RESEARCH ARTICLE

Stroke Among SARS-CoV-2 Vaccine Recipients in Mexico

A Nationwide Descriptive Study

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Abstract

Background and Objectives
Information on stroke among severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines remains scarce. We report stroke incidence as an adverse event following immunization (AEFI) among recipients of 79,399,446 doses of 6 different SARS-CoV-2 vaccines (BNT162b2, ChAdOx1 nCov-19, Gam-COVID-Vac, CoronaVac, Ad5-nCoV, and Ad26.COV2-S) between December 24, 2020, and August 31, 2021, in Mexico.

Methods
This retrospective descriptive study analyzed stroke incidence per million doses among hospitalized adult patients (≥18 years) during an 8-month interval. According to the World Health Organization, AEFIs were defined as clinical events occurring within 30 days after immunization and categorized as either nonserious or serious, depending on severity, treatment, and hospital admission requirements. Acute ischemic stroke (AIS), intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), and cerebral venous thrombosis (CVT) cases were collected through a passive epidemiologic surveillance system in which local health providers report potential AEFI to the Mexican General Board of Epidemiology. Data were captured with standardized case report formats by an ad hoc committee appointed by the Mexican Ministry of Health to evaluate potential neurologic AEFI against SARS-COV-2.

Results
We included 56 patients (31 female patients [55.5%]) for an overall incidence of 0.71 cases per 1,000,000 administered doses (95% CI 0.54–0.92). Median age was 65 years (interquartile range [IQR] 55–76 years); median time from vaccination to stroke (of any subtype) was 2 days (IQR 1–5 days). In 27 (48.2%) patients, the event was diagnosed within the first 24 hours after immunization. The most frequent subtype was AIS in 43 patients (75%; 0.54 per 1,000,000 doses, 95% CI 0.40–0.73), followed by ICH in 9 (16.1%; 0.11 per 1,000,000 doses, 95% CI 0.06–0.22) and SAH and CVT, each with 2 cases (3.6%; 0.03 per 1,000,000 doses, 95% CI 0.01–0.09). Overall, the most common risk factors were hypertension in 33 (58.9%) patients and diabetes in 22 (39.3%). Median hospital length of stay was 6 days (IQR 4–13 days). At discharge, functional outcome was good (modified Rankin Scale score 0–2) in 41.1% of patients; in-hospital mortality rate was 21.4%.

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Glossary

AEFI = adverse event following immunization; **AIS** = acute ischemic stroke; **CVD** = cardiovascular disease; **CVT** = cerebral venous thrombosis; **ICH** = intracerebral hemorrhage; **IQR** = interquartile range; **mRS** = modified Rankin Scale; **SAH** = subarachnoid hemorrhage; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **TOAST** = Trial of ORG 10172 in Acute Stroke Treatment; **VITT** = vaccine-induced immune thrombotic thrombocytopenia; **WHO** = World Health Organization.

Discussion

Stroke is an exceedingly rare AEFI against SARS-CoV-2. Preexisting stroke risk factors were identified in most patients. Further research is needed to evaluate causal associations between SARS-COV-2 vaccines and stroke.

The global burden of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections motivated an unprecedented effort by multiple research groups worldwide to develop effective vaccines against it. Due to the devastating effects of SARS-COV-2, these vaccines received emergency approval after demonstrating efficacy in phase 3 randomized clinical trials with limited information about their potential side effects.[1,2] Therefore, health organizations worldwide faced the challenge of identifying, evaluating, and reporting the potential adverse events following immunization (AEFI) of these newly developed vaccines. Between December 24, 2020, and August 31, 2021, the Mexican Ministry of Health granted emergency approval for the use of 6 SARS-COV-2 vaccines from different manufacturers: BNT162b2 (Pfizer-BioNTech), ChAdOx1 nCov-19 (AstraZeneca-Oxford), Gam-COVID-Vac (Sputnik V), CoronaVac (Sinovac), Ad5-nCoV (CanSino), and Ad26.COV2-S (Janssen-Johnson & Johnson).[3]

Arterial and venous thrombotic events at unusual sites with associated thrombocytopenia have been recently reported with the ChAdOx1 nCov-19 and Ad26.COV2-S vaccines,[4-8] including acute ischemic stroke (AIS) and cerebral venous thrombosis (CVT) cases.[9-12] According to the World Health Organization (WHO) Global Database for Individual Case Safety Reports (VigiBase), between December 13, 2020, and March 16, 2021, a total of 361,734,967 doses of any of the available vaccines were applied worldwide; during that interval, 795 venous and 1,374 arterial thrombotic events were reported.[13] In the United States, the Vaccine Adverse Event Reporting System reported that by March 2, 2021, a total of 51,755,447 vaccines doses were applied with 9,442 AEFI reports, including 17 strokes.[14]

Here, from a nationwide registry of severe neurologic AEFI in Mexico, we aim to report the incidence of acute stroke among recipients of 79,399,446 doses of the 6 different vaccines against SARS-COV-2 approved and in use during the study interval; we also evaluate the presence of well-known cardiovascular disease (CVD) risk factors and clinical outcomes at hospital discharge.

Methods

Study Design and Population

We conducted a nationwide retrospective descriptive study evaluating the incidence of stroke among recipients of the BNT162b2, ChAdOx1 nCov-19, Gam-COVID-Vac, CoronaVac, Ad5-nCoV, and Ad26.COV2-S vaccines in Mexico between December 24, 2020, and August 31, 2021,[3] using official data provided by the Mexican Ministry of Health. We included only confirmed stroke cases presenting within the first 30 days after vaccination and excluded those with an alternate diagnosis explaining the acute neurologic deficit or those in whom neuroimaging studies suggested alternative diagnoses. All patients with stroke were followed up until hospital discharge.

The Mexican Ministry of Health monitors and collects information on all AEFI through a passive epidemiologic surveillance system, including no less than 23,300 public and private medical units distributed across the country. Due to the passive nature of this system, events are reported by the health institution, by the attending physician, or directly by the recipient to the local or state health authorities; the last reports all cases to the General Board of Epidemiology, which is the governmental institution responsible for processing and obtaining follow-up information on each serious AEFI every 24 hours.[15,16]

Mexico started its vaccination program against SARS-CoV2 on December 24, 2020. Within days, the surveillance system detected a suspicious cluster of potentially serious neurologic AEFIs; hence, the Mexican Ministry of Health appointed an ad hoc committee consisting of 5 experienced neurologists and a neuroradiologist (all of them authors of this article and reviewers of the collected data) to perform a thorough analysis of every potentially serious neurologic AEFI, aiming to establish causality of the events.[15] This committee continuously evaluates the clinical data, imaging studies, and evolution of each serious neurologic AEFI case through virtual sessions carried out 3 times a week with direct interaction with the attending physicians of each patient.

Standard Protocol Approvals, Registrations, and Patient Consents

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. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.[17]

Definitions of AEFIs

AEFIs were defined according to the WHO operational definition,[18] which includes all events potentially attributable to immunization occurring in the first 30 days after vaccination; those events are classified as nonserious or serious. Nonserious AEFIs are those meeting the following criteria: (1) do not pose an imminent risk of death, (2) do not require hospitalization, (3) disappear with or without symptomatic treatment, and (4) do not cause long-term disability such as local (e.g., injection-site pain, swelling, rash, or local infections treated on an outpatient basis) or systemic (e.g., headache, fever, malaise, diarrhea, muscle or joint pain) events. Serious AEFIs are those presenting with any clinical manifestation meeting 1 or more of the following criteria: (1) put life in imminent danger, (2) require or prolong in-hospital treatment, (3) lead to persistent or significant disability, (4) lead to death, or (5) in the case of pregnant women, cause in utero malformations. If presenting within the proposed time frame by the WHO, serious neurologic AEFIs may include cases of stroke, Guillain-Barré syndrome, acute transverse myelitis, and acute disseminated encephalomyelitis, to name a few. However, in all, causality must be determined after the exclusion of other potential etiologies.

Stroke Case and Outcome Definitions

Stroke subtypes were classified according to the American Heart Association/American Stroke Association updated definition of stroke.[19] AIS was defined as the presence of an acute neurologic deficit lasting >24 hours and confirmed by head CT scan, MRI, or both. If AIS was diagnosed, putative etiologies were stratified according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification.[20] Intracerebral hemorrhage (ICH) was defined as bleeding into the brain parenchyma and classified as hypertensive or traumatic. Subarachnoid hemorrhage (SAH) was defined as the extravasation of blood into the subarachnoid space between the pial and arachnoid membranes and classified as aneurysmal or not. CVT was defined as the presence of a thrombus in the cerebral veins, sinuses, or both. Functional outcomes at hospital discharge were measured with the modified Rankin Scale (mRS) and further classified as good (mRS score 0–2), poor (mRS score 3–5), or fatal (mRS score 6).[21]

Data Collection

Deidentified data were collected and entered into a secure online database with the use of standardized stroke case report formats filled in and reviewed by at least 2 members (researchers) of the aforementioned ad hoc committee during the virtual sessions, one of them an experienced stroke neurologist (A.A), and a third member adjudicated for any differences between the primary reviewers. Data collection included demographic (age and sex) information; history of CVD risk factors (hypertension, diabetes, obesity, smoking, and end-stage chronic kidney disease); history of any cardiac heart disease (e.g., atrial fibrillation or patent foramen ovale); history or concomitant SARS-CoV-2 infection; type of administered vaccine and in the case of 2-dose vaccine regimen the number of doses received; interval in days between vaccine administration and stroke symptom onset; platelet count; stroke treatments such as thrombolysis, thrombectomy, and craniectomy; and the functional outcome. The total number of administered doses nationwide of each vaccine for this analysis was obtained from the Mexican Ministry of Health throughout the General Board of Epidemiology.

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 proportion for each stroke subtype per 1,000,000 administered doses; 95% CIs for these proportions were calculated using the Wilson interval method.[22] A statistical power calculation was not performed; instead, all stroke cases were included. Cases with missing data were analyzed and are reported separately. Some percentages may not add up to 100% due to rounding. Statistical analyses were performed with IBM SPSS statistics version 26 (IBM Corp, Armonk, NY). Statistical figures were created with GraphPad Prism, version 9 (GraphPad Software, La Jolla, CA).

Data Availability

The article provides all the collected data. Deidentified data to replicate our results will be available to qualified researchers on written request to the corresponding author.

Results

During the study period, 79,399,446 doses of 6 different SARS-CoV-2 vaccines were administered in Mexico, for which the Mexican Epidemiologic Surveillance System received and processed 28,646 AEFI reports. Among those, 27,968 (98%) were classified as nonserious and 681 (2%) as serious. Sixty-eight patients were initially reported as stroke cases. After evaluation by the ad hoc committee, 5 were excluded due to an alternative diagnosis (1 each: meningioma, peripheral neuropathy, septic shock, sensitive neuropathy, and pneumonia); in 7 patients, the diagnosis of stroke was not supported by imaging, and those patients were therefore excluded, 1 of them a patient with a TIA diagnosis.

Fifty-six patients with confirmed stroke were included for the final analysis (8.2% of all serious AEFIs); 31 (55.5%) were female; median age was 65 years (IQR 55–76 years). Baseline characteristics, CVD risk factors, stroke subtype, and clinical outcome according to the type of vaccine are shown in Table 1. Five patients had a history of SARS-CoV-2 infection, but none tested positive for active infection at stroke onset; in 41 (73.2%), the event occurred after the first vaccine dose. There were no stroke reports with the Ad26.COV2-S vaccine. The overall observed acute stroke incidence was 0.71 cases per 1,000,000 administered doses (95% CI 0.54–0.92). Ad5-nCoV was the vaccine with the highest observed incidence (Table 2).

Stroke Subtypes

The most frequent stroke subtype was AIS in 43 (76.8%) patients (0.54 per 1,000,000 doses; 95% CI 0.40–0.73), followed by ICH in 9 (16.1%; 0.11 per 1,000,000 doses; 95% CI 0.06–0.22) and SAH and CVT in 2 (3.6%) each (0.03 per 1,000,000 doses; 95% CI 0.01–0.09). Unadjusted incidences

Table 1 Baseline Characteristics, Vaccination Details, Stroke Subtypes, and Clinical Outcomes

	ChAdOx1 nCov-19 (n = 23)	BNT162b2 (n = 17)	Gam-COVID-vac (n = 1)	Ad5-nCoV (n = 6)	CoronaVac (n = 9)
Age, median (IQR), y	68 (48–76)	59 (53–67)	82	62 (50–69)	76 (64–86)
Sex, n (%)					
Female	11 (47.8)	11 (64.7)	1 (100)	2 (33.3)	6 (66.7)
Male	12 (52.2)	6 (35.3)	0 (0)	4 (66.7)	3 (33.3)
Medical history, n (%)					
Hypertension	14 (60.9)	7 (41.2)	1 (100)	3 (50)	8 (88.9)
Diabetes	13 (56.5)	5 (29.4)	1 (100)	0 (0)	3 (33.3)
Obesity, BMI ≥30 kg/m^2	2 (8.7)	1 (5.9)	0 (0)	1 (16.7)	0 (0)
Smoking	7 (30.4)	0 (0)	0 (0)	1 (16.7)	1 (11.1)
Atrial fibrillation	3 (13)	4 (23.5)	0 (0)	2 (33.3)	0 (0)
Other heart disease[a]	6 (26.1)	1 (5.9)	0 (0)	0 (0)	0 (0)
End-stage kidney disease	1 (4.3)	0 (0)	0 (0)	0 (0)	0 (0)
Past SARS-CoV-2 infection	0 (0)	2 (11.8)	0 (0)	1 (16.7)	2 (22.2)
Time from immunization to stroke, median (minimum–maximum), d	2 (0–30)	2 (0–30)	0 (0)	1 (0–26)	1 (0–22)
Vaccine dose, n (%)					
First	19 (82.6)	8 (47.1)	0	6 (100)	8 (88.9)
Second	4 (17.4)	9 (52.9)	1 (100)	NA[b]	1 (11.1)
Stroke subtype, n (%)					
Acute ischemic stroke	19 (82.6)	11 (64.7)	1 (100)	6 (100)	6 (66.7)
Intracranial hemorrhage[c]	2 (8.7)	6 (35.3)	0 (0)	0 (0)	3 (33.3)
Cerebral venous thrombosis	2 (8.7)	0 (0)	0 (0)	0 (0)	0 (0)
Length of stay, median (IQR) d	7 (5–13)	6 (4–13)	2 (0)	4 (3–4)	5 (4–13)
Clinical outcomes, n (%)					
Good outcome, mRS score 0–2	8 (34.8)	8 (47.1)	1 (100)	2 (33.3)	4 (44.4)
Poor outcome, mRS score 3–5	11 (47.8)	4 (23.5)	0 (0)	2 (33.3)	4 (44.4)
Death, mRS score 6	4 (17.4)	5 (29.4)	0 (0)	2 (33.3)	1 (11.1)

Abbreviations: BMI = body mass index; IQR = interquartile range; mRS = modified Rankin scale; NA = not applicable; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
Ad26.COV2-S is not included in this table because there were no stroke reports with this vaccine.
[a] Includes 4 patients with ischemic heart disease and heart failure, valvular heart disease, and congenital cardiomyopathy, each in 1 patient.
[b] Ad5-nCoV is a single dose vaccine regimen; the rest are 2-dose vaccine regimens.
[c] Intracranial hemorrhage includes all patients with intracerebral hemorrhage and subarachnoid hemorrhage.

Table 2 Observed Incidence of Any Acute Stroke Subtype Among 6 Different Vaccines Against SARS-COV-2

Vaccine	Total doses, n	Cases, n	Incidence (95% CI)[a]
BNT162b2	24,416,970	17	0.70 (0.43–1.12)
ChAdOx1 nCov-19	29,157,558	23	0.79 (0.53–1.18)
CoronaVac	13,906,520	9	0.65 (0.34–1.23)
Gam-COVID-Vac	4,450,465	1	0.22 (0.04–1.27)
Ad5-nCoV	5,122,301	6	1.17 (0.54–2.56)
Ad26.COV2-S	1,345,632	0	NA
All vaccines	79,399,446	56	0.71 (0.54–0.92)

Abbreviations: NA = not applicable; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
[a] Incidence per 1,000,000 doses administered.

for each stroke subtype according to the different vaccines hereby analyzed are reported in eTables 1 through 3 (links.lww.com/WNL/B867). The median time from vaccination to stroke (of any subtype) was 2 days (IQR 1–5 days; minimum–maximum range 0–30 days), and in 27 (48.2%) patients, the event occurred within the first 24 hours after vaccination. Figure 1 shows the timing of each stroke subtype in weeks. The most common risk factors for all subtypes were hypertension in 33 (58.9%) and diabetes in 22 (39.3%) patients. Overall, the median hospital length of stay was 6 days (IQR 4–13 days); functional outcome at hospital discharge was good for 23 (41.1%) patients and poor for 21 (37.5%). There were 12 in-hospital deaths, for an all-cause mortality rate of 21.4%.

Demographic characteristics, risk factors, acute treatments, and clinical outcomes for the 43 patients with an AIS are shown in eTable 4 (links.lww.com/WNL/B867). Twenty-two (51.1%) of all AISs occurred in male patients. The median age was 67 (54–74) years. According to the TOAST classification, 14 (32.6%) AIS cases were secondary to large artery atherosclerosis; 15 (34.9%) were cardioembolic; 5 (11.6%) were lacunar, and 2 (4.7%) were due to other determined etiology (carotid artery dissection and myeloproliferative syndrome). Seven (16.3%) cases were classified as undetermined etiology (Figure 2). Regarding the treatment of patients with AIS, 3 (6.9%) received IV thrombolytic therapy, 2 (4.7%) were treated by mechanical thrombectomy, and 2 (4.7%) required decompressive craniectomy. The functional outcomes of all patients according to stroke subtype are shown in Figure 3.

Eleven (19.6%) patients developed an intracranial hemorrhage (ICH or SAH): 9 (81.8%) women and 2 (18.2%) men with a median age of 60 years (IQR 57–77 years). Eight cases of ICH (88.9%) were deemed hypertensive, and 1 (11.1%) were due to traumatic brain injury. In all of the patients for whom the mechanism was deemed hypertensive, uncontrolled blood pressure was found at the first evaluation. Among patients with ICH, 1 was treated with craniectomy, 3 died, and 1 was discharged with an mRS score of 5. Of patients with SAH, in 1 patient, an aneurysm was documented, while in the other, the initial approach to determine the etiology was inconclusive. In both patients, the vaccine given was BNT162b2.

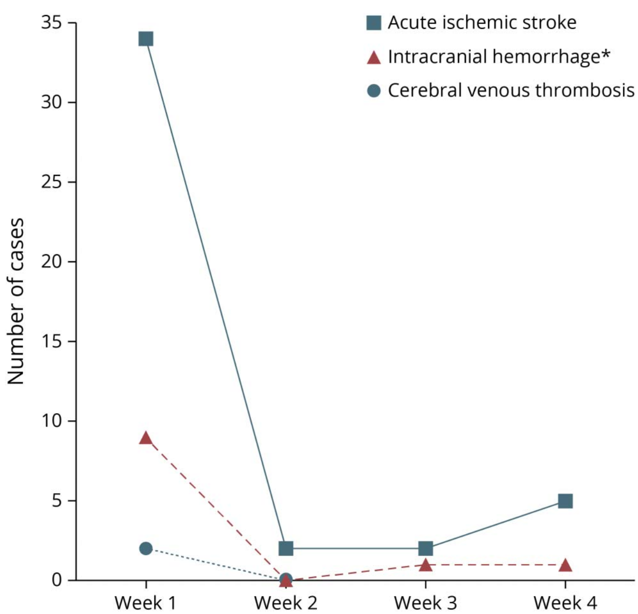
A case of vaccine-induced immune thrombotic thrombocytopenia (VITT) was documented in a 25-year-old pregnant woman; the diagnosis was made 24 hours after immunization with the first dose of ChAdOx1 nCov-19. This patient developed sudden-onset headache and new-onset seizures; thrombocytopenia and anti–platelet factor-4 antibodies were documented. Brain MRI revealed an extensive thrombosis of the superior sagittal sinus; she died 21 days after being diagnosed.

The other CVT case was a 34-year-old man also immunized with the first dose of ChAdOx1 nCov-19. Thrombocytopenia was not detected, and determination of anti–platelet factor-4 antibodies was not performed. This patient presented 24 hours after vaccination with new-onset seizures. A superficial cerebral vein thrombosis was diagnosed by brain MRI. Severe dehydration was found as the only precipitating factor for the event and was treated with warfarin. He evolved favorably and was discharged with an mRS score of 0 at 16 days after admission.

Discussion

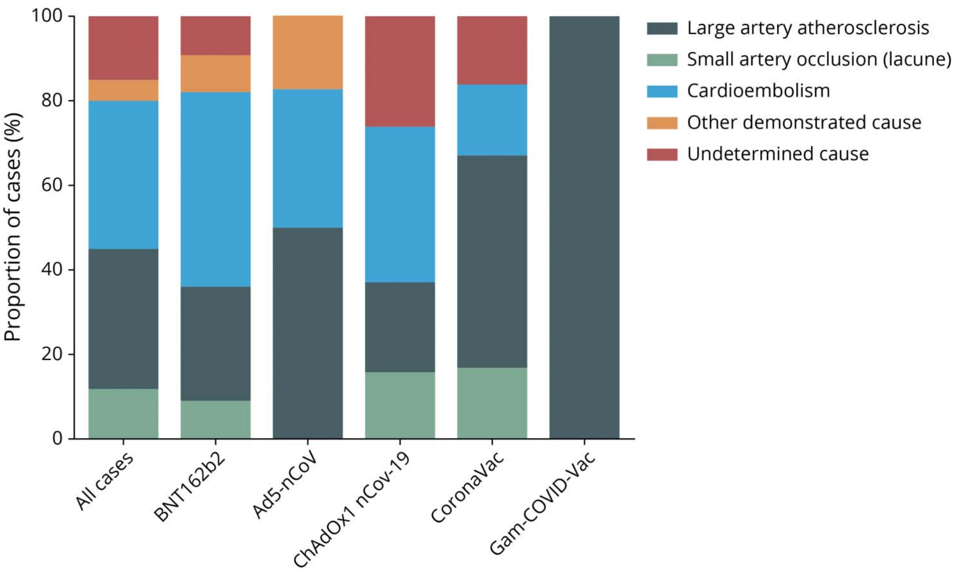
Real-word pharmacovigilance reports are crucial for identifying safety concerns that may not be detected during

Figure 1 Timing From Vaccination to Stroke Onset According to Stroke Subtype



Ad26.COV2-S is not included because there were no stroke reports with this vaccine. *Intracranial hemorrhage includes all patients with intracerebral hemorrhage and subarachnoid hemorrhage.

Figure 2 Acute Ischemic Stroke Etiology According to the TOAST Classification

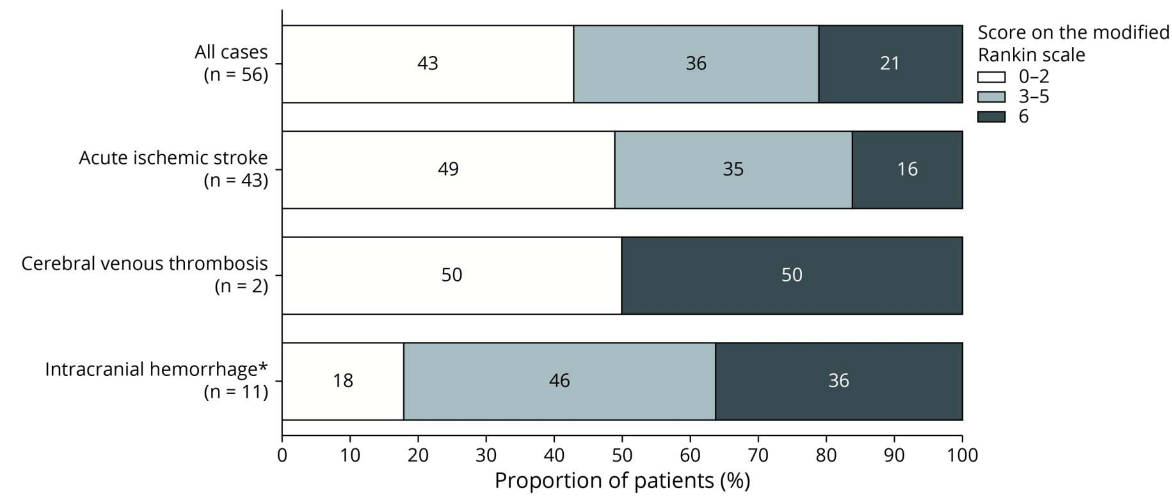


Ad26.COV2-S is not included because there were no stroke reports with this vaccine. TOAST = Trial of ORG 10172 in Acute Stroke Treatment.

vaccine clinical trials, particularly under the time constraints of the ongoing pandemic.[1] In this analysis of passive surveillance monitoring of >79.3 million doses of 6 different vaccines in Mexico, we found only 56 patients with acute stroke (43 with AIS, 9 with ICH, 2 with SAH, and 2 with CVT), suggesting that stroke per se may be an exceedingly rare adverse event of SARS-CoV-2 vaccines. However, in most patients, a stroke etiology was identified, and there was only a temporal relationship with the vaccine. In fact, in only 7 patients with AIS, we were unable to determine a preexisting or concurrent causal etiology, although in 3 of them, the causality study protocol was incomplete.

In a recent study describing 3 patients with AIS following immunization with ChAdOx1 nCoV-19, AIS was associated with large vessel occlusion in all, and in 2 of them, concomitant portal vein thrombosis or CVT was detected, suggesting that immune-mediated coagulopathy may have been mechanistically associated.[9] In our series, except for the fatal case of VITT, we did not find widespread evidence suggestive of coagulopathy, synchronic systemic thrombosis, or thrombocytopenia,

Figure 3 Modified Rankin Scale Score at Hospital Discharge According to Stroke Subtype



Ad26.COV2-S is not included in this figure because there were no stroke reports with this vaccine. *Intracranial hemorrhage includes all patients with intracerebral hemorrhage and subarachnoid hemorrhage.

indicating other potential triggering mechanisms. Although it seems speculative, these patients should likely be studied as having embolic infarcts of undetermined source, something beyond the scope and feasibility of our study that will need to be addressed in future studies.

Skepticism about and hesitancy toward these novel vaccines, mixed with the psychological stressors surrounding the coronavirus disease 2019 pandemic, might trigger AEFIs known as immunization stress-related responses, characterized by anxiety, panic attacks, nonspecific transient sensory symptoms, tachycardia, and transient increases in blood pressure after vaccination.[23-26] Therefore, because most ICH events occurred in patients with hypertension, we hypothesize that transient blood pressure increases resulting from these responses might play a mechanistic role in the rupture of chronically damaged small vessels. Still, the mechanisms for developing this stroke subtype as an AEFI are yet to be elucidated.

Previous reports suggest that many potential external triggers may raise blood pressure, and their concurrence may favor intracranial hemorrhage, particularly in patients with hypertension.[27] In this study, 90% of ICH cases were related to hypertension; in only 1 patient, the event was secondary to trauma. Again, in cases of SAH, the only possible trigger appears to be an increase in blood pressure. SAH cases were temporally coincident with vaccination in our series, with no other pathophysiologic, immunologically mediated explanation leading to aneurysm rupture. A study investigating the prevalence of skin, nose, and gingival bleedings after receiving adenovectored or mRNA vaccines against SARS-CoV-2 reports a higher prevalence of mild bleeding episodes among adenovectored vaccine recipients.[28] Taking those findings into account, we hypothesize that the increased odds for mild bleeding episodes among adeno-vectored vaccine recipients, in combination with transient blood pressure increases, may play a role in the development of intracranial hemorrhages as an AEFI. A potential association could be addressed in future studies.

Compared to the total number of administered ChAdOx1 nCov-19 doses worldwide, only a handful of CVT cases as an AEFI with this vaccine have been reported.[29-31] Here, we report another patient with ChAdOx1 nCov-19–associated VITT. As a result of possible increased risk of CVT and severe thrombocytopenia after Ad26.COV2-S and ChAdOX1 nCov-19, several European countries restricted the use of these vaccines, especially in younger patients.[32,33] However, in low- and middle-income countries, the incidence of VITT may be lower (or underdiagnosed), despite the fact that these countries are more dependent on adenovirus-vectored vaccines, something that will need to be validated or refuted in larger studies.[34-36]

Despite the concerns related to morbidity and mortality with these newly developed vaccines, stroke was a rare AEFI in our series. Moreover, in almost all of our evaluated patients, a stroke cause was found. Although there are several reports of neurologic events associated with the current SARS-CoV-2 vaccines, including all stroke subtypes, currently the risk of stroke associated with SARS-COV-2 (0.8%–1.4%) seems to be much greater than that associated with vaccination.[37-39] Of the AIS cases we detected (eTable 4, links.lww.com/WNL/B867), 80% occurred among first-dose recipients of both mRNA-based and adenovectored vaccines. Some authors have suggested that the neurologic spectrum of VITT may include arterial thrombotic events.[9] However, these events have been reported mostly among recipients of the ChAdOx1 nCoV-19 vaccine,[9,40] and little information exists regarding this stroke subtype among recipients of BNT162b2.[41-43] However, with the present analysis, we are unable to establish causation.

There is still limited information on the absolute risk of stroke after SARS-CoV-2 vaccination. The overall stroke incidence of 0.71 cases per 1,000,000 administered doses we observed seems much lower than the 270.7 cases per 100,000 inhabitants or 27.1 cases per 1,000,000 inhabitants in 2011 reported by the only Mexican epidemiologic study on stroke that exists.[44] However, our results should be taken with caution because the current stroke incidences in our country among the unvaccinated population or those fully vaccinated with a 2-dose regimen are currently unknown.

This report has some limitations. First, interpretation of the study is limited by its descriptive nature and lack of statistical power to establish causality due to the low frequency of stroke we observed. Second, our analysis is prone to selection bias due to the passive nature of the Mexican epidemiologic surveillance system and by the fact that only patients evaluated by the ad hoc committee were included. Third, because AEFI reports rely on local health care providers, some stroke subtypes may be underdiagnosed, particularly minor AIS and CVT cases presenting with mild or nondisabling symptoms or sequelae, as well as those occurring in rural settings, those with limited access to medical services, patients treated at home, or patients for whom medical attention was not sought.[44-46] All of the limitations mentioned above are some of the weaknesses of passive surveillance systems, which are less likely to detect cases than active ones.[47,48] Last, we were unable to analyze strokes according to dose for vaccines requiring a 2-dose regimen.

Our observations suggest that stroke remains an exceedingly rare event among recipients of 6 different vaccines against SARS-CoV-2. Although real-world data analysis is useful to identify potential safety signals requiring further investigation, our results cannot be used to determine causation. Therefore, further research is still needed to analyze the potential causal associations between stroke and the different vaccines against SARS-COV-2 currently available worldwide.

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Appendix (continued)

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