A randomized double-blinded trial to assess recurrence of systemic allergic reactions following COVID-19 mRNA vaccination

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Background: Systemic allergic reactions (sARs) following coronavirus disease 2019 (COVID-19) mRNA vaccines were initially reported at a higher rate than after traditional vaccines.
Objective: We aimed to evaluate the safety of revaccination in these individuals and to interrogate mechanisms underlying these reactions.
Methods: In this randomized, double-blinded, phase 2 trial, participants aged 16 to 69 years who previously reported a convincing sAR to their first dose of COVID-19 mRNA vaccine were randomly assigned to receive a second dose of BNT162b2 (Comirnaty) vaccine and placebo on consecutive days in a blinded, 1:1 crossover fashion at the National Institutes of Health. An open-label BNT162b2 booster was offered 5 months later if the second dose did not result in severe sAR. None of the participants received the mRNA-1273 (Spikevax) vaccine during the study. The primary end point was recurrence of sAR following second dose and booster vaccination; exploratory end points included biomarker measurements.
Results: Of 111 screened participants, 18 were randomly assigned to receive study interventions. Eight received BNT162b2 second dose followed by placebo; 8 received placebo followed by BNT162b2 second dose; 2 withdrew before receiving any study intervention. All 16 participants received the booster dose. Following second dose and booster vaccination, sARs recurred in 2 participants (12.5%; 95% CI, 1.6 to 38.3). No sAR occurred after placebo. An anaphylaxis mimic, immunization stress-related response (ISRR), occurred more commonly than sARs following both vaccine and placebo and was associated with higher predose anxiety scores, paresthesias, and distinct vital sign and biomarker changes.
Conclusions: Our findings support revaccination of individuals who report sARs to COVID-19 mRNA vaccines. Distinct clinical and laboratory features may distinguish sARs from ISRRs. (J Allergy Clin Immunol 2024;■■■:■■■-■■■.)

Key words: *Anaphylaxis, COVID-19, mRNA, vaccine, immunization stress-related response, ISRR, allergic reaction, PEG*

Within days of coronavirus disease 2019 (COVID-19) mRNA vaccination in the general public, reports of systemic allergic reactions (sARs) emerged, prompting global health authorities to advise against subsequent vaccination in affected individuals.[1,2] A meta-analysis estimated the anaphylaxis rate following the first dose of COVID-19 mRNA vaccines to be 7.91 per 1 million vaccinations, severalfold higher compared with estimated anaphylaxis rates of 0.3 to 2.9 per 1 million doses for conventional non–COVID-19 vaccines and 1.35 to 1.83 per 1 million doses following influenza vaccination.[3-6] However, the true rate may be lower, depending on the surveillance method employed (passive reporting vs active surveillance) and criteria used to define anaphylaxis, as noted by more recent reports that found the anaphylaxis rates to be in the same range as for other common non–COVID-19 vaccines.[7,8] Reported reactions were rapid in onset and predominantly affected middle-aged women with a prior history of allergy. The mechanism by which mRNA vaccines trigger sARs remains unknown. Excipients, including polyethylene glycol (PEG), have been hypothesized to trigger anaphylaxis through IgE-mediated or non-IgE–mediated pathways,[9,10] but current evidence is insufficient to support these mechanisms as the cause of mRNA

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Abbreviations used
AE: Adverse event
CoFAR: Consortium of Food Allergy Research
COVID-19: Coronavirus disease 2019
FDA: Food and Drug Administration
HR: Heart rate
IQR: Interquartile range
ISRR: Immunization stress–related response
NIAID: National Institute of Allergy and Infectious Diseases
NIH: National Institutes of Health
PEG: Polyethylene glycol
sAR: Systemic allergic reaction
SBP: Systolic blood pressure

vaccine–associated sARs. Current US Centers for Disease Control and Prevention guidance, the manufacturer's instructions per the Food and Drug Administration (FDA) insert, and the Summary of Product Characteristics) state that the mRNA vaccines are contraindicated in individuals with a history of severe allergic reaction to these vaccines or to any of the excipients in the vaccines.[11-13] As multiple vaccine doses are needed to provide optimal protection against severe COVID-19 and with growing applications for mRNA technology, we conducted the COVID-19 Vaccine-Associated Allergic Reaction (COVAAR) trial to determine whether individuals who reported sARs to their first dose of COVID-19 mRNA vaccine could safely receive subsequent doses and to interrogate the underlying mechanisms.

METHODS

Study design and participants

This phase 2, randomized, double-blinded, placebo-controlled, crossover study was conducted at the National Institutes of Health (NIH) Clinical Center in Bethesda, Maryland. Individuals 16 to 69 years of age who reported an sAR following their first dose of BNT162b2 (Comirnaty; Pfizer-BioNTech, New York, NY) or mRNA-1273 (Spikevax; Moderna, Cambridge, Mass) COVID-19 mRNA vaccine were enrolled. The sARs were defined using the modified Consortium of Food Allergy Research (CoFAR) grading scale, Version 3.0 (see Table E1 in this article's Online Repository at www.jacionline.org),[14] as CoFAR grade 1 reactions with elevated tryptase (>1.2 × baseline + 2 ng/mL) or grade 2 or 3 reactions within 3 hours of vaccine administration. A complete list of inclusion and exclusion criteria is available with the protocol (see the Online Repository at www.jacionline.org). Additional details about study design are provided in the Online Repository.

The protocol was approved by the NIH Institutional Review Board. All participants provided written informed consent before participation. An independent Data and Safety Monitoring Board had access to unblinded data and conducted safety reviews after the first 5 participants received initial study intervention and then every 6 months until study completion. The trial is registered with ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT04977479).

Randomization and blinding

Using block randomization, participants were randomly assigned in a 1:1 ratio to receive second dose of BNT162b2 vaccine and saline placebo in opposite arms on consecutive days in a crossover fashion. The pharmacists prepared blinded doses according to the randomization scheme generated by the statisticians and were responsible for maintaining security of the assignments. The syringes containing blinded doses were concealed with a white label to avoid unintentional blinding. The participants, the clinical staff, and the study team were blinded to the order of study vaccine assignments for second vaccine dose and placebo. Primary analysis including reaction type and sAR grading was completed before unblinding. The study team was unblinded after all participants completed second doses. Participants were unblinded at the end of the study. The booster dose was administered open-label.

Procedures

A 0.3-mL dose of 100 μg/mL of monovalent BNT162b2 mRNA vaccine (targeting original WH-1 strain) was administered in the deltoid muscle in all except 1 participant as the second and booster vaccine dose. Bivalent BNT162b2 vaccine (targeting original WH-1 and Omicron BA.4/BA.5 strains) was available for only 1 participant's booster dose based on the timing of emergency use authorization by the FDA. The manufacturer's instructions were followed to store, prepare, and administer the vaccine.[12] None of the participants received mRNA-1273 vaccine during the study, including the 1 participant who had received mRNA-1273 for their first dose. Normal saline placebo was prepared in a similar manner at room temperature.

Following blinded second vaccine dose and placebo, participants were directly observed for 3 hours and monitored for a total of 24 hours in the intensive care unit to assess for adverse events (AEs). Follow-up visits were conducted by telephone within 7 days and in person approximately 30 days from the time of initial study intervention. Participants who did not have a severe (CoFAR grade 3 or higher) sAR to either blinded second dose were offered an unblinded BNT162b2 booster dose 5 months later that was administered in an outpatient setting and followed by direct observation for 2 hours. Skin testing to BNT162b2 vaccine and excipients was also performed during this visit. Skin testing was intentionally not performed at the initial study visit to avoid influence of the skin testing results on participants' blinded dose reactions. Participants were assessed for AEs via telephone call within 7 days and in person approximately 30 days following booster and were unenrolled if no AEs of concern remained. AEs were evaluated with additional consultations and testing as needed. A large panel of mechanistic blood and urinary biomarkers were performed before dose and 35 minutes and 2 hours after dose, and some biomarkers were performed at baseline and 1, 5, and 6 months following visit 1. Additional details are available in the Online Repository (at www.jacionline.org).

Outcomes

The primary end point was defined as the proportion of participants who developed a recurrent sAR following in-study BNT162b2 vaccine dose or doses within 3 hours after vaccination. Secondary end points included proportion of participants who, following in-study vaccine doses, developed (1) recurrent severe sAR (CoFAR grade 3 or higher), (2) recurrent mild or moderate allergic reaction (CoFAR grade 1 or 2 irrespective of tryptase), (3) recurrent anaphylactic reaction (level 1-3 original

Brighton Collaboration criteria),[15] (4) recurrent sAR of grade 2 or higher following in-study second vaccine dose compared with placebo, and (5) recurrent lower- or higher-grade sAR following second or booster dose. The safety analysis, including solicited and unsolicited AEs, is provided as descriptive data. Due to the brief washout period between second dose of BNT162b2 and placebo, the reported AEs overlapped with a significant bias potential if an attempt was made to assign causality to vaccine or placebo and hence are provided together. AEs following booster doses are reported separately.

Statistical analysis

While the goal was to enroll up to 100 participants, it was recognized before recruitment that enrollment may be limited to a much smaller cohort, such as 5 to 10 subjects, and that this would still provide valuable data. The ability to recruit was impacted by the rarity of these allergic reactions in the population, pandemic-related travel and other restrictions, acceptability of repeat vaccination, and a 4-day hospital stay among individuals who had these reactions. As the primary goal of the study was estimation, example Clopper-Pearson 95% exact CIs were presented for the primary end point and estimation of the risk difference of active vaccine versus placebo using the McNemar approach as a function of varying sample size and varying outcomes to illustrate achievable precision of estimates. The primary end point estimates and all secondary end points looking at only the blinded vaccine result were estimated using Clopper-Pearson CIs. The secondary end point that compares sARs in the blinded vaccine versus placebo within a participant was estimated using an exact CI based on McNemar test. Comparison of sAR grade in prestudy vaccine with study vaccines was analyzed with a signed-rank test as prespecified, but a paired *t* test–based CI was added to provide easy interpretability. As the study is mainly descriptive, no adjustments for multiplicity were incorporated; all comparative results are presented as two-sided 95% CIs instead of *P* values. All participants who received one or more study dose were included in per-protocol primary and safety analyses.

Analyses of exploratory end points such as mechanistic biomarkers and anxiety scores were post hoc, where associations with various reaction categories were assessed. As results for each of 3 doses per participant could appear in a single analysis, all CIs of differences between reaction categories or within a reaction category used a small sample modification to generalized estimating equations[16] where possible and controlled for the dose type; see the Online Repository (at www.jacionline.org) for details. In contrast to the generalized estimating equation analyses that estimate effect sizes of differences, figures that plot data points show simple means and SE bars within reaction categories. That is, the plotted SEs treat observations as independent and should be considered approximate. Data analysis was performed using R Version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism Version 9.4.1 (GraphPad Software, Boston, Mass).

Data availability

The deidentified clinical trial results (primary and secondary end points, and safety data including AEs) were submitted to https://clinicaltrials.gov (identifier NCT04977479) on June 17, 2023, and have been made publicly available. Additional information to ensure appraisal of the quality and robustness of the findings and the study protocol and statistical analysis plan with all changes are available in the Online Repository (at www.jacionline.org).

RESULTS

Between September 8, 2021, and June 17, 2022, 111 individuals were screened. Of these, 18 underwent randomization. One of these individuals was deemed ineligible due to partial second vaccination, and another was lost to follow-up; neither received any study interventions. Finally, 16 participants received all study interventions and were included in primary and safety analyses (Fig 1). During the double-blinded crossover phase, 8 participants received BNT162b2 vaccine on the first day and placebo the next day; another 8 participants received placebo on the first day and vaccine the next day. All participants elected to receive an open-label BNT162b2 booster dose (median 156 days from day 1 of study, interquartile range [IQR] 154-160 days).

Median age of participants was 45.5 years (IQR 36–51 years), 50% were White (non-Hispanic), and all but one were female. Past history of allergic disease and anaphylaxis was common (Table I; Table E2 in the Online Repository at www.jacionline.org). None of the participants reported a clinical history of allergy to PEG-containing medications or vaccines. Fifteen (94%) participants received BNT162b2 and 1 (6%) participant received mRNA-1273 as their first vaccine of a 2-dose series in a community setting. Fifteen (94%) participants reported symptoms consistent with CoFAR grade 3 (severe) sAR, and 1 (6%) participant reported CoFAR grade 2 (moderate) sAR.[14] All first-dose reactions met National Institute of Allergy and Infectious Diseases (NIAID)/Food Allergy and Anaphylaxis Network anaphylaxis criteria,[17] 12 (75%) met original Brighton Collaboration criteria[15] and 8 met revised Brighton criteria for anaphylaxis (Table II).[18] Median time to symptom onset was 5 minutes (range 1-35 minutes). Common symptoms included dizziness (81%), throat tightness (75%), shortness of breath (69%), paresthesias (56%), coughing (31%), and hives (25%). Notable signs included tongue angioedema (19%), hypotension (12%), hypoxia (6%), and stridor (6%) (Fig E1 in the Online Repository at www.jacionline.org). Intramuscular epinephrine was administered in 10 participants (62.5%); 1 participant additionally received epinephrine infusion for persistent hypotension.

Regarding our primary end point, among the 16 participants, the same 2 participants (12.5%) (participants A and B [Fig 2, *A*]) (95% CI, 1.6 to 38.3) developed sARs meeting CoFAR criteria following their second vaccine and the booster doses. Of these, sARs in only 1 participant (6.3%) (participant A) (95% CI, 0.2 to 30.2) met original Brighton criteria for anaphylaxis following the second and booster vaccine doses (level 2 for both doses). When adjudicated against recently revised Brighton criteria, sARs in both participants A and B met level 3 diagnostic certainty for anaphylaxis after the second dose, and sAR in participant A met level 3 criteria after their booster dose (Table II). No participants experienced sAR following placebo, yielding a risk difference of 12.5% (95% CI, −13.4, 38.3) for developing sAR after active vaccine. Additionally, 1 participant had a CoFAR grade 1 nonsystemic allergic reaction after their second vaccine dose and no allergic reaction following booster.

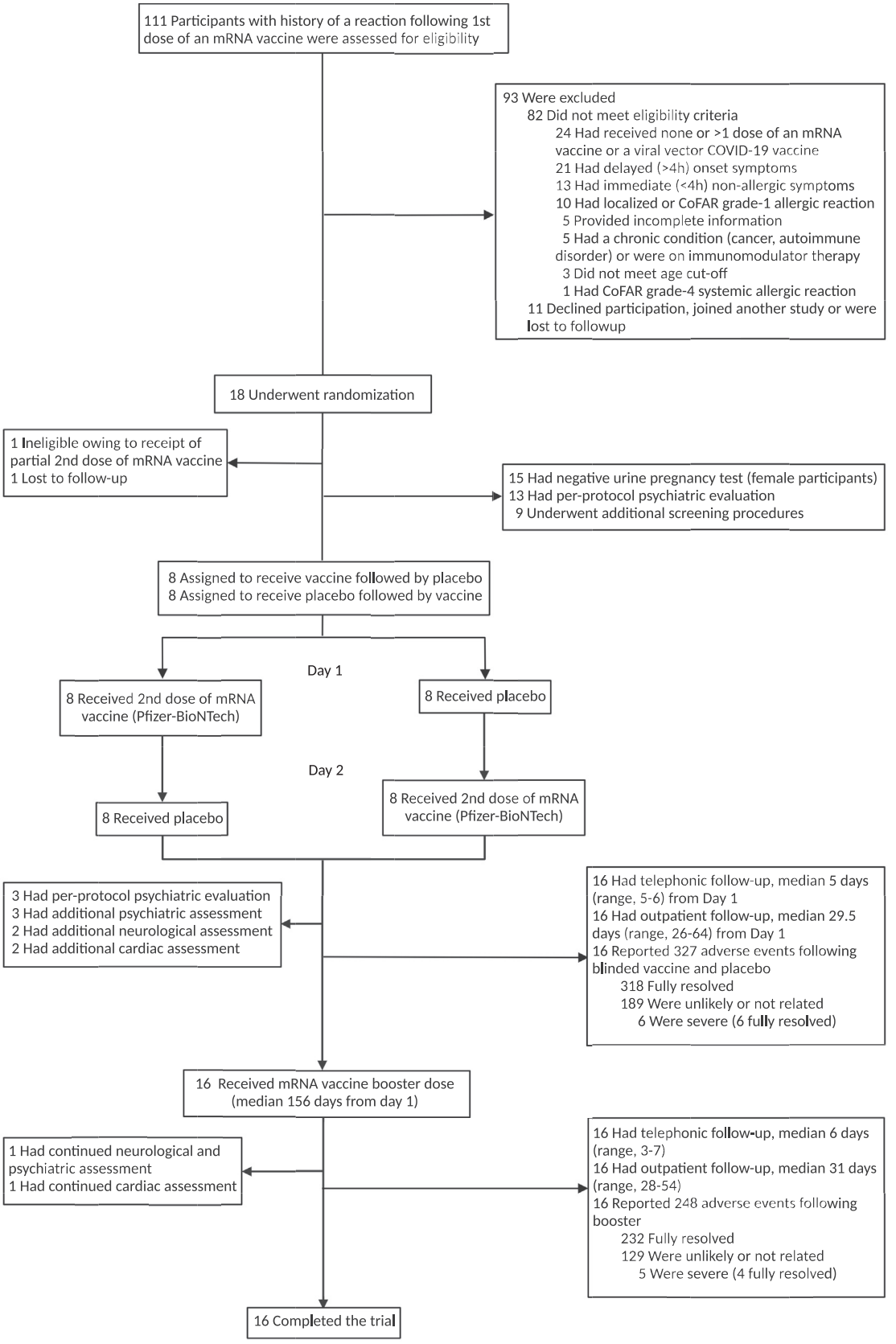

FIG 1. Study design: screening, randomization and follow-up. The data cutoff for primary analysis was June 17, 2022. Participants who received blinded doses (second BNT162b2 dose and placebo) and unblinded BNT162b2 booster dose were included in the full analysis. Additional screening procedures included

TABLE I. Baseline patient characteristics

Characteristic	Participants (n = 16)
Sex, no. (%)	
Female	15 (93.8)
Male	1 (6.2)
Age (y), mean (IQR)	45.5 (36-51)
Race or ethnic origin, no. (%)	
White (non-Hispanic)	8 (50)
Hispanic	5 (31.3)
Asian	2 (12.5)
Black	1 (6.3)
Reported allergy history, no. (%)	16 (100)
Chronic seasonal or perennial rhinitis*	14 (87.5)
Previous anaphylaxis†	12 (75)
Medication allergies or intolerances‡	12 (75)
Food allergies*	10 (62.5)
Asthma	10 (62.5)
Non–COVID-19 vaccine allergic reaction§	4 (25)

*Sensitization to environmental allergens and food allergens was confirmed in 9 (56.3%) and 3 (18.8%) participants, respectively, by presence of allergen-specific IgE greater than 0.35 kU_A/L.

†Previous anaphylaxis episodes were reported due to triggers (excluding first dose of mRNA vaccine) including food in 6 (37.5%), medications in 6 (37.5%), insect venom in 2 (12.5%), and idiopathic in 4 (25%) participants. Number of reported anaphylaxis episodes per participant irrespective of trigger (excluding first dose of mRNA vaccine): 6 by 1 (6.3%), 5 by 1 (6.3%), 4 by 2 (12.5%), 2 by 4 (25%), and 1 episode by 4 (25%) participants.

‡Includes computed tomography or magnetic resonance imaging contrast.

§Three reactions were reported following influenza, and 1 was reported following pneumococcal vaccine. One participant (not included) reported past history of a reaction suggestive of severe dissociative neurologic symptom reaction that did not meet allergic reaction criteria following concurrent TDaP (tetanus, diphtheria, and acellular pertussis) and hepatitis B immunization.

With regard to secondary end points, recurrent mild or moderate (CoFAR grade 1 or 2, irrespective of tryptase) allergic reactions occurred in 3 participants (18.8%) (participants A, B, and C [Fig 2, *A*]) (95% CI, 4 to 45.6) following second vaccine dose and 1 participant (participant B) following booster. No participant had a severe (CoFAR grade 3 or higher) sAR after the second vaccine dose; however, participant A, who had a grade 2 sAR to the second dose, developed a CoFAR grade 3 sAR following booster. All 3 allergic reactions following second vaccine doses were less severe compared with the participants' reactions to their first dose. Following booster, 1 participant (participant A) had the same sAR severity (CoFAR grade 3), and 1 participant (participant B) had a lower grade severity compared with their first dose reaction (Fig 2, *A*; Table E3 in the Online Repository at www.jacionline.org). Overall, severity of sARs following first vaccine doses (prestudy) was greater compared with in-study second vaccine and booster doses ($P < .001$ and $P < .001$ respectively) (Table E4 in the Online Repository at www.jacionline.org).

All participants reported AEs following second vaccine dose/placebo and booster (Tables E5-E9 in the Online Repository at www.jacionline.org). There were no serious AEs or study discontinuation owing to AEs. The most common AEs were injection site pain, blood pressure increase, fatigue, and headache. At study completion, 9 of 327 AEs following blinded interventions (all unrelated) remained unresolved. Of 248 AEs following booster, 16 were unresolved at study completion, all unrelated except 1 AE (fatigue), which was possibly related to booster. Only 6 of 327 and 5 of 248 AEs following blinded interventions were grade 3, and all were unrelated except 1 sAR following booster. One grade 3 AE (migraine, unrelated) following booster was unresolved.

Most reactions following both placebo and vaccine doses did not meet sAR criteria, but rather were consistent with immunization stress–related response (ISRR), a nonallergic rapid-onset clinical reaction due to the immunization process and not vaccine components.[19] Among the 16 participants, 2 (12.5%) who had recurrent sARs following vaccine doses also had ISRR following placebo, 7 (43.8%) had ISRRs following all in-study doses (vaccines and placebo), and 6 (37.5%) had ISRR following at least 1 vaccine dose or placebo; only 1 participant (6.3%) had no reaction following all in-study doses (Fig 2, *A*). Of the 48 total in-study doses, sARs occurred following 4 (8%), ISRRs occurred following 34 (71%), and no reaction occurred following 10 doses (21%) (Fig 2, *B*). With regard to specific doses, 2 (12.5%) participants had sAR, 10 (62.5%) had ISRR, and 4 (25%) had no reaction after the second vaccine dose. Following placebo, ISRR occurred in 12 (75%) participants, and no reaction occurred in 4 (25%) participants. Booster was followed by sAR in 2 (12.5%) participants and by ISRR in 12 (75%) participants; 2 (12.5%) participants had no reaction (Fig 2, *C*). ISRRs had a rapid onset (median 3 minutes [IQR 2-9 minutes]) similar to sARs (median 3 minutes [IQR 2-4.5 minutes]) (Table II; Table E10 in the Online Repository at www.jacionline.org), but peaked sooner (ISRR: median 9.5 minutes [IQR 4-23 minutes]; sAR: median 19 minutes [IQR 13-24 minutes]) and resolved earlier than sARs (ISRR: median 71 minutes [IQR 22-144 minutes]; sAR: median 133.5 [IQR 99-146 minutes]). One participant (participant A [Fig 2, *A*]) who had CoFAR grade 3 sAR, had >30% decrease in systolic blood pressure (SBP) from baseline and received intramuscular epinephrine; all other in-study sARs and ISRRs resolved without treatment.

Due to their heterogeneous presentation, we devised a novel ISRR classification system post hoc (before considering any relationships to potential predictors) including severity grades

spirometry (n = 8), otolaryngology consultation (n = 2), echocardiogram (n = 2), electrocardiogram (n = 2), and chest x-ray (n = 1). Additional psychiatric assessment included evaluation by a psychiatrist for acute neuropsychiatric symptoms, on top of per-protocol baseline psychiatric assessment for all participants performed before visit 1 (n = 13) or visit 4 (n = 3). Neurologic assessment included evaluation by a consultant neurologist for neuropsychiatric symptoms and additional imaging such as magnetic resonance imaging if clinically indicated. Cardiac assessment was performed to exclude myocarditis or pericarditis and included evaluation by a consultant cardiologist, serial serum troponin measurements, electrocardiogram, echocardiogram, and additional investigations as indicated. All 6 grade 3 AEs following second dose of vaccine and placebo were unlikely or not related to study intervention. Only 1 of the 5 grade 3 AEs (CoFAR grade 3 systemic allergic reaction) following booster was definitely related; the other 4 were unlikely or not related. Migraine was the only AE following booster that remained unresolved and was not related to study intervention. Complete description of AEs is provided in Tables E5-E9 (in the Online Repository at www.jacionline.org). Created with BioRender.com.

TABLE II. COVID-19 mRNA vaccine allergic reactions in study participants

mRNA vaccine dose number*	First (n = 16)	Second (n = 16)	Booster (n = 16)
Vaccine type, no. (%)			
BNT162b2 (Pfizer-BioNTech)	15 (93.8)	16 (100)	16 (100)
mRNA-1273 (Moderna)	1 (6.3)	0	0
CoFAR allergic reaction grade, no. (%)†	16 (100)	3 (18.8)	2 (12.5)
Grade 1 (mild)	0	1 (6.3)	0
Grade 2 (moderate)	1 (6.3)	2 (12.5)	1 (6.3)
Grade 3 (severe)	15 (93.8)	0	1 (6.3)
Anaphylaxis, original Brighton criteria (level 1-3), no. (%)‡	12 (75)	1 (6.3)	1 (6.3)
Anaphylaxis, revised Brighton criteria (level 1-3), no. (%)‡	8 (50)	2 (12.5)	1 (6.3)
Anaphylaxis, NIAID/FAAN criteria, no. (%)	16 (100)	0	1 (6.3)
Onset of systemic allergic reaction (min), median (range)	5 (1-35)	3 (2-4)	3.5 (2-5)
Antihistamine use before vaccination (≤4 h), no. (%)	3 (18.8)	0	0
Acute treatment following reaction, no. (%)	16 (100)	0	1 (6.3)
Antihistamine (oral or intravenous)	15 (93.8)	0	0
Epinephrine (intramuscular)	10 (62.5)	0	1 (6.3)
1 dose	6 (37.5)	0	1 (6.3)
>1 dose	3 (18.8)	0	0
3 doses followed by intravenous	1 (6.3)	0	0
Systemic corticosteroids	8 (50)	0	0
Supplemental oxygen‖	6 (37.5)	0	0
Albuterol (inhaled)	4 (25)	0	0
Management location no. (%)			
Vaccination site only	2 (12.5)	NA	NA
Vaccination site and ED	10 (62.5)	NA	NA
Vaccination site, ED, and ICU	1 (6.3)	NA	NA
Home only	3 (18.8)	NA	NA
Duration of observation in ED (h), median (IQR)¶	4 (2-6)	NA	NA

ED, Emergency department; *FAAN,* Food Allergy and Anaphylaxis Network; *ICU,* intensive care unit, *NA,* not applicable.

*First dose was administered before study enrollment. Second vaccine dose and placebo (blinded) and booster (unblinded) were administered as study interventions. No allergic reactions occurred following in-study placebo, and hence this information is not displayed. Data for second dose only include blinded second in-study vaccine dose.

†Allergic reactions were graded using the CoFAR Grading Scale (Modified Version 3.0) (see Table E1 in the Online Repository at www.jacionline.org). Prestudy reactions in 14 (87.5%) participants were confirmed by medical records, referring physician, or both. Two reactions were reported by patients only. None of the participants had serum tryptase levels measured within 4 hours of reaction following first dose of vaccine (prestudy). One participant (participant G; Fig 2, *A*) had a biphasic reaction within 48 hours requiring additional epinephrine and a visit to the ED. No allergic reactions occurred following in-study placebo.

‡Brighton collaboration case definition criteria (original, ie, version 1, and revised, ie, version 2) for anaphylaxis levels 1 to 3 correlated with the level of certainty in diagnosis of anaphylaxis. For those following dose 1 (prestudy), using original criteria, 5 met level 1 (including participant A), 6 met level 2, and 1 met level 3 (participant B) diagnostic certainty, and the remaining 4 were considered level 4 (reported as anaphylaxis with insufficient evidence to meet anaphylaxis of any certainty). When using revised Brighton criteria, 2 met level 1, 2 met level 2, 4 met level 3 (including participant A), and another 8 (including participant B) were considered level 4 due to lack of sufficient information available to ascertain anaphylaxis diagnosis. In contrast, only 1 participant (participant A; Fig 2, *A*) following in-study vaccine dose 2 and booster met level 2 diagnostic certainty, whereas using revised criteria, 2 participants (participants A and B) met level 3 diagnostic certainty following in-study vaccine dose 2, and 1 participant (participant A) met level 3 diagnostic certainty following booster. All other reactions were consistent with level 5 (not anaphylaxis) using original and revised Brighton criteria.

‖Supplemental oxygen was provided by nasal cannula or nonrebreather mask. None of the participants required noninvasive or invasive mechanical ventilation.

¶n = 10 participants. Among the other 6, 3 self-managed at home, 2 were managed at vaccination site and observed for 1 hour, and 1 was admitted in the intensive care unit and discharged after 1 day.

based on patient-reported symptom severity and investigator-observed distress level as well as duration and symptom distribution (Fig 3, *A*). Mild ISRRs occurred twice as often as other grades (Fig 2, *D*). Moderate-severe ISRRs were more frequent than very mild–mild ISRRs following placebo (59%), but not second vaccine (40%) or booster (25%) doses (Fig 2, *E*). Of all ISRRs (n = 34), 59% were prolonged (lasting ≥30 minutes per episode), 12% were episodic (more than 1 episode during the same vaccination event; range 2-4), and 15% were chronic (lasted >48 hours; range, 3 days to >6 months after dose) (Fig 2, *F*). Two participants had unresolved symptoms at study completion, paresthesias in one and palpitations in the other, for whom additional evaluations excluded alternative etiologies. Moderate-severe ISRRs were quicker in onset and more likely to be episodic and chronic compared with very mild–mild ISRRs. Most ISRRs had mixed distribution (76.5%), and only 8 (23.5%) had isolated organ system involvement, of which 7 were very mild–mild ISRRs. Paresthesias were the most common symptom in ISRRs (56%) and were not seen with in-study sARs, followed by dizziness, throat tightness, and difficulty swallowing (Fig 3, *B* and *C*; Fig E2 and Table E10 in the Online Repository at www.jacionline.org). One participant with severe ISRR after placebo developed stroke-like sensory and motor symptoms. Participants across all reaction categories experienced vital sign changes, more pronounced in moderate-severe ISRRs. In moderate-severe ISRRs, mean heart rate (HR) increased by 21.4 beats/minute (95% CI, 8.6 to 34.3) from baseline compared with 8.3 beats/minute (95% CI, 1.8 to 14.8) in asymptomatic participants. Similarly, mean SBP increased by 23.9 mm Hg (95% CI, 15.2 to 32.7) from baseline in moderate-severe ISRRs compared with 9.3 mm Hg (95% CI, 3.2 to 15.4) in asymptomatic participants (Fig 2, *G* and *H*; Tables E11 and E12 in the Online Repository at

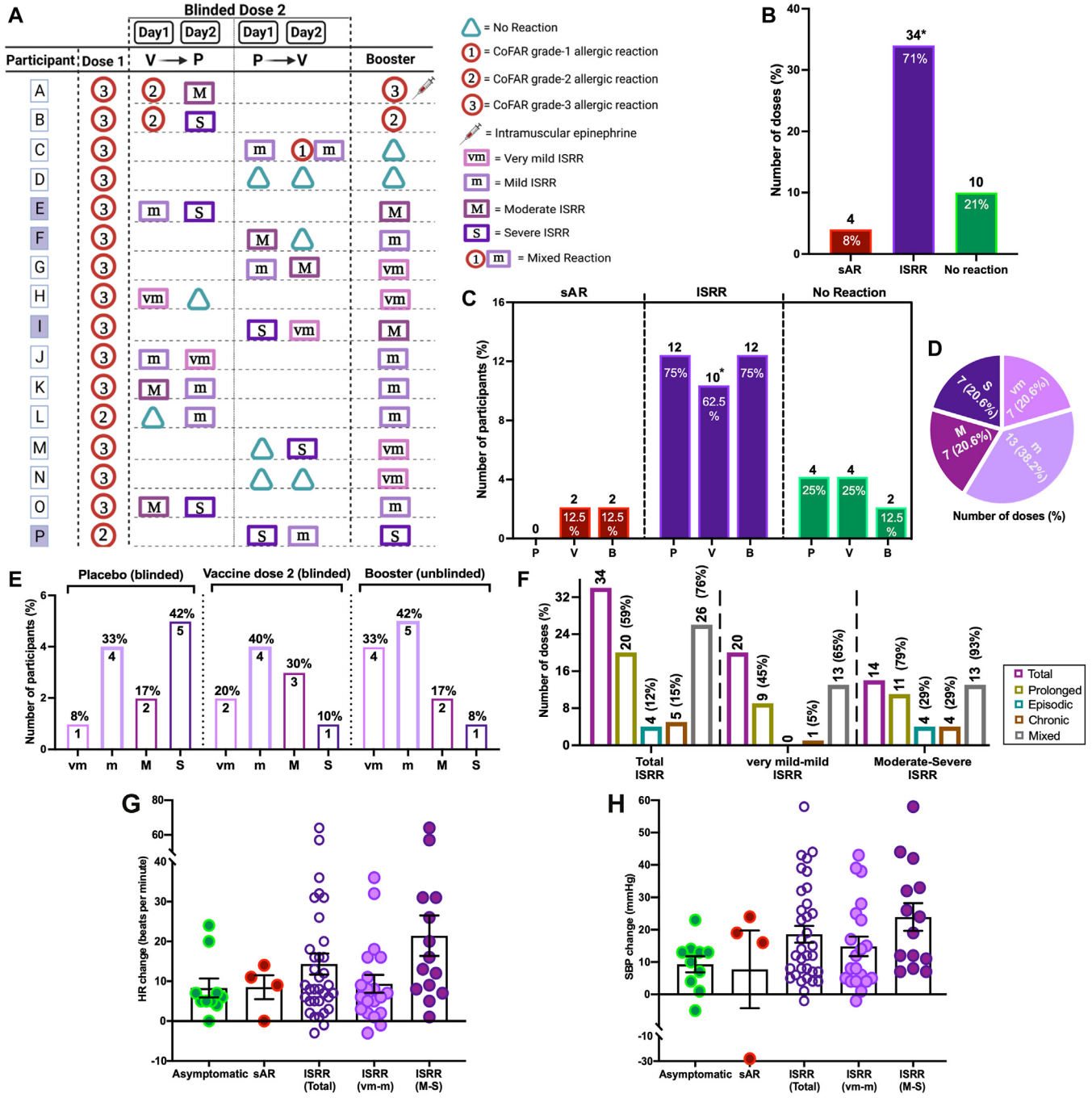

FIG 2. Frequency and characteristics of in-study reactions. **(A)** Summary of reactions following first dose of mRNA vaccine (prestudy dose 1) and all in-study doses, ordered by reaction type. Participant C, the only male participant, had a mixed reaction (nonsystemic mild allergic reaction [CoFAR grade 1] and mild ISRR) following BNT162b2 second dose (blinded). Created with BioRender.com. **(B)** Frequency of reactions following all in-study doses (n = 48) including second BNT162b2 dose (blinded), placebo (blinded), and booster (unblinded). *One participant who had a mixed reaction is included with ISRRs. **(C)** Frequency of reaction types following individual in-study doses. **(D)** Frequency of all in-study ISRRs (n = 34) based on severity grades irrespective of dose. **(E)** Frequency of ISRRs based on severity grades following individual in-study doses. **(F)** Frequency of prolonged (lasting ≥30 minutes), episodic (>1 episode of symptoms), chronic (lasting >48 hours), and mixed (>1 organ symptom) total ISRRs (n = 34), very mild-mild ISRRs (n = 20), and moderate-severe ISRRs (n = 14) following all in-study doses. **(G)** Mean HR (beats per minute) change (SEM): difference of maximal HR (within 60 minutes after dose) from same-day baseline. **(H)** Mean SBP (mm Hg) change (SEM): difference of maximal SBP change (within 60 minutes of dosing) from same-day baseline. *B,* Booster (unblinded); *m,* mild ISRR; *M,* moderate ISRR; *P,* placebo (blinded); *S,* severe ISRR; *V,* second dose of mRNA vaccine (blinded); *vm,* very mild ISRR.

A

NIAID ISRR Classification	
Symptoms Severity	
Very Mild (vm)	No visible distress; minimal symptoms, casually reported by patient. No progressive worsening during the same episode.
Mild (m)	Mild distress; symptoms noticeable but minimally bothersome. No or minimal progressive worsening during the same episode.
Moderate (M)	Moderate distress; visible upon patient interaction, may prompt further evaluation or treatment. May start as mild and progressively worsen (typically minutes) during the same episode.
Severe (S)	Severe distress; overtly visible patient distress prompting further evaluation or treatment. May start as mild or moderate and progressively worsen (typically minutes) during the same episode.
Symptoms Duration	
Transient	Single episode lasting ≤30 minutes after onset.
Prolonged	Single episode lasting >30 minutes after onset.
Chronic	Lasting >48 hours after a single vaccination event, irrespective of number of episodes.
Episodic	>1 episode recurring without another plausible etiology, observed after the same vaccination event and where previous episode fully resolved before onset of new episode.
Symptoms Distribution	
Isolated	Involving one organ system excluding vital signs
Mixed	Involving >1 organ system including vital signs

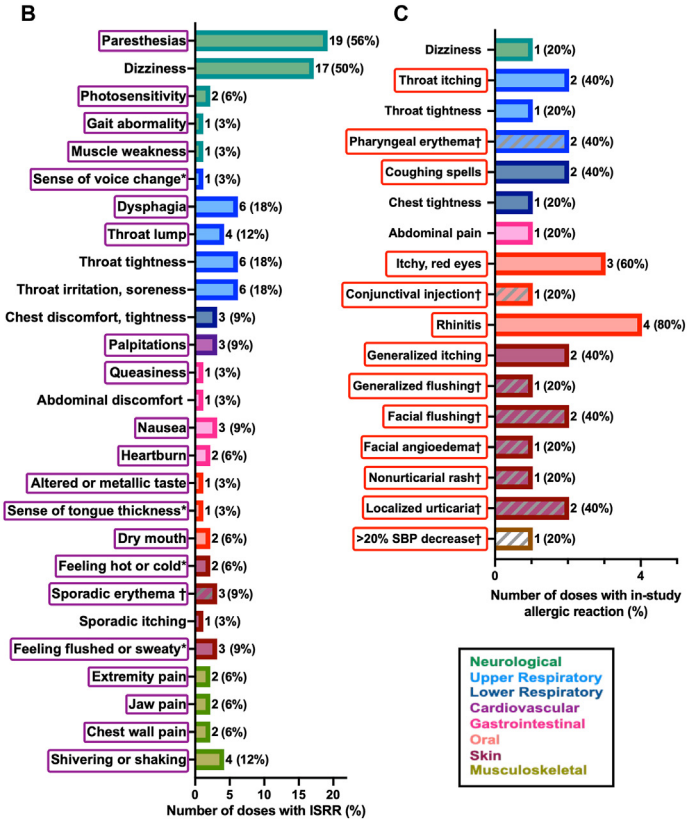

FIG 3. Clinical reactions phenotype. **(A)** NIAID ISRR classification. **(B)** Frequency of symptoms or signs following all in-study ISRRs (n = 34). *Symptoms were subjective only (patient-reported without changes on physical examination or measurements). †Symptoms were confirmed on examination. **(C)** Frequency of symptoms following in-study allergic reactions (n = 5) to second and booster vaccine doses. No allergic reactions occurred following placebo. For the 1 participant who had a mixed reaction, only the allergic symptom (generalized flushing) was included here; all other symptoms were attributed to and included with ISRRs. †Signs or vital sign changes were confirmed on physical examination or measurements. Symptoms uniquely reported with in-study ISRRs and sARs are indicated by *purple* and *red box*, respectively.

www.jacionline.org). In moderate-severe ISRRs compared, with the few asymptomatic participants in whom a ≥15% HR or ≥10% SBP increase occurred, increase in HR peaked and resolved earlier, and SBP developed and resolved later (Fig E3 in the Online Repository at www.jacionline.org). Before unblinding and after receiving both blinded second vaccine and placebo, all participants were asked to guess the day when they received the second blinded vaccine dose. Four participants (25%) (participants E, F, I, and P [Fig 2, *A*]) incorrectly guessed and assumed receiving it on the day they received placebo and had moderate-severe ISRR despite experiencing expected vaccination-related AEs on the true vaccination day.

The activating *KIT* mutation (p.816V) was not detected in peripheral blood of any individual. One participant (6%) (participant G [Fig 2, *A*]) had *TPSAB1* copy number gain (ααααββ) and elevated baseline tryptase (14-18 ng/mL, normal <11.4 ng/mL), consistent with hereditary α-tryptasemia that affects 4% to 6% of the general population.[20] Two participants (participants A and B [Fig 2, *A*]) with recurrent sARs had higher mean total IgE at baseline (before second dose and booster) that tended to increase 1 month after dose (Fig E4 in the Online Repository at www.jacionline.org). Anti-PEG IgE was detectable for both participants A and B with recurrent sARs at the same time points (ie, baseline, 1 month, 5 months, and 6 months) using 2 different assays (FDA in-house assay and commercial dual cytometric bead assay) (Fig E5 in the Online Repository at www.jacionline.org). The commercial assay additionally detected low levels of anti-PEG IgE in 4 other participants (participants D, F, J, and O) during one or more study visit. Anti-PEG IgG was detectable at high titers in participants A, B, and D during 3 or more visits and was weakly positive in 2 participants (participants C and H) during 2 visits and in 3 participants (participants F, K, and M) during 1 visit. Anti-PEG IgM was not detected in participants with recurrent sARs; however, it was strongly positive in 2 other participants (participants D and I) at all visits and weakly positive in 3 participants (participants C, H, and I) during 1 or more visit. It is noteworthy that participant C had a mixed (CoFAR grade 1 and ISRR) reaction following second dose, participant D had no reaction following any in-study doses, and other participants had ISRR or no reaction following in-study doses.

Numerous biomarkers were evaluated for immediate postdose changes within a reaction category and compared between moderate-severe ISRRs or sARs and asymptomatic-mild ISRRs (asymptomatic, very mild, or mild ISRRs). None of the sARs or ISRRs had clinically significant postdose tryptase elevation (ie, >2 + 1.2 × basal serum tryptase),[21] though mean percent change from baseline to 35 minutes was higher in sARs compared with asymptomatic-mild ISRRs (Δ = 6.8%; 95% CI, 1.3 to 12.3) (Fig E4). Mean urine LTE_4 and plasma histamine in sARs were

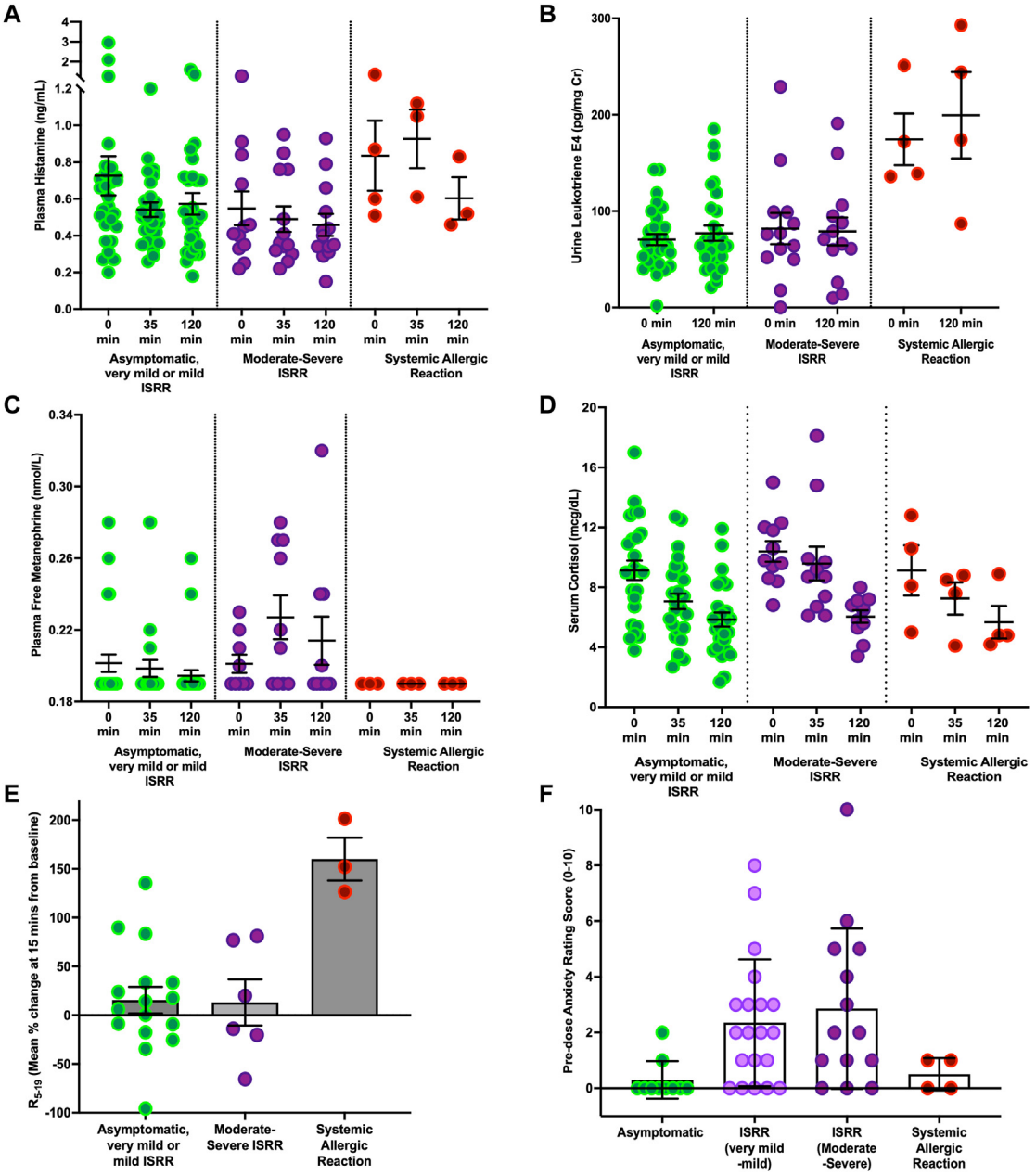

FIG 4. Biomarkers, airway resistance, and anxiety score measurements. **(A)** Plasma histamine (normal reference: <1 ng/mL) was measured within 60 minutes before dose (n = 44), and at 35 ± 15 minutes after dose (n = 43) and at 120 ± 30 minutes after dose (n = 48). **(B)** Urine LTE_4 (normal reference: ≤104 pg/mg Cr) was measured for all in-study doses in a predose void (within 60 minutes; n = 47) and first postdose void (approximately 2 hours postdose; n = 46). **(C)** Plasma free metanephrine ([epinephrine metabolite], reference: <0.50 nmol/L) was measured for all in-study doses within 60 minutes before dose (n = 39), at 35 ± 15 minutes after dose (n = 40), and at 120 ± 30 minutes after dose (n = 40). One sAR, for which participant received epinephrine 12 minutes following the dose, was excluded from analysis due to iatrogenic elevation of metanephrine, an epinephrine metabolite. **(D)** Total serum cortisol (reference before 10 AM: 3.7-19.4; after 5 PM: 2.9-17.3 μg/dL) was measured for all in-study doses within 60 minutes before dose (n = 41) and at 35 ± 15 minutes after dose (n = 42) and at 120 ± 30 minutes after dose (n = 42). **(E)** Mean percent change at 15 minutes after dose from baseline of difference between small airway resistance (cm H_2O/[L/seconds]) at 5 Hz and 19 Hz (n = 25). **(F)** Predose anxiety rating score (scale 1-10) for all in-study doses (n = 48) administered within 60 minutes before doses in response to single question: "How anxious are you right now about the COVID-19 vaccine?" The measure of distribution for *(A-F)* is represented by SEM.

elevated at baseline compared with asymptomatic-mild ISRRs (Δ LTE_4 = 111.2 pg/mg Cr; 95% CI, −26.3 to 248.7; Δ histamine = 0.1 ng/mL; 95% CI, −0.8 to 1.0) and uptrended at first postdose void (LTE_4 mean change from baseline = 25.0 pg/mg Cr; 95% CI, −381.6 to 431.6) and 35 minutes (histamine mean change from baseline = 0.01 ng/mL; 95% CI, −0.5 to 0.6), respectively (Fig 4, *A* and *B*). Plasma free metanephrine showed a mean increase of 0.02 nmol/L (95% CI, 0.002 to 0.04) in moderate-severe ISRRs and higher mean percent change (Δ = 11.9%; 95% CI, 2.8 to 20.9) at 35 minutes from baseline compared with asymptomatic-mild ISRRs (Fig 4, *C*). Mean cortisol decreased in all reaction categories at 35 minutes after dose, consistent with expected diurnal change[22] except in those with moderate-severe ISRRs in whom levels were higher compared with asymptomatic-mild ISRRs at baseline (Δ = 1.1 μg/dL; 95% CI, −0.5 to 2.7) and 35 minutes after dose (Δ = 10.5%; 95% CI, −11.3 to 32.3) (Fig 4, *D*).

Mean plasma complement protein C3 levels substantially decreased following sARs at 35 minutes (−4.7 mg/dL; 95% CI, −23.4 to 14.1) and 120 minutes (−11.8 mg/dL; 95% CI, −5.0 to −18.5) compared with baseline, which was not observed following asymptomatic-mild ISRRs or moderate-severe ISRRs. Similarly, mean plasma C4 decreased after sARs at 35 minutes (−1.7 mg/dL; 95% CI, −0.6 to −2.7) and 120 minutes (−2.5 mg/dL; 95% CI, −2.5 to −2.5). Furthermore, mean C3 and C4 levels were prominently higher at baseline in participants experiencing sARs compared with asymptomatic-mild ISRRs (Δ C3 = 45.7; 95% CI, 15.5 to 75.8; Δ C4 = 12.1; 95% CI, 6.3 to 17.9). Plasma C3a (active fragment) increased at 35 minutes and 120 minutes in participant A with severe sAR (CoFAR grade 3) following booster; this was not observed following other in-study (CoFAR grade 2) sARs. Plasma C5a did not change in sARs, but uptrended from baseline in moderate-severe ISRRs by means of 0.5 ng/mL (95% CI, −0.2 to 1.1 ng/mL) at 35 minutes and 0.3 ng/mL (95% CI, −0.1 to 0.6 ng/mL) at 120 minutes (Fig E6 in the Online Repository at www.jacionline.org). No clinically relevant changes were observed in plasma total complement (CH50), C5b9, kallikrein activity, high-molecular-weight kininogen, platelet-activating factor, or urinary histamine or prostaglandin metabolites (Figs E4, E6, and E7 in the Online Repository).

To objectively assess acute respiratory symptoms, we used forced oscillation technique, a method with higher sensitivity for detecting reactive airway changes compared with spirometry.[23] In our study, forced oscillation technique detected 136.6% (95% CI, 57.0% to 216.1%) greater change in mean difference of resistance between 5 and 19 Hz ($R_{5\text{-}19}$) at 15 minutes from baseline following sARs compared with asymptomatic-mild ISRRs (Fig 4, *E*). An increase in total airway resistance at 5 Hz during expiration and inspiration was also observed in participants with sARs (Fig E8 in the Online Repository at www.jacionline.org).

Of 2 participants who had recurrent sARs, one (participant A [Fig 2, *A*]) had positive BNT162b2 (1:100) intradermal testing, and the other (participant B) did not undergo further testing after an exaggerated response to negative control. Another participant who was asymptomatic (participant D) following all in-study doses had positive BNT162b2 intradermal testing (1:100) (Fig E9 in the Online Repository at www.jacionline.org). The remaining 13 had negative immediate BNT162b2 skin testing (1:100 and 1:10); however, 9 (69%) noted painless erythema, induration, or both at the 1:10 testing site within 18 to 48 hours of testing that resolved in 1 to 5 days, suggesting appropriate T cell–mediated immune response (Fig E10 in the Online Repository at www.jacionline.org). All 15 participants with valid controls had negative skin prick testing to liposomal PEG-2000, PEG-3350, and polysorbates (Table E13 in the Online Repository at www.jacionline.org).

All participants underwent baseline psychiatric assessment, in which 13 (81.3%) endorsed a lifetime psychiatric diagnosis and 11 (68.8%) an active psychiatric diagnosis, most commonly anxiety and mood disorders. All reported one or more occupational (81.3%), travel-related (81.3%), psychological (62.5%), and/or interpersonal difficulties (62.5%) due to the COVID-19 pandemic or incomplete vaccination (Table E14 in the Online Repository at www.jacionline.org). A 1-question anxiety scale to rate COVID-19 vaccine–associated anxiety was administered during all study visits. Compared with asymptomatic participants, mean predose anxiety scores were similar in participants who had sARs (Δ score = 0.1; 95% CI, −1.4 to 1.5) but greater in very mild-mild ISRRs (Δ score = 2.1; 95% CI, 0.6 to 3.7) and moderate-severe ISRRs (Δ score = 2.5; 95% CI, 0.7 to 4.3) (Fig 4, *F*). Anxiety scores 3 hours following both blinded doses decreased from predose scores in the cohort. These scores were lower before booster compared with preblinded doses and overall decreased by study conclusion (Fig E11 in the Online Repository at www.jacionline.org). Validated surveys were administered to assess generalized anxiety, depression, post-traumatic stress, event-based stress, and disability. No participants reported moderate or severe anxiety or depression at baseline. No notable score changes occurred throughout the study except in 2 participants who had worsening depression due to events unrelated to the study (Table E15 in the Online Repository at www.jacionline.org).

DISCUSSION

In this phase 2, double-blinded, placebo-controlled trial of second and booster BNT162b2 vaccine doses in individuals who reported an sAR to their first dose of COVID-19 mRNA vaccine, only 2 (12.5%) participants experienced a recurrent sAR. All sARs were milder compared with pre-study sARs except in 1 participant who developed the same grade sAR (CoFAR grade 3) following booster that was easily treatable in an outpatient setting. Multiple studies over time have consistently found a low recurrence rate of allergic reactions in individuals who reported an allergic reaction following the first dose of COVID-19 mRNA vaccine. Our prospective data thus support the growing number of these retrospective studies on the safety of revaccination including in individuals who had moderate to severe allergic reactions.[3,24-31]

The mechanism underlying allergic reactions to the COVID-19 mRNA vaccines is not known. Proposed hypotheses have included classical IgE-mediated mast cell degranulation triggered by anti-PEG IgE and complement activation by anti-PEG IgM and/or IgG immune complexes leading to release of anaphylatoxins C3a and C5a that can cause anaphylaxis with or without activating mast cells. Although the small number of in-study sAR events limited study power, we observed modest trends of mast cell degranulation suggested by postdose increases in plasma histamine and serum tryptase and mast cell activation indicated by postdose increase in urine LTE_4. Additionally, complement components C3 and C4 decreased after dose in sARs, and C3a increased acutely in the participant with the most severe sAR observed during the study (participant A following booster), potentially indicating complement pathway activation. Forced

oscillation technique detected acute postvaccine increase in small (R_{5-19}) and total airway resistance in sARs as would be expected during an allergic response.[32] None of these changes were observed in participants who experienced ISRRs or no reaction. Postvaccine biomarker levels for participants without sAR were similar to observed postplacebo levels, indicating that the vaccine itself had little effect on the biomarkers measured.

The 2 participants who had recurrent sARs had strongly positive anti-PEG IgE and IgG titers. However, anti-PEG antibodies were detected in other participants as well. The role of anti-PEG antibodies in predicting reactions to the COVID-19 mRNA vaccines has been controversial, potentially due to differences in the methods for measuring PEG antibodies and how allergic reactions were assessed and defined. Warren et al[33] and Zhou et al[34] reported absence of anti-PEG IgE in individuals with sARs, while Mouri et al[35] found higher levels of anti-PEG IgE and IgG in subjects with sARs compared with control subjects.[33-35] PEG IgE-mediated mast cell degranulation is unlikely to be the primary mechanism driving sARs to the COVID-19 mRNA vaccines because patients with known IgE-mediated PEG allergy have been reported to tolerate the mRNA vaccines. Activation of complement by anti-PEG IgM/IgG immune complexes could explain the lack of sAR reoccurrence in the majority of participants who reacted to their first dose, as anaphylaxis triggered by complement activation is often characterized by reduced reactogenicity with repeated administration. However, healthy individuals can possess detectable levels of anti-PEG IgE or IgG or both, so while these antibodies may play a role in the pathogenesis, the presence of anti-PEG antibodies alone is not sufficient to cause allergic reactions to the mRNA vaccines. This is true for other types of drug allergy as well, where both IgE- and IgG-mediated mechanisms have been shown to play a role in anaphylaxis but anti-drug antibodies were also detected in healthy control subjects.[36] One finding that distinguished the 2 participants with recurrent sARs in our study was high baseline levels of total IgE, plasma histamine, urinary *N*-methylhistamine and LTE_4, C3, C4, and C3a, suggesting that individuals who have recurrent sARs may have a predisposing phenotype with priming of specific cells and/or pathways before vaccine exposure along with presence of anti-PEG antibodies. Thus, the pathogenesis of sARs to the COVID-19 mRNA vaccines is likely multifactorial and requires further investigation.

We found that skin testing with BNT162b2 vaccine provided poor predictability, and excipient skin testing offered no value. Negative skin testing to liposomal PEG-2000 in all participants may be attributable to suboptimal concentrations, selected cautiously to avoid irritant reactions; however, concurrent negative skin testing to PEG-3350 and lack of past history of PEG allergy in all participants also points toward a non-IgE mechanism of sARs.

Nonallergic reactions, ISRRs, occurred 5.5 times more commonly than sARs following in-study vaccine doses. ISRRs have primarily been reported retrospectively in younger populations in nonpandemic circumstances.[37,38] Our study is the first to observe ISRRs in real time, allowing direct assessment of the unique features and biomarkers that distinguish these from anaphylaxis. ISRRs can manifest diversely as an acute stress response and have symptoms that overlap with sARs such as dizziness, throat and chest tightness, and abdominal pain. Both reactions have rapid onset after injection. The triad of neurologic symptoms (most commonly paresthesias), acute HR and SBP elevation, and absence of physical signs strongly suggests ISRR. Moderate-severe ISRRs tended to be prolonged (single episode lasting ≥30 minutes), episodic (>1 episode), and/or chronic (lasting >48 hours) with neurologic (eg, sensory abnormalities) or other organ symptoms (Table E10). In contrast to sARs, ISRRs were associated with rapid postdose elevation in plasma metanephrine, cortisol, and C5a, indicating stress-induced sympathetic nervous system, hypothalamus-pituitary axis, and complement activation, which has been shown to occur in the setting of acute stressful events.[39]

Lifetime mental health disorders including anxiety and depression were more common in this cohort than the general population,[40] but this may reflect increased reporting due to the detailed per-protocol psychiatric evaluation. A single question assessing vaccine-associated predose anxiety on a 0-to-10 scale appeared to predict high risk of ISRR in our cohort. A score ≥2 may serve as a convenient ISRR risk screening tool at vaccination sites, aiding the vaccination staff in early identification of individuals at risk for developing an ISRR.

Our findings underscore the importance of both primary care and specialist physicians considering ISRR in the differential diagnosis when evaluating postvaccine adverse reactions. We acknowledge that these reactions were observed in a controlled environment by trained allergists with the capability of strict monitoring, which can be different from real-world vaccination circumstances. The overlapping features make distinguishing ISRR from anaphylaxis challenging. In such situations, a potentially lifesaving intervention such as epinephrine may be appropriate in an acute setting; however, if correctly identified, behavior modification techniques can be used to manage ISRRs acutely.[41] A retrospective review by a specialist to identify ISRR features and predose anxiety score can further aid in managing subsequent vaccination-related reactions, provide a plan for safe revaccination, and prevent or reduce severity of ISRR following subsequent doses.

The strengths of our study included a rigorous, prospective, double-blinded, and placebo-controlled design with follow-up for both second and booster doses in a controlled environment, accompanied by extensive biomarker analysis, and direct observations and comparison across reaction types by the same investigators. Our study population reflected key features of the individuals who most commonly reported anaphylactic reactions to the COVID-19 mRNA vaccines, as all but 1 participant in our study were female, and all reported a positive allergic history. In a first of its kind vaccine challenge study, small sample size was a limitation. This was due to the rarity of true allergic reaction events to COVID-19 mRNA vaccines, strict inclusion and exclusion criteria including only individuals who had yet to receive any other vaccine dose except first mRNA dose, conduction of the study during the COVID-19 pandemic peak with associated travel and health-related challenges, and robustness and intensity of the study design that required multiday stays and several visits to the hospital. Intensive care unit admission for blinded interventions may have worsened participant stress from being in a high-intensity environment, but alternatively may have improved anxiety due to the reassurance of being vaccinated in a controlled environment. Lastly, information regarding past allergic and medical history and first-dose reactions was collected retrospectively, although every effort was made to obtain thorough details of the reactions using medical records from the vaccination site, emergency department visit, or an allergist or

another physician where possible. Most of the participants received their first dose at mass vaccination sites during the earlier phase of the vaccination campaign (between December 2020 and June 2021), where there was limited if any recording of reactions. To increase the reliability of first dose reactions as sARs in context of the limitations of each scoring system, we used 3 different criteria (CoFAR scale, Brighton criteria, and NIAID and Food Allergy and Anaphylaxis Network anaphylaxis criteria) and further adjudicated with revised Brighton criteria published after study completion. All entry reactions met CoFAR grade 2 or higher and anaphylaxis level 1 or higher criteria (Table 2); however, the possibility of some of these being ISRRs cannot be excluded.

Circumstances surrounding the COVID-19 mass vaccination campaign may have been conducive to ISRRs with introduction of a new vaccine platform, unconventional vaccination settings, health care system mistrust fueled by reports of vaccine-related AEs in the news and social media, and isolation and stress created by the pandemic. Misclassification of ISRRs as sARs may contribute to the unexpectedly high rates of reported anaphylaxis to the COVID-19 mRNA vaccines, which is detrimental to both public health and individual well-being. After experiencing sAR following their first dose of mRNA vaccine, all but 1 participant consulted an allergist or other physician and were denied a second dose in accordance with the guidelines. For most participants, alternative COVID-19 vaccine platforms were not available. As a result of incomplete vaccination, participants reported work, travel, interpersonal, and psychological difficulties. Interestingly, a previous study reported lower anti-spike IgG1 levels in individuals who had COVID-19 vaccine–induced allergic reactions compared with individuals who did not. Therefore, a delay in subsequent vaccinations may interfere with the ability to mount a sufficient and sustained immune response and highlights the importance of these individuals being vaccinated in a timely fashion. More research is needed to assess if these individuals require doses in addition to what is recommended currently.[42] Furthermore, inappropriate labeling of individuals as allergic to the mRNA vaccines or their components may unnecessarily prevent them from accessing future mRNA or other vaccine technologies. Our findings underscore the need for further research to elucidate the mechanisms underlying sARs to the COVID-19 mRNA vaccines, for increased awareness of ISRR among clinicians and vaccination staff, and for revaccination of individuals with suspected allergic reactions to the COVID-19 mRNA vaccines.[31]

DISCLOSURE STATEMENT

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Disclosure of potential conflict of interest: L. Chatman is employed by the Kelly Services contracting agency at NIAID, NIH. E. P. Feener is an employee of KalVista Pharmaceuticals, Inc. S. K. Lai receives funding from the grants R01 HL141934 and 3UM1AI109565-08S1, is a founder of Polyon Pharmaceuticals, has a patent on methods to overcome anti-PEG antibodies licensed by Polyon Pharmaceuticals from the University of North Carolina Chapel Hill, and has consulted for Takeda on the topic of anti-PEG antibodies. L. B. Schwartz invented the tryptase assay licensed to Thermo Fisher Scientific by Virginia Commonwealth University, and royalties received by Virginia Commonwealth University are shared with L. B. Schwartz. The rest of the authors declare that they have no relevant conflicts of interest.

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Clinical implications: Prospective data indicate supervised revaccination of individuals with reported sARs following first dose of COVID-19 mRNA vaccine is safe. Skin testing to vaccine and vaccine components offered no diagnostic utility.

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