

Original Article

Clinical Phenotypes of Immediate First-Dose Reactions to mRNA COVID-19: A Multicenter Latent Class Analysis

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What is already known about this topic? Diverse immediate-onset reactions to a first dose of an mRNA coronavirus disease 2019 (COVID-19) vaccine have been reported by patients and allergy specialists.

What does this article add to our knowledge? Using latent class analysis, we identified 3 distinct clinical phenotypes of immediate-onset potential allergic reactions to mRNA COVID-19 vaccines: (1) Limited or Predominantly Cutaneous, (2) Sensory, and (3) Systemic.

How does this study impact current management guidelines? Clinical phenotyping of mRNA vaccine reactions using clustering of signs and symptoms may be useful for vaccine counseling and for studies assessing reaction mechanisms.

BACKGROUND: Although immediate potentially allergic reactions have been reported after dose 1 of mRNA coronavirus disease 2019 (COVID-19) vaccines, comprehensively defined subtypes have not been clearly distinguished.

OBJECTIVE: To define distinct clinical phenotypes of immediate reactions after dose 1 of mRNA COVID-19

vaccination, and to assess the relation of clinical phenotype to mRNA COVID-19 vaccine second dose tolerance.

METHODS: This retrospective study included patients with 1 or more potentially allergic symptoms or signs within 4 hours of receiving dose 1 of an mRNA COVID-19 vaccine and assessed by allergy/immunology specialists from 5 U.S. academic medical

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Abbreviations used

- COVID-19- Coronavirus disease 2019
 IgE- Immunoglobulin E
 NIAID/FAAN- National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network
 PEG- Polyethylene glycol
 SARS-CoV-2- Severe acute respiratory syndrome coronavirus 2

centers (January–June 2021). We used latent class analysis—an unbiased, machine-learning modeling method—to define novel clinical phenotypes. We assessed demographic, clinical, and reaction characteristics associated with phenotype membership. Using log-binomial regression, we assessed the relation between phenotype membership and second dose tolerance, defined as either no symptoms or mild, self-limited symptoms resolving with antihistamines alone. A sensitivity analysis considered second dose tolerance as objective signs only.

RESULTS: We identified 265 patients with dose-1 immediate reactions with 3 phenotype clusters: (1) Limited or Predominantly Cutaneous, (2) Sensory, and (3) Systemic. A total of 223 patients (84%) received a second dose and 200 (90%) tolerated their second dose. Sensory cluster (all patients had the symptom of numbness or tingling) was associated with a higher likelihood of second dose intolerance, but this finding did not persist when accounting for objective signs.

CONCLUSIONS: Three novel clinical phenotypes of immediate-onset reactions after dose 1 of mRNA COVID-19 vaccines were identified using latent class analysis: (1) Limited or Predominantly Cutaneous, (2) Sensory, and (3) Systemic. Whereas these clinical phenotypes may indicate differential mechanistic etiologies or associations with subsequent dose tolerance, most individuals proceeding to their second dose tolerated it. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;■:■■)

Key words: COVID-19; SARS-CoV-2; mRNA; Vaccine; Adverse reaction; Allergy; Hypersensitivity; Anaphylaxis; Phenotype; Cluster

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an unprecedented global health crisis. The development, testing, and rollout of effective COVID-19 vaccinations occurred expeditiously, aided by key vaccine research that had occurred over the preceding decades.¹ Among the just-in-time advances was the use of vaccine technology that relied upon mRNA to deliver the blueprint for the SARS-CoV-2 spike protein in a way that the immune system could recognize this molecule in the future.¹ Two mRNA-based vaccinations, the Pfizer-BioNTech and the Moderna COVID-19 vaccines, were authorized for use in the United States in December 2020.^{2,3}

The first reports of anaphylaxis associated with mRNA COVID-19 vaccines were from the United Kingdom on the first day of vaccination; additional reports followed in the United States and internationally.⁴ Whereas severe anaphylactic events were shown to be rare, occurring in approximately 8 per million first-

dose vaccinations,^{5–7} allergic symptoms after vaccination were more common, reported in up to 2% of mRNA COVID-19 vaccinated individuals.⁶ Owing to high efficacy against SARS-CoV-2 with an mRNA immunization series, early reports explored the safety of second mRNA COVID-19 vaccine dose in individuals who had potential allergic reactions to the first dose.^{8–11}

Immediate-type potentially allergic reactions to mRNA COVID-19 vaccinations present with variable allergic signs and symptoms.^{8,10,12,13} Whereas most patients with a first-dose reaction to an mRNA COVID-19 vaccine who receive a second dose appear to tolerate it, some patients do not proceed with a second dose and a few patients have recurrent signs and/or symptoms with second dose administration.⁸ Some immediate reactions, when carefully evaluated, reveal preexisting clinical risk factors for mimicking anaphylaxis, such as vocal cord dysfunction,¹⁴ and others appear related to the nonallergic phenotype, immunization stress-related response.¹⁵ Although most evidence to date suggests that most immediate reactions are not truly allergic or immunoglobulin E (IgE)-mediated, we use the terms potentially allergic and allergic to describe these immediate reactions in this study. To date, all clinical phenotyping of these immediate reactions has been hypothesis-driven (ie, groupings based on prior clinical knowledge of allergy specialists). Although unbiased, machine-learning methods have provided important insights for clinical phenotyping in other areas of allergy/immunology, such as asthma,^{16–18} these methods have not been used to study phenotypes of vaccine reactions. In this study, we sought to determine whether potentially allergic signs or symptoms from clinical history after mRNA COVID-19 vaccination clustered into distinct clinical phenotypes using a machine-learning clustering technique, latent class analysis, and whether those phenotypes were associated with differential second mRNA COVID-19 vaccine–dose tolerance.

METHODS

Study design

We conducted a multicenter, retrospective study at Massachusetts General Hospital, Brigham and Women's Hospital, Vanderbilt University Medical Center, Yale School of Medicine, and University of Texas Southwestern Medical Center from January 1, 2021, through June 30, 2021. At the time of study conduct, no COVID-19 vaccines had yet received full U.S. Food and Drug Administration (FDA) approval, although full approval has subsequently been given to both the Pfizer BioNTech vaccine (Comirnaty) and the Moderna vaccine (Spikevax).¹⁹ We included consecutive patients who experienced an immediate and potential allergic reaction to dose 1 of an mRNA COVID-19 Vaccine (Pfizer-BioNTech or Moderna) specified as (1) onset of symptoms within 4 hours, (2) at least 1 potentially allergic symptom, and (3) in-clinic or telehealth assessment by an allergy and immunology specialist performed after dose 1 of an mRNA COVID-19 vaccine. Potential allergic symptoms and signs included hives; swelling in the lips, eyes, tongue, or throat; throat tightness; metallic taste; numbness; tingling; flushing; erythema; tachycardia; hypertension; wheezing; shortness of breath; nausea or vomiting; abdominal pain; dizziness; lightheadedness; hypotension; or hypoxia.

Allergy and immunology assessment

Allergy and immunology assessment occurred in-person or by telehealth within each site. Excipient skin testing with polyethylene

TABLE I. Demographic, clinical, and reaction characteristics overall and by phenotype cluster

Characteristic*	All (n = 265)	Limited or Predominantly Cutaneous †(n = 185)	Sensory (n = 46)	Systemic (n = 34)
Age (y), mean (SD)	44 (15)	43 (15)	46 (14)	42 (12)
Sex				
Female	228 (86)	151 (82)	44 (96)	33 (97)
Male	37 (14)	34 (18)	2 (4)	1 (3)
Race/ethnicity				
White	185 (70)	126 (68)	36 (78)	23 (68)
Black	26 (10)	19 (10)	4 (9)	3 (9)
Asian	20 (8)	14 (8)	1 (2)	5 (15)
Other/unknown	34 (13)	26 (14)	5 (11)	3 (9)
History of atopic disease	204 (77)	143 (77)	38 (83)	23 (68)
Prior anaphylaxis	54 (20)	37 (20)	8 (17)	9 (26)
Chronic urticaria	19 (7)	14 (8)	2 (4)	3 (9)
Mast cell disorder	2 (<1)	2 (1)	0 (0)	0 (0)
Stinging insect allergy	7 (3)	4 (2)	3 (7)	0 (0)
Drug allergy	138 (52)	97 (52)	26 (57)	15 (44)
Vaccine manufacturer				
Moderna	188 (71)	134 (72)	33 (72)	21 (62)
Pfizer	80 (30)	55 (30)	14 (30)	11 (32)
Site				
MGH	102 (38)	70 (38)	20 (43)	12 (35)
BWH	76 (29)	58 (31)	14 (30)	4 (12)
VUMC	38 (14)	30 (16)	4 (9)	4 (12)
YSM	42 (16)	25 (14)	7 (15)	10 (29)
UTSW	7 (3)	2 (1)	1 (2)	4 (12)
First dose anaphylaxis				
Brighton Level 1	6 (2)	2 (1)	0 (0)	4 (12)
Brighton Level 2	28 (11)	19 (10)	2 (4)	7 (21)
Brighton Level 3	6 (2)	4 (2)	0 (0)	2 (6)
NIAID/FAAN	20 (8)	10 (5)	1 (2)	9 (26)
First dose reaction grade†				
Grade 1	32 (12)	24 (13)	6 (13)	2 (6)
Grade 2	11 (4)	9 (5)	1 (2)	1 (3)
Grade 3	0 (0)	0 (0)	0 (0)	0 (0)
Grade 4	0 (0)	0 (0)	0 (0)	0 (0)
Second dose antihistamine premedication	58 (22)	40 (22)	9 (20)	9 (26)

MGH, Massachusetts General Hospital; BWH, Brigham and Women's Hospital; VUMC, Vanderbilt University Medical Center; YSM, Yale School of Medicine; UTSW, University of Texas Southwestern.

*n (%) unless specified.

†Ring and Messmer grade.²⁰

glycol (PEG) and/or polysorbate was used at the discretion of the treating allergist.

A shared clinical approach was used by the sites that included obtaining dose-1 reaction history (timing, symptoms, severity) and any prior evidence of possible sensitization to PEG and/or polysorbates.¹ Second doses were administered with or without allergy/immunology supervision present depending on the site, with a minimum 30-minute observation after vaccination. All second dose mRNA vaccine administrations were given according to the FDA emergency use authorization, without dilution or split dosing, except for the first patient evaluated by Yale School of Medicine who was given the second dose of vaccine in 2 steps. For any individuals who did not have their second vaccination observed by allergy/immunology, follow-up phone calls were made by their treating allergist to elicit any second dose-related signs or symptoms.

Second-dose tolerance was defined as either no symptoms or mild, self-limited symptoms resolving with antihistamines alone.

Data collection

At each site, electronic health records were retrospectively reviewed for patient demographics, vaccine dose-1 history (manufacturer, reaction symptoms and signs, reaction timing, and treatment), allergist clinical assessment (including whether excipient skin testing was performed), and second-vaccine dose administration outcomes (receipt, timing of receipt, premedication, reaction symptoms and signs, and treatment as reported).^{11,13} Owing to the pragmatic nature of this study featuring real-world clinical data obtained while treating patients at each site, the symptoms and signs during the reported initial vaccine reactions were obtained from the clinical history and should be primarily thought of as "the signs and

TABLE II. Reported first dose symptoms and signs by cluster membership.

First dose symptoms and signs	Limited or Predominantly Cutaneous (n = 185) n (%)	Sensory (n = 46) n (%)	Systemic (n = 34) n (%)
Flushing/erythema	50 (27)	6 (13)	14 (41)
Numbness/tingling	0 (0)	46 (100)	22 (65)
Dizziness/lightheadedness	37 (20)	2 (4)	28 (82)
Swelling	33 (18)	7 (15)	13 (38)
Throat tightness	33 (18)	9 (20)	9 (26)
Respiratory	29 (16)	4 (9)	14 (41)
Tachycardia	33 (18)	0 (0)	15 (44)
Hives	45 (24)	1 (2)	2 (6)
Gastrointestinal symptoms	18 (10)	0 (0)	18 (53)
Hypertension	13 (7)	1 (2)	10 (29)
Metallic taste	3 (2)	3 (7)	0 (0)
Hypotension	0 (0)	0 (0)	2 (6)

symptoms as reported by the patient and observers of the reaction.² Anaphylaxis was classified using the Brighton Collaboration Criteria² and the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN)³ criteria. Ring and Messmer²⁰ was used for reaction severity.

Statistical analysis

We report descriptive statistics such as means with SDs or medians with interquartile ranges for continuous variables and numbers with frequencies for categorical variables, as appropriate.

To define novel clinical phenotypes, we performed latent class analysis using all symptoms and signs that comprised dose-1 reactions. Latent class analysis is a machine-learning modeling method to classify things into mutually exclusive and exhaustive types, or latent classes, based on their pattern on a set of categorical indicator variables.²¹ We compared fit between the different number of clusters using Akaike information criterion and selected the number of clusters with the best fit.²² We constructed a radar plot for each sign or symptom by latent class to describe the overall relationship of signs and symptoms to their latent class cluster.

Then, using multinomial regression, we assessed the relationship between demographic, clinical, and reaction characteristics and latent class phenotype membership. Next, we performed log-binomial regression to assess the relationship between latent classes and the outcome of second dose intolerance (tolerance was defined as either no symptoms or mild, self-limited symptoms resolving with antihistamines alone). We performed a sensitivity analysis that defined second dose intolerance as objective signs only. We report relative risks with their associated 95% CIs. *P* values of less than .05 were considered statistically significant.

This study was reviewed and approved by the Massachusetts General Brigham Human Research Committee with waiver of informed consent. Statistical analysis was performed using SAS (Version 9.4 SAS Institute Inc.).

RESULTS

Patient characteristics

We identified 265 patients with immediate reactions after the first dose of mRNA COVID-19 vaccine (34 [13%] anaphylaxis by Brighton Collaboration Criteria and 20 [8%] anaphylaxis by NIAID/FAAN criteria) across the 5 sites, for whom the mean age was 44 years (SD 15; range 18–89 years), 228 (86%) were

female, 204 (77%) had a history of prior atopy, and 54 (20%) had a history of prior anaphylaxis (Table I).

Latent class analysis of first dose symptoms and signs demonstrated 3 phenotype clusters (Table II and Figure 1). Cluster 1, which we refer to as Limited or Predominantly Cutaneous (70%), was the largest cluster and was defined primarily by the presence of hives or flushing, with rare secondary features of wheezing/shortness of breath, swelling, tachycardia, and throat tightness. Cluster 2, which we refer to as Sensory (17%), was defined primarily by tingling or numbness and the absence of hives, with less-frequent throat tightness and swelling. Cluster 3, which we refer to as Systemic (13%), was defined primarily by the presence of dizziness/lightheadedness, gastrointestinal symptoms, and tachycardia in the absence of hives, with less-frequent flushing, tingling, and numbness.

In univariate analyses, female sex was associated with an increased relative risk of being in the Sensory cluster (*n* = 44; 96% of members) and the Systemic cluster (*n* = 33; 97% of members), compared with the Limited or Predominantly Cutaneous cluster (*n* = 151; 82% of members) as the reference (χ^2 *P* value .07; Table I). Indeed, almost all of the members of the Sensory and Systemic clusters were women. A history of atopy was associated with membership in the Sensory cluster (*n* = 38; 83% of members) but not the Systemic cluster (*n* = 23; 68% of members), compared to the Limited or Predominantly Cutaneous cluster (*n* = 143; 77% of members) (χ^2 *P* value .29). Meeting the NIAID/FAAN criteria for anaphylaxis was associated with the Systemic cluster (*n* = 9; 26% of members) compared with the Limited or Predominantly Cutaneous Symptoms cluster (*n* = 10; 5% of members) and Sensory (*n* = 1; 2% of members) (χ^2 *P* value < .001).

Results of the multinomial regression model showed that female sex was associated with increased risk of Sensory cluster membership (relative risk [RR] 4.95; 95% CI 1.14–21.44) and Systemic cluster membership (RR 7.43; 95% CI 0.98–56.22; Table E1; available in this article's Online Repository at www.jaci-inpractice.org). First dose reactions meeting NIAID/FAAN anaphylaxis criteria were associated with an increased risk of Systemic cluster membership (RR 6.30; 95% CI 2.33–17.01).

Second dose tolerance

There were 223 patients (84%) who received a second mRNA COVID-19 vaccine dose and 200 (90%) of those who received a second dose tolerated it. The frequency of proceeding to the

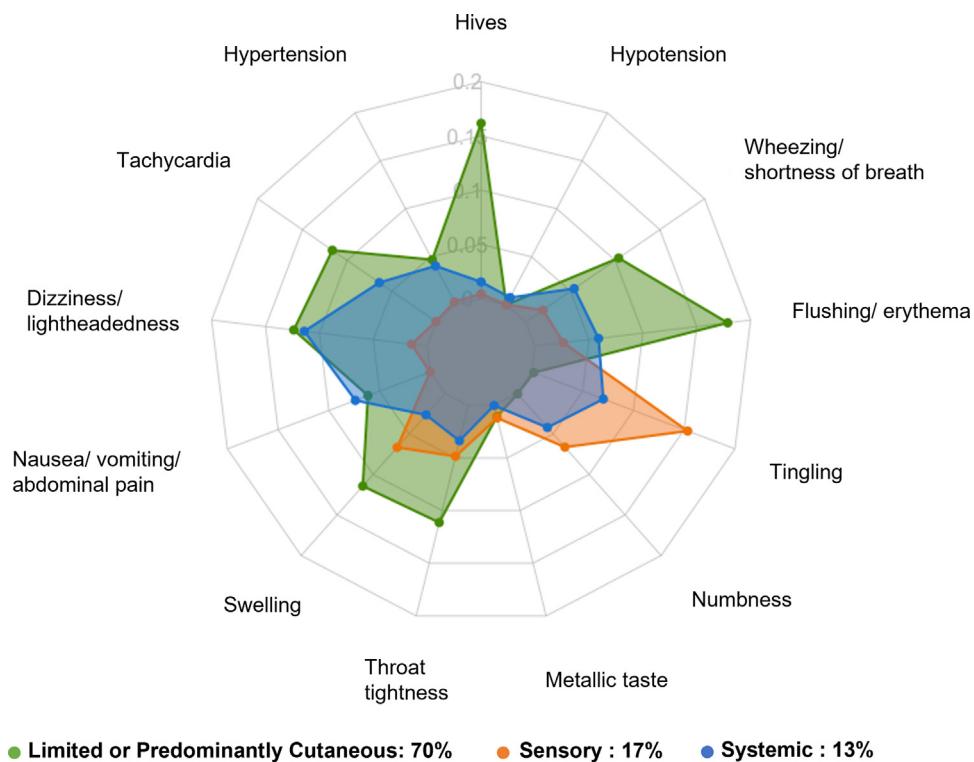


FIGURE 1. Radar plot of first dose mRNA COVID-19 vaccine potentially allergic symptoms and signs, created using latent class analysis of first dose symptoms and signs. Three phenotypes are defined: (1) Limited or Predominantly Cutaneous, (2) Sensory, characterized by tingling, numbness, throat tightness, swelling, and/or metallic taste, and (3) Systemic, characterized by gastrointestinal symptoms, dizziness, lightheadedness, hypotension, wheezing, and/or shortness of breath. Potentially allergic symptoms and signs were patient-reported or allergist-documented during the clinical history and included hives; swelling in the lips, eyes, tongue, or throat; throat tightness; metallic taste; numbness; tingling; flushing; erythema; tachycardia; hypertension; wheezing; shortness of breath; nausea or vomiting; abdominal pain; dizziness; lightheadedness; hypotension; and hypoxia.

TABLE III. First dose symptoms and signs and second dose tolerance

	First dose reactions (n = 265)	Second doses received (n = 223)	Second doses tolerated (n = 200)
Symptom	First dose symptoms and signs n (% of total patients)	Received second dose n (% of those who experienced the symptom)	Tolerated the second dose n (% of those who received the second dose)
Flushing/erythema	69 (26)	56 (81)	55 (98)
Numbness/tingling	68 (26)	57 (84)	47 (82)
Dizziness/lightheadedness	66 (25)	50 (76)	45 (90)
Swelling	52 (20)	44 (85)	34 (77)
Throat tightness	50 (19)	34 (68)	30 (88)
Respiratory	47 (18)	37 (79)	34 (92)
Tachycardia	48 (18)	34 (71)	34 (100)
Hives	47 (18)	40 (85)	34 (85)
Gastrointestinal symptoms	35 (13)	29 (83)	26 (90)
Hypertension	24 (9)	18 (75)	16 (89)
Metallic taste	6 (2)	4 (67)	3 (75)
Hypotension	2 (0.75)	1 (50)	1 (100)

second dose and tolerance of the second dose by specific signs and symptoms of the first dose reactions are displayed in Table III.

Among those assigned to each cluster, 157 of 185 patients (85%) in the Limited or Predominantly Cutaneous Symptoms

cluster went on to receive a second dose despite their first dose reaction, compared with 41 of 46 patients (89%) in Sensory and 25 of 34 patients (74%) in Systemic (Table IV). Among those assigned to each cluster who received a second mRNA COVID-19 vaccine dose, tolerance was 144 of 157 (92%) for

TABLE IV. Relation between clinical phenotype (latent class cluster) and second dose intolerance

Latent class phenotype*	Received second dose (n = 223) (n, %)	Second dose intolerance†		Second dose intolerance (Sensitivity analysis definition, any objective signs)	
		Events‡ n (%)	Unadjusted RR, 95% CI	Events n (%)	Unadjusted RR, 95% CI
Limited or Predominantly Cutaneous	157 (70)	13 (8)	Reference	7 (4)	Reference
Sensory	41 (18)	8 (20)	3.43 (1.09–10.79)	2 (5)	1.10 (0.22–5.50)
Systemic	25 (11)	2 (8)	1.32 (0.40–4.34)	2 (8)	1.86 (0.37–9.53)

*See Table II for signs and symptoms in each cluster.

†Cluster Limited or Predominantly Cutaneous as reference.

‡Of the 23 patients with second dose intolerance, 22 (96%) were female.

Limited or Predominantly Cutaneous, 33 of 41 (80%) for Sensory, and 23 of 25 (92%) for Systemic.

In unadjusted log-binomial regression assessing the relationship between latent classes and second dose intolerance, using Limited or Predominantly Cutaneous as the reference cluster, the risk of second dose intolerance was increased for Sensory (RR 3.43; 95% CI 1.09–10.79) and Systemic (RR 1.32; 95% CI 0.40–4.34; Table IV). With the definition of second dose intolerance as any objective sign with second dose and using Limited or Predominantly Cutaneous as the reference cluster, there was a nonsignificant increased risk of second dose intolerance with Sensory cluster membership (unadjusted RR 1.10; 95% CI 0.22–5.50) or Systemic cluster (unadjusted RR 1.86; 95% CI 0.37–9.53; Table IV).

DISCUSSION

Since mRNA COVID-19 vaccination began in late 2020, allergy specialists have observed and reported on the varied clinical presentations among those with immediate-onset potentially allergic reactions and identified different phenotypes.^{11,23,24} Unbiased, machine-learning cluster analytic methods have proved useful in diverse areas of medicine,^{25,26} including asthma^{16,17} and atopic dermatitis²⁷; as such, we hypothesized that clinical phenotyping of immediate reactions after mRNA vaccines has the potential to be highly relevant in elucidating potential reaction mechanisms. In the midst of the ongoing COVID-19 pandemic with recommendations for booster mRNA COVID-19 vaccinations, granular information stratified by sign, symptom, phenotype, and/or cluster is immediately useful to patients and clinicians in vaccine counseling. Using the unbiased method latent class analysis, we identified 3 distinct phenotype clusters: (1) Limited or Predominantly Cutaneous, (2) Sensory, and (3) Systemic. Similar to what we have reported from more than 250 first dose immediate reactors,⁹ in this study, there was a high frequency of second dose tolerance (90%) in those who received their second dose despite experiencing a first dose reaction.

Although potential allergic reactions after receipt of mRNA COVID-19 vaccines remain rare, the overall incidence of anaphylaxis after mRNA COVID-19 vaccines is higher than the previously described 1.3 per million dose rate of anaphylaxis associated with non-mRNA vaccines.^{5,28} The underlying mechanism of allergic and potentially allergic reactions to these vaccines, including anaphylaxis, is not known. Elucidation of the mechanisms behind COVID-19 mRNA vaccine associated allergic and potentially allergic reactions is important not only to

risk-stratify patients and guide current diagnosis and management but also to inform development of future vaccines and therapeutics that rely on mRNA technology. Immediate reaction mechanisms may include cases of IgE-mediated allergy (eg, rare PEG allergy),^{24,29,30} non-IgE-mediated mechanisms such as IgG/IgM and complement activation-related pseudoallergy,^{31,32} exacerbation of underlying disorders such as chronic idiopathic urticaria/angioedema, and nonallergic reactions such as vocal cord dysfunction,³³ vasovagal reactions, and immunization stress-related responses.^{34,35} As has been previously posited, our identification of phenotype clusters supports the assumption that there may be multiple distinct and heterogeneous mechanistic pathways that lead to immediate-onset potentially allergic mRNA COVID-19 vaccine reactions. In addition, our findings suggest that mechanistic studies must strongly consider studying mechanisms within a homogeneous phenotype, rather than including reaction cases based exclusively on timing of symptom onset.^{31,32}

Identification of phenotype membership may also associate with outcomes of future doses. In this study, patients in the Limited or Predominantly Cutaneous cluster appeared most likely to both take and tolerate their second mRNA COVID-19 vaccine dose, which may suggest, for example, a non-IgE-mediated urticaria could be treated with antihistamine premedication. We hypothesize that patients in the Sensory cluster, characterized by tingling or numbness and the absence of hives, and lesser reports of throat tightness or swelling, may represent those with nonallergic symptoms including vocal cord dysfunction and immunization stress-related responses. Clinical management of patients in this cluster may include direct observation of subsequent doses with real-time evaluation of symptoms by those with expertise in vocal cord dysfunction, anxiety, and/or biofeedback. Patients in the Systemic phenotype cluster, characterized by dizziness/light-headedness, gastrointestinal symptoms, and tachycardia in the absence of hives, with less prevalent flushing, tingling, and numbness, most frequently met NIAID/FAAN criteria for anaphylaxis. However, this group could potentially also include those with vasovagal symptoms, immunization stress-related response and anxiety, in whom reassurance, prehydration, and body positioning may improve tolerance. Clinical management of patients in this cluster may be improved by direct observation of subsequent doses by physicians capable of critically evaluating and managing anaphylaxis. Inclusion of vital signs and laboratory assessments (eg, tryptase, complement, cytokines, and other mediators) may help to further refine immediate-reaction phenotypes into biologically distinct clusters.

Strengths of this study include specific reaction details in a large sample of patients from multiple sites who experienced

potentially allergic reactions to their first dose of an mRNA COVID-19 vaccine and received an allergy consultation. However, although the overall study included a large number of patients, the tolerance analysis had limited power given that few individuals did not tolerate their second dose. As such, we presented only an unadjusted analysis. Our study may be limited by information bias. Owing to the study's pragmatic nature, there was no opportunity for prospective definitions of signs and symptoms captured during the allergist's clinical history, and thus, these variables are not standardized nor delineated as to their objectivity. Furthermore, symptoms or signs reported by patients during an immediate reaction are not always objectively verifiable by an observer. Our study may also suffer from a referral bias, in that all of the patients were assessed by allergy specialists. In addition, selection bias may be present in second dose tolerance assessments given that patients in the different phenotype clusters had differential uptake of second dose (ie, lowest in the Systemic cluster). However, we observed a high frequency of tolerance among those who did receive their dose, even those in the Systemic cluster. Similar to other studies and with other vaccines, vaccine reactors in our multicenter cohort were predominantly women, and as such, our findings may not generalize to males. Because this study only examined those with first dose reactions and receipt of second dose, it is not known whether similar trends or patterns will extend to booster doses that are now routinely recommended. Despite these limitations, we consider these findings to have substantial clinical value to an allergist when evaluating a patient with an immediate-onset vaccine reaction and to the researcher trying to understand the mechanisms of these reactions, generate testable hypotheses that can be prospectively evaluated, and design the next generations of mRNA vaccines and therapeutics.

In summary, we describe 3 distinct phenotype clusters for first dose vaccine reactions to mRNA COVID-19 vaccines. While we are unable to conclude that these phenotype clusters are etiologically or mechanistically distinct and/or associated with differential outcomes of second dose intolerance, we consider our presentation of phenotype clustering across a large group of patients to be hypothesis-generating and useful for clinical care and vaccine counseling. Future research is needed to validate and/or refine phenotypes and understand their mechanistic basis.

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REFERENCES

- Dolgin E. The tangled history of mRNA vaccines. *Nature* 2021;597:318-24.
- Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;384:403-16.
- Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020;383:2603-15.
- de Vrieze J. Pfizer's vaccine raises allergy concerns. *Science* 2021;371:10-1.
- Greenhawt M, Abrams EM, Shaker M, Chu DK, Khan D, Akin C, et al. The risk of allergic reaction to SARS-CoV-2 vaccines and recommended evaluation and management: a systematic review, meta-analysis, GRADE assessment, and international consensus approach. *J Allergy Clin Immunol Pract* 2021;9:3546-67.
- Blumenthal KG, Robinson LB, Camargo CA Jr, Shenoy ES, Banerji A, Landman AB, et al. Acute allergic reactions to mRNA COVID-19 vaccines. *JAMA* 2021;325:1562-5.
- Klein NP, Lewis N, Goddard K, Fireman B, Zerbo O, Hanson KE, et al. Surveillance for adverse events after COVID-19 mRNA vaccination. *JAMA* 2021;326:1390-9.
- Krantz MS, Kwah JH, Stone CA Jr, Phillips EJ, Ortega G, Banerji A, et al. Safety evaluation of the second dose of messenger RNA COVID-19 vaccines in patients with immediate reactions to the first dose. *JAMA Intern Med* 2021;181:1530-3.
- Krantz MS, Bruusgaard-Mouritsen MA, Koo G, Phillips EJ, Stone CA Jr, Garvey LH. Anaphylaxis to the first dose of mRNA SARS-CoV-2 vaccines: don't give up on the second dose. *Allergy* 2021;76:2916-20.
- Wolfson AR, Robinson LB, Li L, McMahon AE, Cogan AS, Fu X, et al. First dose mRNA COVID-19 vaccine allergic reactions: limited role for excipient skin testing. *J Allergy Clin Immunol Pract* 2021;9:3308-20. e3.
- Rasmussen TH, Mortz CG, Georgsen TK, Rasmussen HM, Kjaer HF, Bindslev-Jensen C. Patients with suspected allergic reactions to COVID-19 vaccines can be safely revaccinated after diagnostic work-up. *Clin Transl Allergy* 2021;11:e12044.
- Shimabukuro T, Nair N. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine. *JAMA* 2021;325:780-1.
- Shimabukuro T. Allergic reactions including anaphylaxis after receipt of the first dose of Pfizer-BioNTech COVID-19 vaccine—United States, December 14–23, 2020. *Am J Transplant* 2021;21:11332-7.
- Leong P, Al-Harrasi M, Carr B, Leahy E, Bardin PG, Barnes S. Vocal cord dysfunction/inducible laryngeal obstruction(s) mimicking anaphylaxis during SARS-CoV-2 (COVID-19) vaccination. *J Allergy Clin Immunol Pract* 2022;10:1380-1.
- World Health Organization. Immunization Stress-Related Response. A Manual for Program Managers and Health Professionals to Prevent, Identify and Respond to Stress-Related Responses Following Immunization. Geneva: WHO; Accessed June 29, 2022. <https://apps.who.int/iris/bitstream/handle/10665/330277/9789241515948-eng.pdf>.
- Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218-24.
- Siroix V, Basagana X, Boudier A, Pin I, Garcia-Aymerich J, Vesin A, et al. Identifying adult asthma phenotypes using a clustering approach. *Eur Respir J* 2011;38:310-7.
- Siroix V, Gonzalez JR, Bouzigon E, Curjoric I, Boudier A, Imboden M, et al. Genetic heterogeneity of asthma phenotypes identified by a clustering approach. *Eur Respir J* 2014;43:439-52.
- U.S. Centers for Disease Control and Prevention. Stay Up to Date with Your COVID-19 Vaccines. Atlanta, GA: U.S. CDC. Accessed June 29, 2022. <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html>
- Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977;1:466-9.
- Mori M, Krumholz HM, Allore HG. Using latent class analysis to identify hidden clinical phenotypes. *JAMA* 2020;324:700-1.
- Burnham KP, Anderson DR, editors. Model Selection and Multimodel Inference: A Practical Information-Theoretic Approach. New York: Springer; 2007.
- Kaplan B, Farzan S, Coscia G, Rosenthal DW, McInerney A, Jongeo AM, et al. Allergic reactions to COVID-19 vaccines and addressing vaccine hesitancy: Northwell Health experience. *Ann Allergy Asthma Immunol* 2021;128:161-168.e1.
- Sellaturry P, Nasser S, Islam S, Gurugama P, Ewan PW. Polyethylene glycol (PEG) is a cause of anaphylaxis to the Pfizer/BioNTech mRNA COVID-19 vaccine. *Clin Exp Allergy* 2021;51:861-3.
- Grant RW, McCloskey J, Hatfield M, Uratsu C, Ralston JD, Bayliss E, et al. Use of latent class analysis and k-means clustering to identify complex patient profiles. *JAMA Netw Open* 2020;3:e2029068.
- Wallace ZS, Zhang Y, Perugino CA, Naden R, Choi HK, Stone JH. Clinical phenotypes of IgG4-related disease: an analysis of two international cross-sectional cohorts. *Ann Rheum Dis* 2019;78:406-12.
- Roduit C, Frei R, Depner M, Karvonen AM, Renz H, Braun-Fahrlander C, et al. Phenotypes of atopic dermatitis depending on the timing of onset and progression in childhood. *JAMA Pediatr* 2017;171:655-62.
- McNeil MM, DeStefano F. Vaccine-associated hypersensitivity. *J Allergy Clin Immunol* 2018;141:463-72.
- McSweeney MD, Mohan M, Commins SP, Lai SK. Anaphylaxis to Pfizer/BioNTech mRNA COVID-19 vaccine in a patient with clinically confirmed PEG allergy. *Front Allergy* 2021;2:715844.
- Picard M, Drolet JP, Masse MS, Filion CA, AL F, Fein M, et al. Safety of COVID-19 vaccination in patients with polyethylene glycol allergy: a case series. *J Allergy Clin Immunol Pract* 2022;10:620-625.e1.

31. Warren CM, Snow TT, Lee AS, Shah MM, Heider A, Blomkalns A, et al. Assessment of allergic and anaphylactic reactions to mRNA COVID-19 vaccines with confirmatory testing in a US regional health system. *JAMA Netw Open* 2021;4:e2125524.
32. Lim XR, Leung BP, Ng CYL, Tan JW, Chan GYL, Loh CM, et al. Pseudo-anaphylactic reactions to Pfizer BNT162b2 vaccine: report of 3 cases of anaphylaxis post Pfizer BNT162b2 vaccination. *Vaccines (Basel)* 2021; 9:974.
33. Leong P, Al-Harrasi M, Carr B, Leahy E, Bardin PG, Barnes S. Vocal cord dysfunction/inducible laryngeal obstruction(s) mimicking anaphylaxis during SARS-CoV-2 (COVID-19) vaccination. *J Allergy Clin Immunol Pract* 2022;10:1380-1.
34. Risma KA, Edwards KM, Hummell DS, Little FF, Norton AE, Stallings A, et al. Potential mechanisms of anaphylaxis to COVID-19 mRNA vaccines. *J Allergy Clin Immunol* 2021;147:2075-20782 e2.
35. Kelso JM. Misdiagnosis of systemic allergic reactions to mRNA COVID-19 vaccines. *Ann Allergy Asthma Immunol* 2021;127:133-4.

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TABLE E1. Demographic and clinical characteristics associated with clinical phenotype (latent class) membership*

Characteristics	Limited or Predominantly Cutaneous (n = 185) RR (95% CI)	Sensory (n = 46) RR (95% CI)	Systemic (n = 34) RR (95% CI)
Age	Reference	1.01 (0.99–1.04)	1.00 (0.97–1.02)
Sex			
Female	Reference	4.95 (1.14–21.44)	7.43 (0.98–56.22)
Male	Reference	Reference	Reference
Race/ethnicity			
White	Reference	1.49 (0.53–4.15)	1.58 (0.44–5.66)
Black	Reference	1.09 (0.26–4.63)	1.37 (0.25–7.54)
Asian	Reference	0.37 (0.04–3.50)	3.10 (0.64–14.91)
Other/unknown	Reference	Reference	Reference
History of atopic disease	Reference	1.40 (0.60–3.22)	0.61 (0.28–1.36)
Prior anaphylaxis	Reference	0.84 (0.36–1.96)	1.44 (0.62–3.35)
Chronic urticaria	Reference	0.56 (0.12–2.53)	1.18 (0.32–4.36)
Mast cell disorder	Reference	-	-
Stinging insect allergy	Reference	3.16 (0.68–14.63)	-
Drug allergy	Reference	1.21 (0.63–2.34)	0.89 (0.41–1.92)
Vaccine manufacturer			
Moderna	Reference	0.97 (0.47, 1.98)	0.61 (0.29, 1.32)
Pfizer	Reference	1.03 (0.51, 2.07)	1.36 (0.61, 3.04)
First-dose anaphylaxis			
Brighton level 1	Reference	-	-
Brighton level 2	Reference	-	-
Brighton level 3	Reference	-	-
NIAID/FAAN	Reference	0.39 (0.05–3.12)	6.30 (2.33–17.01)
First-dose reaction grade‡			
Grade 1	Reference	1.01 (0.39–2.63)	0.42 (0.09–1.86)
Grade 2	Reference	0.43 (0.05–3.52)	0.59 (0.07–4.84)
Grade 3 or 4	Reference	-	-
Second-dose antihistamine premedication	Reference	0.88 (0.39–1.98)	1.31 (0.56–3.02)

*Bold indicates statistical significance.

‡Ring and Messmer grade.²⁰