the highest seizure incidence.

To our knowledge, this is the first country-wide study describing the incidence of seizures after COVID-19 vaccine administration. We found several studies that aimed to describe COVID-19 vaccination among individuals with epilepsy, but none that evaluated seizures after vaccination in general.^{20,21} However, our study also has several limitations. The first results from the passive nature of the Mexican epidemiological surveillance system, in which reports rely on local health care authorities or providers. Given that it is a passive surveillance system, sensitivity is likely suboptimal. However, as an evaluation performed by a neurology team was included, specificity is likely

very high. Thus, our numbers may underestimate seizures following vaccination. Second, events that do not present as a stereotyped seizure may be hard to diagnose and easy to confuse with other entities, such as syncope. This means we may be documenting only the most overt of seizures, which may also imply underestimating seizure risk. We also do not have information on previous seizure frequency among patients with epilepsy, so we cannot assess whether improvement or deterioration presented after vaccination. Additionally, we do not know whether people with new onset seizures had recurring events after the study period. Finally, not all patients had complete or standardized seizure workup, given the variability of real-world clinical practice and hospital resources. Therefore, obscure causes of seizures, such as autoimmune encephalitis, or other seizure-inducing neurologic AEFI, may have been missed. However, after billions of SARS-CoV-2 vaccine doses applied worldwide, potential secondary causes of seizure remain anecdotal (including autoimmune encephalitis, posterior reversible encephalopathy, and demyelinating diseases, to name a few).

In conclusion, seizures are exceedingly rare AEFI to SARS-CoV-2 vaccines. Most of the events occurred in persons who had a history of seizures or had a concurring competing event as an explainable cause. Less than half of reported seizures had no other explainable cause. The infrequency of seizures observed and the limited data on background seizure incidence do not allow us to conclude that an increased risk of seizures exists after SARS-CoV-2 vaccination.

AUTHOR CONTRIBUTIONS

Isaac Núñez: Conceptualization (lead), writing—original draft (lead), formal analysis (lead), writing—review and editing (equal). Miguel García-Grimshaw: Conceptualization (lead), writing—original draft (lead), formal analysis (lead), writing—review and editing (equal). Carlos Yoel Castillo Valencia: Data curation (supporting). Daniel Eduardo Aguilera Callejas: Data curation (supporting). Mónica Libertad Moya Alfaro: Data curation (supporting). María del Mar Saniger-Alba: Resources (equal), project administration (equal). Alonso Gutiérrez-Romero: Resources (equal), project administration (equal). Roger Carrillo-Mezo: Resources (equal), project administration (equal). Santa Elizabeth Ceballos-Liceaga: Resources (equal), project administration (equal). Raúl C. Baptista-Rosas: Resources (equal). Hugo López-Gatell: Resources (equal), project administration (equal). Gustavo Reyes-Terán: Resources (equal), project administration (equal). Jose Luis Díaz-Ortega: Resources (equal), project administration (equal). Antonio Arauz: Supervision (equal). Sergio Iván Valdés-Ferrer: Supervision (equal), writing—review &

editing (equal). Laura E. Hernández-Vanegas: Supervision (equal), writing—review & editing (equal).

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CONFLICT OF INTEREST


None of the authors has any conflict of interest to disclose.


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