Original Article

Population-Based Incidence, Severity, and Risk Factors Associated with Treated Acute-Onset COVID-19 mRNA Vaccination–Associated Hypersensitivity Reactions

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What is already known about this topic? Acute-onset hypersensitivity COVID-19 mRNA vaccine–associated reactions have been widely reported, and uncertainty as to their frequency and severity may be inhibiting vaccine uptake in the population.

What does this article add to our knowledge? This is the first population-based data on the frequency, severity, and risk factors associated with treated acute-onset hypersensitivity reactions associated with first and second dose exposures to COVID-19 mRNA vaccines.

How does this study impact current management guidelines? Treated acute-onset hypersensitivity reactions are more likely in females with similar risk factors as for multiple drug intolerance syndrome, are mild, more likely to occur with first doses, and unlikely to be immunologically mediated.

BACKGROUND: COVID-19 mRNA vaccination–associated acute-onset hypersensitivity reactions have caused anxiety and may be contributing to vaccine hesitancy.
OBJECTIVE: To determine the incidence, severity, and risk factors for treated acute-onset COVID-19 mRNA vaccination–associated hypersensitivity reactions in a well-characterized population.
METHODS: All Kaiser Permanente Southern California (KPSC) members who received COVID-19 mRNA vaccinations between December 15, 2020, and March 11, 2021, at a KPSC facility were identified and characterized, along with all treated acute-onset vaccination-associated hypersensitivity events.
RESULTS: We identified 391,123 unique vaccine recipients (59.18% female, age 64.19 ± 17.86 years); 215,156 received 2 doses (53.54% Moderna), 157,615 only a first dose (50.13% Moderna) (1961 [1.46%] >2 weeks late getting a second dose), and 18,352 (74.43% Moderna) only a second dose. Only 104 (0.028%) (85.58% female, age 53.18 ± 15.96 years) had treated first dose events, 68 (0.030%) Moderna. Only 32 (0.014%) (93.75% female, age 57.28 ± 17.09 years) had treated second dose events, 21 (0.016%) Moderna. Only 2 (0.00033%) vaccinations resulted in anaphylaxis. Only 27 (20.77%) of those with treated first dose reactions failed to get a second dose. Only 6 of 77 (7.8%) with first dose reactions also had second dose reactions. Individuals with treated events were more likely to be female ($P < .0001$), younger ($P < .0001$), and had more pre-existing drug "allergies" (2.11 ± 2.12 vs 1.02 ± 1.41 [$P < .0001$] for average recipients).
CONCLUSIONS: Treated acute-onset hypersensitivity events were mostly benign, more common with first COVID-19 mRNA vaccine doses, more likely to occur in younger females with typical risk factors associated with multiple drug intolerance syndrome, and very unlikely to be primarily immunologically mediated. **(J Allergy Clin Immunol Pract 2022;■:■-■)**

Key words: *Acute-onset hypersensitivity; Anaphylaxis; COVID-19 mRNA vaccines; Incidence; Multiple drug intolerance syndrome; Population; Severity*

The 2 novel COVID-19 mRNA vaccines produced by Pfizer-BioNTech and Moderna were the first large population-based exposures to an mRNA-containing nanoparticle pharmaceutical agent. There has been intense interest in acute hypersensitivity reactions in individuals receiving these vaccines. Within weeks of initial release in the United States on December 14, 2020, the Centers for Disease Control and Prevention (CDC) COVID-19

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Abbreviations used
BAT- Basophil activation test
CDC- Centers for Disease Control and Prevention
EHR- Electronic health record
FAAN- Food Allergy and Anaphylaxis Network
FDA- United States Food and Drug Administration
KPSC- Kaiser Permanente Southern California
MDIS- Multiple drug intolerance syndrome
NIAID- National Institute of Allergy and Infectious Disease
PEG- Polyethylene glycol
VAERS- Vaccine Adverse Events Reporting System

Response Team and the United States Food and Drug Administration (FDA) reviewed in the *MMWR* the initial 21 reported cases of COVID-19 vaccine—associated anaphylaxis reported in the Vaccine Adverse Events Reporting System (VAERS) after only 1,893,360 vaccine doses had been administered.[1] This initially apparently very high rate (11.1 per million doses) of anaphylaxis was amplified by other early reports.[2] Blumenthal et al[2] in *JAMA* noted in March 2021 that there were 16 episodes of self-reported and multipronged prospective system surveillance identified episodes of anaphylaxis in only 64,900 health care system employees receiving their first dose of either mRNA COVID-19 vaccine between December 16, 2020, and February 12, 2021. This was over 20 times the preliminary rate reported in VAERS (247 per million doses). However, only 7 of 16 cases met both the Brighton and National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) anaphylaxis criteria. Hourihane et al[3] noted in May of 2021 that there was a very high probability that the majority of the initially reported COVID-19 vaccine—associated "anaphylaxis" episodes were erroneous because of ascertainment bias. They argued that it was essential to apply objective criteria to vaccine reactions to accurately determine population-based rates of clinically significant anaphylaxis. Krantz et al[4] reported in *JAMA Internal Medicine* in July 2021 on 187 patients with first-dose hypersensitivity reactions. A total of 159 (85%) received a second dose, including 19 with first-dose "anaphylaxis," and all tolerated the second dose. There were 32 (20%) who reported mild, self-limiting reactions with their second doses, which resolved with antihistamine therapy alone.

No reports to date have captured population-based data on all acute-onset hypersensitivity events after both first and second doses of COVID mRNA vaccines using objective criteria. It is not practically possible to identify all acute vaccination-associated adverse reactions, particularly untreated or self-treated events, by electronic health record (EHR) review. It is possible to identify all health plan treated events occurring within 6 hours of vaccination. These events would also be expected to be the most clinically significant and are more likely to influence future vaccinations. No studies to date have reviewed all of the medical records of all vaccinated individuals in a well-defined cohort to get an accurate population-based estimate of the frequency and severity of acute-onset vaccine-associated reactions resulting in treatment based on documented objective findings and the risk factors associated with these events.

The lipid nanoparticles that contain the mRNA coding for the SARS-COV-2 spike protein are coated with carboxy polyethylene glycol (PEG) to help mitigate direct complement activation by the nanoparticles.[5] It has been hypothesized that nanoparticle size heterogeneity, specifically small amounts of relatively larger nanoparticles (>80 nm), contributes most of the observed complement activation because PEG provides poorer shielding of these large particles.[6]

Understanding the epidemiology of acute-onset treated reactions associated with these vaccine exposures can help provide insights into potential mechanisms and help design appropriate management strategies. If there is an adaptive IgE-mediated or other immune response to constituent materials in the vaccines, then the frequency of acute-onset hypersensitivity reactions should increase significantly with second dose exposures. If the reactions are because of innate immune response activation, possibly direct complement activation, from the nanoparticles, perhaps by accidental low-level intravascular exposure during attempted intramuscular administration, then the rates of acute-onset hypersensitivity reactions should remain relatively constant between first and second doses. If the reactions are caused by other nonimmunologic or nondrug specific factor(s), such as anxiety, then the reaction rate may be lower with booster doses.

METHODS

This retrospective review of existing data in EHR was reviewed and approved by the Kaiser Permanente Southern California (KPSC) Institutional Review Board. We identified all unique individuals with active KPSC health plan coverage who received any doses of either COVID-19 mRNA vaccine at a KPSC facility between December 16, 2020, and March 11, 2021. Tracking only individuals with active KPSC health plan coverage who received their COVID mRNA vaccinations at a KPSC facility ensured that any acute-onset hypersensitivity event would be very likely to be treated at a KPSC facility and would ensure that virtually all treated acute-onset hypersensitivity events could be identified.

We defined a clinically significant acute-onset vaccination-associated hypersensitivity event as one that started within 6 hours of vaccine administration and resulted in acute treatment with antihistamines, epinephrine, and/or systemic corticosteroids at a KPSC facility and was documented in the EHR. Individuals who reported benign symptoms that resolved without any therapy administered, even if observed in the Emergency Department or Urgent Care, or who self-treated and the treatment was not entered into the EHR, were not considered to have had a clinically significant acute-onset vaccine-associated hypersensitivity event.

To capture all treated acute-onset hypersensitivity events we undertook the following steps:

1. We identified all unique individuals who had active KPSC health plan coverage and who received either COVID-19 mRNA vaccine at a KPSC facility between December 16, 2020, and March 11, 2021.
2. We identified all individuals who received any clinic-administered epinephrine, antihistamines, or systemic corticosteroids, in the vaccine clinic, primary care, urgent care, or the emergency department, within 6 hours of the vaccination.
3. We identified all individuals who had any International Classification of Diseases, Tenth Revision coded diagnosis compatible with an acute vaccine-associated adverse event or anaphylaxis on the day of vaccination including T50.B95A, T50.Z95A, T50.995, T80.52, T80.62, T78.40, and T88.1 L50.9.
4. The EHRs were manually reviewed to verify that any patient receiving any of the treatments of interest were being treated for a

COVID mRNA vaccine–associated hypersensitivity event, and not some other unrelated condition.
5. We identified the lowest blood pressure measurements and pulse oximetry determinations entered into the EHR within 6 hours of vaccination in the treated subjects.
6. We identified any individuals who had a serum tryptase sent on the date of a vaccination.
7. We defined anaphylaxis as present if the refinement of the World Allergy Organization/NIAID/FAAN clinical criteria for the diagnosis of anaphylaxis criteria were met. Acute hypotension or hypoxia or symptoms affecting 2 organ systems must be involved. We considered that these criteria were met when the following objective findings were documented in the EHR: hives or angioedema, hypotension, hypoxia by pulse oximetry or wheezing on examination, and/or vomiting or diarrhea. Pruritus without any observable skin changes, sensation of throat tightness or dyspnea without hypoxia, dizziness, lightheadedness, or faintness with normal vital signs, and nausea or abdominal pain without vomiting or diarrhea were considered subjective findings and did not meet the criteria for confirming anaphylaxis.
8. The EHRs of individuals who received a diagnostic code indicating possible anaphylaxis, or who were treated with epinephrine, were manually audited by an allergy physician (EM) to determine if the objective clinical findings documented in the EHR met the WHO 2020 criteria for anaphylaxis.[7]
9. We collected the following potential risk factors for treated acute-onset COVID mRNA vaccine–associated hypersensitivity reactions:
   a. Age
   b. Gender
   c. Total drug intolerances ("allergies")
      i. Intolerance to a previous vaccine
      ii. Intolerance to nonsteroidal anti-inflammatory medications
      iii. Intolerance to PEG
      iv. Intolerance to agents capable of direct mast cell activation such as radiocontrast, opiates, or fluoroquinolones
      v. Intolerance to nanoparticle medications including parenteral iron preparations, gadolinium-labeled ferritin, and liposomal antibiotics or cancer chemotherapeutic agents
   d. Medical conditions associated with multiple drug intolerance syndrome (MDIS)
      i. chronic urticaria (L50.x)
      ii. Contact dermatitis (L23.x, L24.x, L25.x)
      iii. Anxiety (F41.x, F40.x, F43.x)
   e. Medical conditions associated with IgE-mediated allergy or previous anaphylaxis
      i. Asthma (J45.x, J82.x)
      ii. Unspecified urticarial syndromes or suspected "allergic" reactions (Z87.x, T78.x, T80.x, T88.x, T39.395A, and R57)
      iii. Environmental allergy (J30.x)
      iv. Food allergy (Z91.01x)
      v. Venom allergy (Z91.03x)
      vi. Mastocytosis or mast cell activation syndrome (D47.01, D47.02, Q82.2, C96.2)
      vii. Previous prescription of epinephrine

Statistical analysis

Continuous data were reported as mean ± standard deviation and were assessed using the Kruskal-Wallis test. Categorical data were reported as absolute values and percentages with the χ^2 or Fisher exact test P values. Comparisons for demographics were made across 2 different vaccine groups by the KPSC members who were fully vaccinated and by the individuals who received only the first dose and were at least 2 weeks late receiving their booster. Demographics and potential risk factors were also compared between the patients with and without treated hypersensitivity events.

A multivariable logistic regression analysis, controlling with gender, MDIS, and age, was used to derive adjusted odds ratios with 95% confidence intervals (CIs) to examine the association between the study outcome and each potential factor. All analyses were performed using SAS version 9.4 (Cary, North Carolina), and P values $< .05$ were considered to be statistically significant.

RESULTS

There were 391,022 unique KPSC health plan members vaccinated with at least 1 dose of either COVID-19 mRNA vaccine at a KPSC facility between December 15, 2020, and March 11, 2021. The demographics of the first 215,251 unique KPSC health Plan members who received 2 doses of either COVID-19 mRNA vaccine, within FDA specified time frames, between December 15, 2020, and March 11, 2021, at a KPSC facility are displayed in Table I. These individuals were primarily older and/or health care workers, based on the vaccine rollout priorities at the time. They were also predominately female (60.8%). There were 156,471 unique individuals who received only a first dose and 18,277 who received only a second dose at a KPSC facility during the study interval.

The demographics of the 1811 unique individuals who received only their first dose of either COVID-19 mRNA vaccine at a KPSC facility during this interval and were at least 2 weeks late on receiving their second dose as of March 11, 2021, are displayed in Table II. Among those only getting a first dose, 25 (1.4%) had a treated acute-onset hypersensitivity event, accounting for 19.2% of all affected individuals, but this was not the dominant factor in failing to get both recommended doses within the recommended time periods.

There were only 2 of 606,273 (0.00033%) vaccinations in the entire cohort that were confirmed to have objective findings of anaphylaxis, for a calculated rate of 3.29 per million vaccine doses administered. One was a 66-year-old woman with hives and wheezing after her first dose of the Moderna vaccine. Her blood pressure was 151/63, pulse O_2 = 98%, and no acute tryptase was obtained. She had 8 unrelated drug intolerances noted in her medical record. The other was a 47-year-old with flushing, coughing, and mild hypotension after her first dose of the Pfizer-BioNTech vaccine. Her blood pressure was 100/62, pulse O_2 = 95%, and no acute tryptase was obtained. She had no drug intolerances noted in her medical record. She had a history of chemical sensitivity, nonallergic rhinitis, and previously had a self-reported "anaphylactic reaction" manifest by coughing and flushing associated with a perfume exposure at work. She carried a clinical diagnosis of asthma, but previously had normal spirometry, no significant improvement in post-bronchodilator forced expiratory volume in 1 second, and a normal exhaled nitric oxide level. Both anaphylaxis episodes were relatively mild and not felt by treating physicians to be life-threatening. Neither was given a second dose of the vaccine associated with their index events, but both subsequently tolerated a dose of the Janssen COVID-19 vaccine.

TABLE I. Demographics of Kaiser Permanente Southern California (KPSC) health plan members receiving both COVID mRNA vaccine doses at KPSC facilities within the recommended time interval between December 15, 2020, and March 11, 2021

Characteristic	Moderna (N = 115,209)	Pfizer (N = 100,042)	Total (N = 215,251)	*P* value
Sex, n (%)				.0054*
Female	70,322 (61.0)	60,477 (60.5)	130,799 (60.8)	
Not female	44,887 (39.0)	39,565 (39.5)	84,452 (39.2)	
Age at first dose				<.0001†
Mean (SD)	65.5 (19.0)	63.46 (18.92)	64.56 (19.01)	
Median	75.0	69.0	72.0	
Q1, Q3	50.0, 80.0	47.0, 79.0	48.0, 80.0	
Range	18.0-107.0	16.0-108.0	16.0-108.0	
Unrelated drug class "allergies"				<.0001†
Mean (SD)	1.1 (1.4)	1.0 (1.4)	1. (1.4)	
Median	1.0	1.0	1.0	
Q1, Q3	0.0, 2.0	0.0, 2.0	0.0, 2.0	
Range	0.0-18.0	0.0-14.0	0.0-18.0	
Had a treated hypersensitivity event, n (%)				.0174*
Yes	37 (0)	16 (0)	53 (0)	
No	115,172 (100)	100,026 (100)	215,198 (100)	

SD, Standard deviation.
*χ^2.
†Kruskal-Wallis.

TABLE II. Demographics of individuals who received only a first dose of either COVID mRNA vaccine between December 15, 2020, and March 11, 2021, and were at least 14 days late receiving their booster dose by March 11, 2021

Characteristic	Moderna (N = 912)	Pfizer (N = 899)	Total (N = 1811)	*P* value
Sex, n (%)				.1295*
Female	630 (69.1)	591 (65.7)	1221 (67.4)	
Not female	282 (30.9)	308 (34.3)	590 (32.6)	
Age at first dose				.1322†
Mean (SD)	54.1 (20.0)	55.7 (21.2)	54.9 (20.6)	
Median	50.0	51.0	50.0	
Q1, Q3	37.5, 75.0	38.0, 77.0	38.0, 76.0	
Range	19.0-100.0	16.0-99.0	16.0-100.0	
Unrelated drug class "allergies"				.6839†
Mean (SD)	1.0 (1.4)	1.0 (1.5)	1.0 (1.5)	
Median	0.0	0.0	0.0	
Q1, Q3	0.0, 2.0	0.0, 2.0	0.0, 2.0	
Range	0.0-9.0	0.0-16.0	0.0-16.0	
Had a treated hypersensitivity event, n (%)				.1482*
Yes	9 (1)	16 (1.8)	25 (1.4)	
No	903 (99)	883 (98.2)	1786 (98.6)	

SD, Standard deviation.
*χ^2.
†Kruskal-Wallis.

The demographics of the 391,022 unique individuals who acutely tolerated 1 or 2 doses between December 15, 2020, and March 11, 2021, and the 130 (0.033%) unique individuals who had a treated acute-onset hypersensitivity reaction after their first and/or second COVID mRNA vaccination are displayed in Table III. Individuals with treated hypersensitivity events were more likely to be female, 86.9%, and were significantly younger than average vaccine recipients. They were much more likely to have underlying MDIS and also more likely to have clinical histories with known risk factors for MDIS. They were approximately 10 times as likely to have previously reported a vaccine-associated adverse reaction. They were more likely to carry diagnoses of chronic urticaria, food "allergy," and anxiety. A key finding was that treated acute-onset hypersensitivity reactions were approximately 2 times more likely to occur with first doses than second doses, 104/372,745 (0.028%) versus 32/233,528 (0.014%). An unexpected finding was that over 11% of all COVID-19 mRNA vaccine recipients had been previously prescribed an epinephrine injector, though how many had ever used their injectors was unknowable.

The clinical manifestations, treatments given, and risk factors identified for experiencing a treated acute-onset hypersensitivity reaction after a first or second COVID mRNA vaccination are displayed in Table IV. Virtually all individuals with treated acute-onset hypersensitivity events had clinical symptoms starting within the first 1 hour (data not shown). No individuals had elevated acute tryptase levels, though this was checked in only a small minority. An unexpectedly high number, almost 30%, were treated acutely with systemic corticosteroids that can suppress T-cell immunity and vaccine effectiveness. There were a total of 60 (57.7%) individuals who received a second dose of the vaccine associated with their index reaction and an additional 12 (11.5%) who received a dose of the Janssen COVID-19 vaccine as of August 23, 2021.

Table V presents the results of the adjusted logistic regression model for risk factors for having a treated acute-onset hypersensitivity event. By controlling the unrelated drug class and age at first dose, we note that the odds for experiencing a treated acute-onset hypersensitivity reaction is 3 times higher for the female group than the male group. By controlling the gender and

TABLE III. Demographics of the all individuals receiving at least 1 dose of a COVID mRNA vaccine at any KPSC facility between December 15, 2020, and March 11, 2021, with and without a treated acute-onset hypersensitivity event

Characteristic	Without treated acute-onset hypersensitivity event (N = 390,892)	With treated acute-onset hypersensitivity event (N = 130)	*P* value
Sex, n (%)			<.0001*
Female	231,307 (59.2)	113 (86.9)	
Not female	159,585 (40.8)	17 (13.1)	
Age at first dose			<.0001†
Mean (SD)	64.2 (17.9)	53.8 (16.1)	
Median	69.0	50.0	
Q1, Q3	51.0, 78.0	42.0, 67.0	
Range	16.0-108.0	25.0-96.0	
Received 2 doses, n (%)			<.0001*
No	156,396 (40)	75 (57.7)	
Yes	234,496 (60)	55 (42.3)	
Unrelated drug class "allergies"			<.0001†
Mean (SD)	1.0 (1.4)	2.1 (2.1)	
Median	1.0	2.0	
Q1, Q3	0.0, 2.0	0.0, 3.0	
Range	0.0-19.0	0.0-10.0	
Multiple drug intolerance syndrome, n (%)			<.0001*
No	341,515 (87.4)	88 (67.7)	
Yes	49,377 (12.6)	42 (32.3)	
Previous vaccine intolerance, n (%)			<.0001*
No	387,267 (99.1)	118 (90.8)	
Yes	3625 (0.9)	12 (9.2)	
Direct mast cell activating agent intolerance, n (%)			<.0001*
No	375,000 (95.9)	110 (84.6)	
Yes	15,892 (4.1)	20 (15.4)	
NSAID intolerance, n (%)			.1406*
No	336,248 (86)	106 (81.5)	
Yes	54,644 (14)	24 (18.5)	
Nonspecific hives, swelling or "allergic reaction," n (%)			<.0001*
No	256,270 (65.6)	17 (13.1)	
Yes	134,622 (34.4)	113 (86.9)	
Chronic urticaria, n (%)			<.0001*
No	375,692 (96.1)	110 (84.6)	
Yes	15,200 (3.9)	20 (15.4)	
Asthma, n (%)			<.0001*
No	336,716 (86.1)	91 (70)	
Yes	54,176 (13.9)	39 (30)	
Allergic rhinitis, n (%)			.0043*
No	317,848 (81.3)	93 (71.5)	
Yes	73,044 (18.7)	37 (28.5)	
Food allergy, n (%)			.0003*
No	341,584 (87.4)	100 (76.9)	
Yes	49,308 (12.6)	30 (23.1)	
Anxiety, n (%)			<.0001*
No	273,195 (69.9)	60 (46.2)	
Yes	117,697 (30.1)	70 (53.8)	
Mastocytosis, n (%)			1.0000‡
No	390,810 (100)	130 (100)	
Yes	82 (0)	0 (0)	

(continued)

TABLE III. *(Continued)*

Characteristic	Without treated acute-onset hypersensitivity event (N = 390,892)	With treated acute-onset hypersensitivity event (N = 130)	*P* value
Previously prescribed an epinephrine injector, n (%)			<.0001*
No	346,735 (88.7)	96 (73.8)	
Yes	44,157 (11.3)	34 (26.2)	
Venom hypersensitivity, n (%)			
No	389,835 (99.7)	128 (98.5)	.0489‡
Yes	1057 (0.3)	2 (1.5)	

NSAID, Nonsteroidal anti-inflammatory medication; *SD*, standard deviation.
*χ^2.
†Kruskal-Wallis.
‡Fisher exact.

age at first dose, we note that each additional drug class intolerance reported in the EHR is associated with an increase of 49% in the odds of experiencing a treated acute-onset hypersensitivity reaction. For each year of increase in age, the estimated odds for experiencing a treated acute-onset hypersensitivity reaction decreases by roughly 4.1%, regardless of the effect of gender and unrelated drug class.

DISCUSSION

This is the first report of a population-based cohort where virtually all treated acute-onset hypersensitivity events occurring within 6 hours of administration of either the Pfizer-BioNTech or Moderna COVID-19 mRNA vaccines were identified and characterized.

We noted that the risk factors for having a treated acute-onset COVID-19 mRNA vaccine-associated hypersensitivity event were analogous to those previously noted to be associated with MDIS.[8-10] Treated acute-onset hypersensitivity reactions were 3 times more likely to occur in females, similar to MDIS being much more prevalent in females. Individuals with treated acute-onset hypersensitivity events had on average twice as many recorded drug intolerances and were approximately 10 times as likely to have reported a previously reported vaccine intolerance. Almost 90% had at least 1 previously coded nonspecific hives, swelling, or "allergic reaction" event. Approximately half had a coded anxiety diagnosis, and almost one-third had underlying MDIS. We have previously noted that anxiety was associated with MDIS, along with a higher overall medication and health care use.[8] Blumenthal et al[9] similarly noted that patients with anxiety and depression have 2-fold increased odds of MDIS compared with those rare individuals with confirmed multiple drug allergy syndrome. Urticarial syndromes help explain only a small fraction of MDIS cases. Omer et al[10] also confirmed that female gender and multiple comorbidities were associated with MDIS. The dramatically lower rate of treated acute-onset hypersensitivity events with second dose vaccine exposures is also compatible with what is seen in MDIS, where most drug challenges are tolerated. IgE-mediated allergy or life-threatening illness is generally not associated with MDIS.

The data we present here are a subset of the data recently reported on by Klein et al.[11] They used a less stringent definition for confirming anaphylaxis and reported anaphylaxis in 4.8 (95% CI, 3.2-6.9) per million doses administered of the Pfizer-BioNTech vaccine and 5.1 (95% CI, 3.3-7.6) with the Moderna vaccine. They similarly concluded that women and individuals with a higher number of drug intolerances are at increased risk of reporting acute hypersensitivity reactions and being diagnosed as having vaccine-associated anaphylaxis. We noted a confirmed anaphylaxis rate at the lower end of the 95% CIs noted by Klein et al,[11] 3.29 per million doses administered, both with first doses, and neither of these cases were felt by treating physicians to be potentially life-threatening. As of October 13, 2021, the CDC was reporting an estimated COVID mRNA vaccine—associated anaphylaxis rate of between 2 and 5 per 1 million doses administered.[12] We noted that having a treated acute-onset hypersensitivity event was not the major factor in failing to get a second vaccine dose in a timely fashion, but individuals failing to get a second dose in a timely fashion accounted for approximately one-fifth of all individuals with a treated reaction.

We identified an unexpectedly high rate of previous epinephrine prescriptions in our overall population, 11.3% versus 26.2% in those with treated acute-onset hypersensitivity events. This finding may warrant further investigation.

We found no evidence to support the idea that IgE-mediated allergy to PEG, or anything else, has any significant impact on the rate of treated reactions. None of our patients with acute-onset treated hypersensitivity reactions had clinical histories compatible with an IgE-mediated allergy to PEG. We noted that of 104 with first-dose treated reactions, 29 (28%) received a second dose by March 11, 2021, of whom only 6 (21%) had another treated acute-onset hypersensitivity event, none more severe than the index event. With additional follow-up on those subjects with treated acute-onset hypersensitivity events through August 23, 2021, an additional 31 (30%) were identified who received a second dose of the vaccine associated with the index event, and all tolerated the administration. This is in agreement with reports by both Krantz et al[4,13] and Greenhawt et al,[14] who noted that the of majority patients with first-dose reactions tolerate second doses without significant reactions. Wolfson et al[15] noted that even patients with positive skin test results to vaccine components, after having a reaction to a first dose, were able to tolerate second doses. Even though they estimated a negative predictive value for PEG skin testing in their study, they were not able to calculate the sensitivity, specificity, or positive predictive value. Greenhawt et al[14] also recommended against PEG skin testing, outside of the research setting, due to its unknown sensitivity and specificity in predicting acute hypersensitivity reactions.

TABLE IV. Demographics of patients with treated hypersensitivity reactions on first versus second

Characteristic	First dose reactions (N = 104)	Second dose reactions (N = 32)	Total* (N = 136)
Sex, n (%)			
Female	89 (85.6)	30 (93.8)	119 (87.5)
Not female	15 (14.4)	2 (6.3)	17 (12.5)
Age at reaction			
Mean (SD)	53.2 (16.0)	57.3 (17.1)	54.1 (16.3)
Median	50.5	51.5	51.0
Q1, Q3	41.0, 66.5	45.0, 68.5	42.0, 67.0
Range	25.0-90.0	31.0-96.0	25.0-96.0
Vaccine, n (%)			
Moderna	68 (65.4)	21 (65.6)	89 (65.4)
Pfizer	36 (34.6)	11 (34.4)	47 (34.6)
Received epinephrine, n (%)			
No	78 (75)	27 (84.4)	105 (77.2)
Yes	26 (25)	5 (15.6)	31 (22.8)
Received antihistamines, n (%)			
No	14 (13.5)	3 (9.4)	17 (12.5)
Yes	90 (86.5)	29 (90.6)	119 (87.5)
Received corticosteroids, n (%)			
No	73 (70.2)	23 (71.9)	96 (70.6)
Yes	31 (29.8)	9 (28.1)	40 (29.4)
Tryptase, n (%)			
Missing	86 (82.7)	27 (84.3)	113 (83.1)
Normal (1.3-6.7)	18 (100)	5 (100)	23 (100)
Hypertension, n (%)			
Missing	8 (7.7)	8 (25.0)	16 (11.8)
No	68 (70.8)	23 (95.8)	91 (75.8)
Yes	28 (29.2)	1 (4.2)	29 (24.2)
Hypotension, n (%)			
Missing	8 (.%)	8 (.%)	16
No	96 (100)	24 (100)	120 (100)
SpO2, n (%)			
Missing	18 (.%)	11 (.%)	29
<92	0 (0)	0 (0)	0 (0)
≥92	86 (100)	21 (100)	107 (100)
Confirmed anaphylaxis, n (%)			
No	102 (98.1)	32 (100)	134 (98.5)
Yes	2 (1.9)	0 (0)	2 (1.5)
Unrelated drug class "allergies"			
Mean (SD)	2.2 (2.2)	1.9 (2.0)	2.1 (2.2)
Median	2.0	1.0	2.0
Q1, Q3	0.0, 3.0	0.5, 2.0	0.0, 3.0
Range	0.0-10.0	0.0-7.0	0.0-10.0
Previous vaccine intolerance, n (%)			
No	93 (89.4)	29 (90.6)	122 (89.7)
Yes	11 (10.6)	3 (9.4)	14 (10.3)
Medication with polyethylene glycol, n (%)			
No	104 (100)	32 (100)	136 (100)
Direct mast cell activating agent intolerance, n (%)			
No	85 (81.7)	31 (96.9)	116 (85.3)
Yes	19 (18.3)	1 (3.1)	20 (14.7)
Nonspecific hives, swelling or "allergic reaction," n (%)			
No	14 (13.5)	3 (9.4)	17 (12.5)

(continued)

TABLE IV. *(Continued)*

Characteristic	First dose reactions (N = 104)	Second dose reactions (N = 32)	Total* (N = 136)
Yes	90 (86.5)	29 (90.6)	119 (87.5)
Chronic urticaria, n (%)			
No	87 (83.7)	28 (87.5)	115 (84.6)
Yes	17 (16.3)	4 (12.5)	21 (15.4)
Asthma, n (%)			
No	74 (71.2)	22 (68.8)	96 (70.6)
Yes	30 (28.8)	10 (31.3)	40 (29.4)
Allergic rhinitis, n (%)			
No	71 (68.3)	27 (84.4)	98 (72.1)
Yes	33 (31.7)	5 (15.6)	38 (27.9)
Food allergy, n (%)			
No	78 (75)	26 (81.3)	104 (76.5)
Yes	26 (25)	6 (18.8)	32 (23.5)
Anxiety, n (%)			
No	44 (42.3)	18 (56.3)	62 (45.6)
Yes	60 (57.7)	14 (43.8)	74 (54.4)
Mastocytosis, n (%)			
No	104 (100)	32 (100)	136 (100)
Previously prescribed an epinephrine injector, n (%)			
No	75 (72.1)	27 (84.4)	102 (75)
Yes	29 (27.9)	5 (15.6)	34 (25)
Venom hypersensitivity, n (%)			
No	102 (98.1)	32 (100)	134 (98.5)
Yes	2 (1.9)	0 (0)	2 (1.5)

SD, standard deviation.
*130 unique patients; 6 patients were counted twice because they had reactions after both doses.

TABLE V. Risk factors for experiencing a treated acute-onset hypersensitivity reaction after a COVID mRNA vaccination

Characteristic	Odds ratio	95% CI		*P* value
Effect				
Sex (female)	3.07	1.83	5.15	<.0001
Unrelated drug class	1.49	1.39	1.60	<.0001
Age at first dose	0.96	0.95	0.97	<.0001

CI, Confidence interval.

Warren et al[16] reported that skin testing to PEG, polysorbate, or vaccine itself did not have any association with clinically significant acute-onset hypersensitivity reactions.[15] They did identify a significant association between a positive basophil activation test (BAT) to PEG and a positive BAT to the mRNA vaccine administered in individuals where anaphylaxis to the vaccination was confirmed using Brighton's criteria. No IgE to PEG was found, but IgG to PEG was noted in these individuals. The presence of anti-PEG IgG has not been implicated in a pathophysiologic role in acute hypersensitivity reactions. It is likely that it is related to prior exposure to the material. Because the number of subjects in this study was very small, further studies are needed to draw conclusions regarding BAT reliability. Although Warren et al[16] conclude that an immune reaction to PEG, albeit not IgE mediated, may be partially responsible for some hypersensitivity reactions, further studies of baseline and a longitudinal evaluation of anti-PEG IgG, BATs, and other molecules will be important to further test mechanisms. We feel that this line of research will only be helpful in explaining a very small minority of treated acute-onset COVID-19 mRNA vaccination—associated reactions.

A weakness of this report is that it is heavily weighted for individuals who are relatively elderly, who are health care providers, and were given vaccines early during their rollout. Females are over-represented because they are more likely to seek medical care, including vaccinations, and predominate in the overall health care workforce. Elderly individuals are also more likely to have accumulated more drug intolerances, commonly mislabeled as drug "allergies."[17] This study is a retrospective analysis of reported treated cases and relies completely on the accuracy and timely entry of reports created by health care professionals. We understand that erroneous entry of data or omission of information could be problematic. Still, if it is not reported in the EHR, it is very unlikely to influence future medical care. Finally, individuals with MDIS tend to use more health care than average health plan members and might have been more likely to get their COVID-19 vaccines earlier than average health plan members.[8]

During the vaccine rollout period, guidance on the treatment of acute-onset hypersensitivity events was provided to the emergency departments, urgent care, and the vaccine administration centers. It was recommended that urticaria associated with COVID mRNA vaccination should be treated with a high dose of a nonsedating antihistamine, such as cetirizine up to 40 mg daily as needed.[18-20] It was noted that the use of systemic corticosteroids was not beneficial in the treatment of acute

urticaria or any cause, and the use of systemic corticosteroids can blunt the development of effective T-cell—mediated immunity.[21] Any time anaphylaxis was suspected, treatment with intramuscular epinephrine was to be provided and an acute tryptase was to be obtained within 3 hours of the onset of the event.[7] Despite guidance during the vaccine rollout on how to manage an acute hypersensitivity event, physicians in the vaccine clinics, urgent care, and the emergency department frequently continued to mistreat individuals with suspected acute-onset hypersensitivity events with systemic corticosteroids.

Kelso et al[22] reported that most of their patients with reactions associated with mRNA COVID-19 vaccinations did not have positive skin test results and were able to tolerate a second dose with mild or no symptoms that generally did not need to be treated. They noted that a wide differential diagnosis needed to be considered when evaluating acute-onset reactions after vaccination. Early onset reactions such as vasovagal reactions, vocal cord spasms, and panic attacks can imitate anaphylaxis. Symptoms such as lightheadedness, syncope, dyspnea, globus, and palpitations need to be carefully examined, and the patient's past medical history needs to be accounted for before labeling a particular reaction as potentially immunologically mediated. Somatic elements of psychosomatic responses have been shown to have physical manifestations.[22]

Hause et al[23] reported on anxiety-related events after receiving viral vector COVID-19 vaccinations. They looked at anxiety-related incidents associated with Janssen COVID-19 vaccination including syncope, dizziness, pallor, diaphoresis, nausea, vomiting, and loss of consciousness. These events were reported disproportionately in younger populations in VAERS. They theorize that media coverage of vaccination, including witness accounts of these reactions at mass vaccination sites and the stress of the pandemic, may have increased anxiety related to any COVID vaccination.[23]

We conclude that most acute reactions to mRNA COVID 19 vaccination are unlikely to be IgE-mediated. We note that treated reactions to second doses were approximately 2 times lower than with first doses. If the reactions were primarily or significantly IgE-mediated, we would expect an increase in both frequency and/or severity with an immunologic booster effect.

We also conclude that the majority of treated acute-onset hypersensitivity events are also not likely to be from a direct nanoparticle irritant effect, because in that case the frequency of reactions should be expected to be very similar between first and second dose administrations.

Understanding our current findings may help providers and patients make better informed decisions regarding COVID-19 mRNA vaccination, including second and booster doses, without resorting to unreliable testing. Treated second dose acute-onset hypersensitivity reactions are less common than first dose reactions, are typically benign, and can be relatively easily managed by direct observation for a reasonable time period after vaccination (up to 1 hour), and typically only require a nonsedating antihistamine for symptom management.

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