Journal of Clinical Immunology (2022) 42:1593–1599
https://doi.org/10.1007/s10875-022-01350-1

ORIGINAL ARTICLE

Anaphylaxis to SARS-CoV-2 Vaccines in the Setting of a Nationwide Passive Epidemiological Surveillance Program

Carla Toledo-Salinas[1] · Selma Cecilia Scheffler-Mendoza[2] · Lina Maria Castano-Jaramillo[3] · José Antonio Ortega-Martell[4] · Blanca Estela Del Rio-Navarro[5] · Ana María Santibáñez-Copado[6] · José Luis Díaz-Ortega[6] · Raúl Baptista-Rosas[7,8] · Paulina Sánchez-Novoa[9] · Miguel García-Grimshaw[10,11] · Sergio Iván Valdés-Ferrer[10,12] · Gustavo Reyes-Terán[1] · David Alejandro Mendoza-Hernández[2]

Received: 11 May 2022 / Accepted: 12 August 2022 / Published online: 17 August 2022

Abstract

Background Information on anaphylaxis among recipients of vaccines against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains scarce.

Objective To identify the observed incidence of anaphylaxis in recipients of different anti-SARS-CoV-2 vaccines.

Methods A nationwide observational study among recipients of 61,414,803 doses of seven different anti-SARS-CoV-2 vaccines, describing the incidence and characteristics of adult patients (age ≥ 18 years) who developed anaphylaxis as an adverse event following immunization (AEFI) against SARS-CoV-2 vaccines between December 24, 2020, and October 15, 2021, in Mexico.

Results Sixty-six patients developed anaphylaxis as an AEFI, for an overall observed incidence of 1.07 cases per 1,000,000 (95% CI 0.84–1.37) administered doses. Eighty-six percent of the patients were female, consistent with previous reports of AEFI to COVID-19 vaccines. mRNA-based vaccine recipients had the highest frequency of anaphylaxis, followed by adenovirus-vectored vaccines and inactivated virus recipients, with an observed incidence of 2.5, 0.7, and 0.2 cases per 1,000,000 doses administered, respectively. Only 46% of the patients received correct treatment with epinephrine as the first-line treatment through the appropriate route and dose. We detected one case of anaphylactic reaction-related death occurring 5 min following immunization with ChAdOx1 nCov-19 for a mortality rate of 1.5% among those who developed this AEFI.

Conclusions In our population, anaphylactic reactions were infrequent. Our study provides further evidence supporting the security of these newly developed vaccines.

Keywords Anaphylaxis · SARS-CoV-2 vaccines · COVID-19 vaccines · Vaccine safety · Vaccine anaphylaxis

✉ David Alejandro Mendoza-Hernández
drdmendoz@gmail.com

[1] Comisión Coordinadora de Institutos Nacionales de Salud Y Hospitales de Alta Especialidad, Mexico City, Mexico

[2] Instituto Nacional de Pediatría, Insurgentes Sur 3700c, Mexico City, Mexico

[3] Fundación Hospital Pediátrico La Misericordia, Bogota, Colombia

[4] Universidad Autónoma de Hidalgo, Pachuca, Mexico

[5] Hospital Infantil de México Federico Gómez, Mexico City, Mexico

[6] Centro Nacional Para La Salud de La Infancia Y Adolescencia, Mexico City, Mexico

[7] Centro Universitario de Tonalá, Universidad de Guadalajara, Tonala, Mexico

[8] Hospital General de Occidente, Guadalajara, Mexico

[9] Coordinación de Vigilancia Epidemiológica de Las Enfermedades Prevenibles Por Vacunación Y ESAVI de La Dirección General de Epidemiologia, Mexico City, Mexico

[10] Department of Neurology, Instituto Nacional de Ciencias Médicas Y Nutrición Salvador Zubirán, Mexico City, Mexico

[11] Hospital General Tijuana, Tijuana, Mexico

[12] Feinstein Institutes for Medical Research, Manhasset, NY, USA

Introduction

Vaccination is the most effective intervention to reduce the global burden of the coronavirus disease 2019 (COVID-19) pandemic. Mexico provides a unique scenario to evaluate the potential adverse events following immunization (AEFI) against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) since eight different vaccines have been granted emergency approval: BNT162b2, mRNA-1273, ChAdOx1 nCov-19, rAd26-rAd5, Ad5-nCov, CoronaVac, BBV152, and Ad26.COV2-S. [1]

The USA reports an incidence of anaphylactic reactions as an AEFI against SARS-CoV-2 of 4.8 cases per 1,000,000 doses of BNT162b2 and 5.1 cases per 1,000,000 doses of mRNA-1273 [2]. However, information on anaphylactic reactions among recipients of other non-mRNA-based vaccines is scarce [3], either because they are still being studied in phase 3 trials or differences in epidemiological surveillance systems data collection protocols. Here, from a nationwide registry of serious AEFI, we aim to report the incidence of anaphylaxis among recipients of 61,414,803 doses of seven different anti-SARS-CoV-2 vaccines in Mexico since the beginning of the vaccination program from December 2020 to October 2021, according to the database of the National Board of Epidemiology, the federal agency responsible for overseeing COVID-19 immunization nationwide. The first vaccines to be administered were BNT162b2 (for healthcare workers), followed by ChAdOx1 nCov-19 and Ad5-nCov (elderly general population and education workers) during the program's first semester.

Methods

A nationwide observational study describing the incidence and characteristics of adult (age ≥ 18 years) patients who developed anaphylaxis as an AEFI against SARS-CoV-2 during 10 months (December 24, 2020, to October 15, 2021). The cases were officially reported to the Mexican Ministry of Health through a passive epidemiological surveillance system. Diagnosis and reports rely upon physician criteria, collecting data from more than 23,300 private and public medical units across the country. The study was reviewed and approved by the *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán* (registry: NER-3903–21-23–1) Ethics and Research Committees, who waived the need for signed informed consent due to its observational nature. This report was generated according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [4].

Since Mexico started its anti-SARS-CoV-2 vaccination campaign on December 24, 2020, the Ministry of Health appointed multidisciplinary ad hoc committees to evaluate each potentially severe AEFI. The hereby-reported cases were reviewed by an expert-led Allergy and Immunology sub-committee through weekly meetings with each patient's attending physician. Details of these ad hoc committees and the Mexican epidemiological surveillance system protocols have been published elsewhere [5–7]. We included patients with reports of anaphylaxis evaluated by the Allergy and Immunology ad hoc committee. Cases with an alternate diagnosis explaining the symptoms were excluded.

Data Collection and Definitions

Data for this report were collected by the ad hoc committee members during the virtual sessions with the patients attending physicians using a standardized case report format and entered into a secure online database. The Allergy and Immunology sub-committee evaluated each case, determined the anaphylaxis diagnostic certainty according to the Brighton Collaboration criteria [8], and assessed the severity according to the Brown grading system [9].

Statistical Analysis

Categorical variables are reported as frequencies and proportions. After testing for normality with the Kolmogorov–Smirnov test, continuous variables are presented as either median with interquartile range (IQR) or mean with standard deviation (SD). We compared the clinical manifestations according to vaccine platforms as mRNA-based (BNT162b2 and mRNA-1273) and other vectors (ChAdOx1 nCov-19, rAd26-rAd5, Ad5-nCov, CoronaVac, BBV152, and Ad26.COV2-S) using the χ^2 or Fisher's exact tests, as appropriate. Observed incidences for each vaccine subtype per 1,000,000 administered doses with 95% confidence intervals (CI) were calculated using the Wilson method [10]. All *p*-values were two-tailed and considered significant with a value < 0.05. Analyses were performed with IBM SPSS Statistics, version 26 (IBM Corp., Armonk, NY, USA).

Results

During the study time frame, 66 patients with anaphylaxis were detected; mean age of 41 ± 11 years; 86% were females (Table 1); for an overall observed incidence of 1.07 cases per 1,000,000 (95% CI 0.84–1.37) administered doses (Table 2). When categorized according to the platform, mRNA (BNT162b2 and mRNA-1273) vaccine recipients had the highest frequency of anaphylaxis, followed

Table 1 Baseline characteristics

Variable	$n=66$
Female sex, *n* (%)	57 (86)
Age, mean (± SD)	41 (11)
History of allergic disease, *n* (%)	46 (70)
Drug allergy	30 (46)
Food allergy	22 (33)
Asthma	12 (18)
Rhinitis or rhinoconjunctivitis	9 (14)
Anaphylaxis	6 (9)
Allergic reaction to the first dose of the COVID-19 vaccine	2 (3)
Allergic reaction to other vaccines	1 (1.5)
Urticaria	1 (1.5)
Comorbidities, *n* (%)	26 (39)
Hypertension	11 (17)
Diabetes	11 (17)
Autoimmune disorders	5 (8)
Obesity	3 (5)
Others	6 (9)
Time from vaccination to reaction, median (IQR), minutes	10 (5–20)
Doses of epinephrine, *n* (%)	
None	13 (19.7)
1	40 (60.6)
2	11 (16.7)
3	1 (1.5)
4	1 (1.5)

Table 2 Unadjusted incidence of anaphylaxis per million doses administered

Vaccine	Number of cases	Doses	Observed incidence (95% CI)*
BNT162b2	35	15,258,253	2.29 (1.65–3.19)
mRNA-1273	6	1,136,468	5.28 (2.42–11.52)
ChAdOx1 nCov-19	13	25,174,907	0.52 (0.30–0.88)
Ad5-nCoV	8	5,902,174	1.36 (0.69–2.67)
rAd26-rAd5	2	3,307,049	0.60 (0.17–2.21)
Ad26.COV2-S	0	1,167,975	0 (0)
CoronaVac	2	9,467,977	0.21 (0.06–0.77)
All vaccines	66	61,414,803	1.07 (0.84–1.37)

Abbreviation: *CI*, confidence interval. *Incidence per 1,000,000 doses administered

by adenovirus-vectored vaccine (ChAdOx1 nCov-19, rAd26-rAd5, and Ad5-nCov) recipients, and inactivated virus (CoronaVac) recipients, with an observed incidence of 2.5, 0.7, and 0.2 cases per 1,000,000 administered doses, respectively. There were no reports of anaphylactic reactions with Ad26.COV2-S and vaccination with BBV152 had not begun at the time of the data collection.

Anaphylaxis cases were reported from 16 out of the 32 states in Mexico, and over half of them (37/66) were from a single state. Over two-fifths of the cases were reported among healthcare workers (44%), mainly nurses (19 patients). Six patients had a history of anaphylaxis, with a median of 1 episode, and two patients had multiple episodes. None of the patients had anaphylaxis reports in the month before vaccination. Thirty-nine percent of patients had other comorbidities; hypertension and diabetes were the most frequent. Most reactions occurred among first-dose recipients (86%), and in 9 (14%) patients, they occurred after the second dose; of the latter, two had reported an allergic reaction to the first dose. The patients did not receive any premedication.

In 59% of patients, reactions occurred within the first 15 min after immunization during the first 15 to 30 min in 24%. The most frequent clinical manifestations were respiratory (94%), cutaneous (71%), and cardiovascular (67%). Figure 1 shows the most frequently reported symptoms. When comparing the clinical manifestations of mRNA-based vaccines to other platforms, there were no statistical differences in cutaneous, gastrointestinal, respiratory, or neurologic manifestations. Cardiovascular manifestations of anaphylaxis were higher among mRNA-based vaccine recipients (Table 3).

According to Brighton Collaboration Criteria, 41% of patients fulfilled a level 1 diagnostic certainty and 44% a level 2. Regarding severity, according to the Brown classification, two-thirds of patients were classified as moderate (Brown 2) and one-third as severe (Brown 3). Three patients even had a history of allergic reactions with the first dose and still received the second dose without a diagnostic approach; two patients developed anaphylaxis to the second dose, and the other one received the second dose using the same platform without any adverse event.

The median time from symptom onset to epinephrine administration was 5 min (IQR 5–11); only 46% of the anaphylaxis treatment had epinephrine as the first-line drug, at an appropriate dose, and through the preferred intramuscular route. Out of the patients who received epinephrine, only 19.7% required multiple doses (Table 1). Furthermore, there was inappropriate route administration of epinephrine, 8% intravenous and 11% subcutaneous. Regarding other non-first-line treatments, systemic corticosteroids were used in 85% and antihistamines in 64%.

Over half of the patients received treatment with two or more drugs, including supplemental oxygen, intravenous fluids, β2 agonists, nebulized epinephrine, and budesonide. Other drugs used as first-line treatments included steroids in one-third of the cases and antihistamines in 8%. Eighty-eight percent of patients required in-hospital supervised

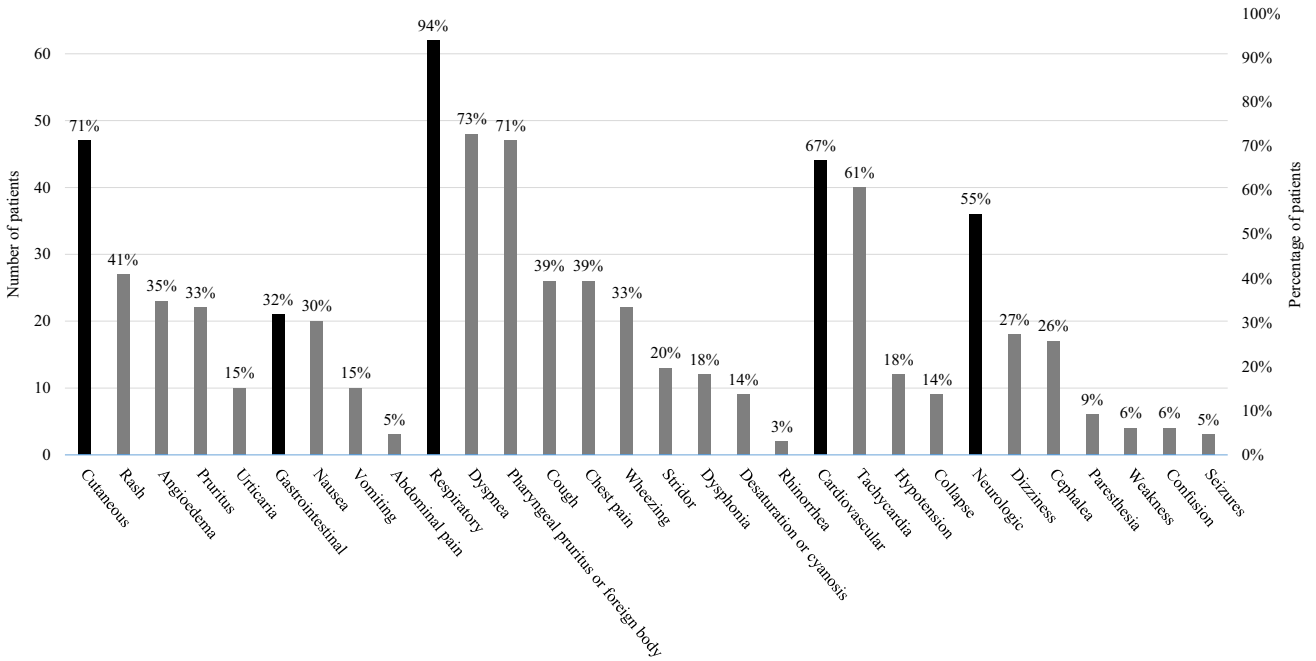

Fig. 1 Clinical manifestations of patients with anaphylaxis to anti-SARS-CoV-2 vaccines

Table 3 Clinical anaphylaxis manifestations according to the vaccine platform

Manifestation, *n* (%)	mRNA-based (*n* = 41)	Other platforms (*n* = 25)	*p*-value
Cutaneous	30 (73)	17 (68)	0.653
Gastrointestinal	16 (39)	5 (20)	0.107
Respiratory	40 (98)	22 (88)	0.114
Cardiovascular	31 (76)	13 (52)	0.048
Neurologic	22 (54)	14 (64)	0.853

treatment for a median duration of 12 h (IQR 5–24), while some declined admission. Five patients were treated at a critical care unit for further monitoring; four were discharged without any complications, and one required intubation due to cardiopulmonary arrest at arrival at the emergency department; this patient died (1.5%). None of the patients had received a follow-up vaccination dose at the moment of data collection.

The anaphylactic reaction-related death occurred 5 min after the first dose of ChAdOx1 nCov-19; the patient did not have a history of allergic disease or previous episodes of anaphylaxis. He presented with sudden altered mental status, fainting, and progressive respiratory failure. He received advanced cardiopulmonary resuscitation (CPR) protocol, but the response was unsuccessful. He was treated with intravenous adrenaline as part of the CPR protocol, anaphylaxis was not suspected during the acute episode, and they did not measure serum tryptase. However, the post-mortem histopathological examination reported edematous airway tissue with mast cell degranulation and positive markers for tryptase, identifying anaphylaxis as the cause of death.

Discussion

In our study, anaphylactic reactions were infrequent AEFIs against SARS-CoV-2. Over two-thirds of our patients had a history of drug or food allergies; a higher proportion is expected in the general population [11, 12]. It is known that females are more likely to develop drug allergies and drug-induced anaphylaxis [13, 14], an association hypothetically linked to sexual dimorphism by other authors; in this series, we found a female to male ratio of 6:1. Also, healthcare workers, particularly nurses, had a higher prevalence of drug allergy concurrent to previous reports [15]. Mortality in our series (1.5%) was somewhat higher than described by other authors [16]. The only patient who died of anaphylaxis had no cutaneous manifestations, which may have delayed the diagnosis. To our knowledge, this is the first report to include a case of fatal anaphylaxis secondary to anti-SARS-CoV-2 vaccines and will be the subject of discussion in another article. It is important to note that less than half of the patients (46%) received correct treatment with epinephrine as the first-line treatment through the intramuscular route and at an appropriate dose.

Over half of the patients were reported in a single state, attributable to the high awareness, index of suspicion, and continuous education about anaphylaxis treatment imparted to the healthcare workers of this state's largest vaccination center. In the beginning, most of the reactions were attributed to BNT162b2 and scattered through the country. Following the first semester, the health authorities started the application of the rest of the platforms. Jalisco — the state that reported the highest number of anaphylaxis — began with educational efforts to identify and treat these reactions promptly. Education to personnel administering COVID-19 vaccines is critical and might improve patients' survival. As a part of the educational training, the sub-committee in Allergy and Immunology has participated in several webinars to share the diagnostic approach and management of allergic reactions to SARS-CoV-2 vaccines. In Mexico, a previous study reported that systemic corticosteroids are more frequently used in anaphylaxis than epinephrine, the cornerstone of treatment [16]. Corticosteroids may help prevent biphasic reactions but have insufficient evidence in the acute setting [17]. In this case series, the correct approach with epinephrine was fortunately used as the first-line treatment in several patients.

In previous reports of anti-SARS-CoV-2 vaccine-related anaphylactic reactions, polyethylene glycol (PEG) and polysorbate 80 (PS80) have been mechanistically associated with the development of allergic reactions. [3, 18, 19] PS80 is present in multiple injectable drugs, such as monoclonal antibodies and vaccines, including conjugated pneumococcal vaccines [3]. The exact underlying immunological mechanisms of these rare but severe reactions are yet to be elucidated [20]. Anaphylaxis is a severe life-threatening, usually immediate AEFI caused by massive mast cells and basophil activation triggering the release of multiple chemokines, promoting anaphylaxis development. This activation can be mediated through different receptors, not always related to mechanisms classically defined as an allergy.

Currently, IgE-receptor-mediated and non-IgE-receptor-mediated reactions are the most likely pathophysiological mechanisms involved in developing anaphylaxis as an AEFI with the current anti-SAR-CoV-2 vaccines. [18] IgE-receptor-mediated reactions to vaccines, also known as classical allergic reactions, are usually caused by inactive ingredients or excipients used as preservatives [18]. Not all excipients that could cause anaphylactic reactions to these COVID-19 vaccines have been entirely determined. Still, the most likely culprits are PEG (in mRNA-based vaccines) and its derivatives, including PS80 (in viral vector vaccines). PEGs are polymers of ethylene oxide that vary in their molecular weights ranging between 200 and 35,000 g/mol [21, 22]. They can be found in many pharmaceutical and cosmetic products. PS80 is commonly used in vaccines, steroids, immunoglobulin formulations, and over 7000 FDA-approved medications [23]. Because they are present in so many widely used products, these compounds can sensitize a person's immune system and predispose them to have reactions of varying severity after exposure [24]. Despite this, it has not always been possible to demonstrate the presence of IgE against these compounds in the skin or in vitro tests. Due to the ease and experience of performing these tests [20], it is common to try to demonstrate this mechanism first. Still, other mechanisms that do not depend on IgE receptors must be investigated when they are negative.

In addition to IgE receptors, mast cells and basophils have many other receptors that activate their degranulation (non-IgE-receptor-mediated reactions). Receptors can also trigger these cells for other immunoglobulins such as IgG, receptors for complement anaphylatoxins such as C3a and C5a, or receptors for proteases such as MRGPRX2 (Mas-related G-protein-coupled receptor member X2) [18, 25]. In particular, the MRGPRX2 receptor has drawn special attention due to its ability to be activated by preservatives and excipients in different drugs and vaccines [18, 19]. The role these receptors may play in anaphylactic reactions to COVID-19 vaccines and their importance in predicting the risk of future reactions continue to be investigated. The PEG- or PS80-stimulated basophil activation test can help demonstrate the participation of these cells by mechanisms dependent on IgE receptors or other receptors [22]. As the exact pathohistological mechanisms are yet to be elucidated, to determine the etiology of the reaction between platforms, the workup for all anaphylactic reactions to anti-SARS-CoV-2 vaccines must include skin testing, specific IgE determination for PEG and PS80, and Sanger sequencing for MRGPRX2. [20]

Our study has limitations. First, despite anaphylaxis being a serious AEFI due to the passive nature of the Mexican epidemiological system where diagnosis and reports rely upon physician criteria, cases presenting with mild symptoms may be underreported or underdiagnosed. At a national level, most states' underreporting seems to be related to a lack of awareness regarding anaphylaxis diagnosis and treatment. Second, as only patients evaluated by the ad hoc committee were included, our analysis is prone to selection bias. Lastly, as the Mexican immunization program against SARS-CoV-2 has reached remote communities, most of them with limited medical resources, we could not establish causality or evaluate the potential mechanisms involved in developing this life-threatening AEFI.

In conclusion, our study provides further evidence supporting the security of these newly developed vaccines. Constant surveillance of adverse reactions attributable to these newly developed vaccines is critical to ensure the safety of future vaccine recipients. The continuous training of healthcare workers involved in vaccination campaigns worldwide to identify anaphylactic reactions is essential for a timely diagnosis and proper treatment.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10875-022-01350-1.

Acknowledgements The authors wish to acknowledge and show their appreciation to the members of the Mexican National Experts Committee in ESAVI, the participant authorities in every involved state, and the primary care physicians. The latter reported and presented these adverse events.

Author Contribution Carla Toledo-Salinas and David Alejandro Mendoza-Hernández: conception and design of the work; data acquisition, analysis, and interpretation; drafting and critically revising the work for important intellectual content.

Selma Cecilia Scheffler-Mendoza, José Antonio Ortega-Martell, and Blanca Estela del Río Navarro: conception and design of the work; data acquisition; drafting the work.

Lina María Castaño-Jaramillo, Miguel García-Grimshaw and Sergio Iván Valdés-Ferrer: analysis and interpretation of data; drafting and critically revising the work for important intellectual content.

Ana María Santibáñez-Copado, Raúl Baptista-Rosas, and Paulina Sánchez-Novoa: data acquisition; drafting the work.

José Luis Díaz-Ortega and Gustavo Reyes Terán: conception of the work; revising the work critically for important intellectual content.

All authors: agreement to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Availability of Data and Material As supplementary material.

Declarations

Ethics Approval The study was reviewed and approved by the *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán* (registry: NER-3903-21-23-1) Ethics and Research Committees, who waived the need for signed informed consent due to its observational nature.

Consent to Participate and Publication Waived.

Competing Interests The authors declare no competing interests.

References

1. Secretaría de Salud. Información de la vacuna. Vacunación Covid. Published October 16, 2021. http://vacunacovid.gob.mx/wordpress/informacion-de-la-vacuna/. Accessed 5 Nov 2021
2. Klein NP, Lewis N, Goddard K, et al. Surveillance for adverse events after COVID-19 mRNA vaccination. JAMA. Published online September 3, 2021. https://doi.org/10.1001/jama.2021.15072
3. Turner PJ, Ansotegui IJ, Campbell DE, et al. COVID-19 vaccine-associated anaphylaxis: a statement of the World Allergy Organization Anaphylaxis Committee. World Allergy Organ J. 2021;14(2): 100517. https://doi.org/10.1016/j.waojou.2021.100517.
4. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344–9. https://doi.org/10.1016/j.jclinepi.2007.11.008.
5. García-Grimshaw M, Michel-Chávez A, Vera-Zertuche JM, et al. Guillain-Barré syndrome is infrequent among recipients of the BNT162b2 mRNA COVID-19 vaccine. Clin Immunol. 2021;230:108818. https://doi.org/10.1016/j.clim.2021.108818.
6. García-Grimshaw M, Ceballos-Liceaga SE, Hernández-Vanegas LE, et al. Neurologic adverse events among 704,003 first-dose recipients of the BNT162b2 mRNA COVID-19 vaccine in Mexico: a nationwide descriptive study. Clin Immunol. 2021;229:108786. https://doi.org/10.1016/j.clim.2021.108786.
7. García-Grimshaw M, Ceballos-Liceaga SE, Michel-Chávez A, et al. Transient sensory symptoms among first-dose recipients of the BNT162b2 mRNA COVID-19 vaccine: a case-control study. Vaccine. 2021;39(48):6975–9. https://doi.org/10.1016/j.vaccine.2021.10.058.
8. Coalition for Epidemic Preparedness and Innovation, The Brighton Collaboration. SPEAC: Safety Platform for Emergency vACcines, AESI Case Definition Companion Guide for 1st Tier AESI. Published online February 5, 2021. Accessed October 19, 2021. https://brightoncollaboration.us/anaphylaxis-case-definition-companion-guide/
9. Brown SGA. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol. 2004;114(2):371–6. https://doi.org/10.1016/j.jaci.2004.04.029.
10. Wilson E. Probable inference, the law of succession, and statistical inference. J Am Stat Assoc. 1927;22(158):209–12. https://doi.org/10.1080/01621459.1927.10502953.
11. Sousa-Pinto B, Fonseca JA, Gomes ER. Frequency of self-reported drug allergy. Ann Allergy Asthma Immunol. 2017;119(4):362-373.e2. https://doi.org/10.1016/j.anai.2017.07.009.
12. Gupta RS, Warren CM, Smith BM, et al. Prevalence and severity of food allergies among US adults. JAMA Netw Open. 2019;2(1):e185630. https://doi.org/10.1001/jamanetworkopen.2018.5630.
13. Thong BYH, Tan TC. Epidemiology and risk factors for drug allergy: epidemiology and risk factors for drug allergy. Br J Clin Pharmacol. 2011;71(5):684–700. https://doi.org/10.1111/j.1365-2125.2010.03774.x.
14. Regateiro FS, Marques ML, Gomes ER. Drug-induced anaphylaxis: an update on epidemiology and risk factors. Int Arch Allergy Immunol. 2020;181(7):481–7. https://doi.org/10.1159/000507445.
15. Zilinskaite L, Tamasauskas D, Kvedariene V, Sitkauskiene B. Self-reported drug allergy in health care workers in conservative and surgical medicine departments. J Investig Allergol Clin Immunol. 2012;22:6.
16. Castaño-Jaramillo L, Toledo-Salinas C, Mendoza D. Causas y tratamiento de anafilaxia en un hospital pediátrico mexicano de tercer nivel. Rev Alerg México. 2021;68(3):160–4. https://doi.org/10.29262/ram.v68i3.904.
17. Cardona V, Ansotegui IJ, Ebisawa M, et al. World Allergy Organization anaphylaxis guidance 2020. World Allergy Organ J. 2020;13(10): 100472. https://doi.org/10.1016/j.waojou.2020.100472.
18. Kounis NG, Koniari I, de Gregorio C, et al. Allergic reactions to current available COVID-19 vaccinations: pathophysiology, causality, and therapeutic considerations. Vaccines. 2021;9(3):221. https://doi.org/10.3390/vaccines9030221.
19. Sampath V, Rabinowitz G, Shah M, et al. Vaccines and allergic reactions: the past, the current COVID-19 pandemic, and future perspectives. Allergy. 2021;76(6):1640–60. https://doi.org/10.1111/all.14840.
20. Vander Leek TK, Chan ES, Connors L, et al. COVID-19 vaccine testing & administration guidance for allergists/immunologists from the Canadian Society of Allergy and Clinical Immunology (CSACI). Allergy Asthma Clin Immunol. 2021;17(1):29. https://doi.org/10.1186/s13223-021-00529-2.
21. Moghimi SM. Allergic reactions and anaphylaxis to LNP-based COVID-19 vaccines. Mol Ther. 2021;29(3):898–900. https://doi.org/10.1016/j.ymthe.2021.01.030.

22. Nilsson L, Csuth Á, Storsaeter J, Garvey LH, Jenmalm MC. Vaccine allergy: evidence to consider for COVID-19 vaccines. Curr Opin Allergy Clin Immunol. 2021; Publish Ahead of Print. https://doi.org/10.1097/ACI.0000000000000762
23. Caballero ML, Krantz MS, Quirce S, Phillips EJ, Stone CA. Hidden dangers: recognizing excipients as potential causes of drug and vaccine hypersensitivity reactions. J Allergy Clin Immunol Pract. 2021;9(8):2968–82. https://doi.org/10.1016/j.jaip.2021.03.002.
24. Stone CA, Liu Y, Relling MV, et al. Immediate hypersensitivity to polyethylene glycols and polysorbates: more common than we have recognized. J Allergy Clin Immunol Pract. 2019;7(5):1533-1540.e8. https://doi.org/10.1016/j.jaip.2018.12.003.
25. Greenhawt M, Shaker M, Golden DBK. PEG/polysorbate skin testing has no utility in the assessment of suspected allergic reactions to SARS-CoV-2 vaccines. J Allergy Clin Immunol Pract. 2021;9(9):3321–2. https://doi.org/10.1016/j.jaip.2021.06.025.