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Risk of Second Allergic Reaction to SARS-CoV-2 Vaccines
A Systematic Review and Meta-analysis

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IMPORTANCE Vaccination against SARS-CoV-2 is a highly effective strategy to prevent infection and severe COVID-19 outcomes. The best strategy for a second dose of vaccine among persons who had an immediate allergic reaction to their first SARS CoV-2 vaccination is unclear.

OBJECTIVE To assess the risk of severe immediate allergic reactions (eg, anaphylaxis) to a second dose of SARS-CoV-2 mRNA vaccine among persons with immediate allergic reactions to their first vaccine dose.

DATA SOURCES MEDLINE, Embase, Web of Science, and the World Health Organization Global Coronavirus database were searched from inception through October 4, 2021.

STUDY SELECTION Included studies addressed immediate allergic reactions of any severity to a second SARS-CoV-2 vaccine dose in persons with a known or suspected immediate allergic reaction (<4 hours after vaccination) after their first SARS-CoV-2 vaccine dose. Studies describing a second vaccine dose among persons reporting delayed reactions (>4 hours after vaccination) were excluded.

DATA EXTRACTION AND SYNTHESIS Paired reviewers independently selected studies, extracted data, and assessed risk of bias. Random-effects models were used for meta-analysis. The GRADE (Grading of Recommendation, Assessment, Development, and Evaluation) approach evaluated certainty of the evidence.

MAIN OUTCOMES AND MEASURES Risk of severe immediate allergic reaction and repeated severe immediate allergic reactions with a second vaccine dose. Reaction severity was defined by the reporting investigator, using Brighton Collaboration Criteria, Ring and Messmer criteria, World Allergy Organization criteria, or National Institute of Allergy and Infectious Diseases criteria.

RESULTS Among 22 studies of SARS-CoV-2 mRNA vaccines, 1366 individuals (87.8% women; mean age, 46.1 years) had immediate allergic reactions to their first vaccination. Analysis using the pooled random-effects model found that 6 patients developed severe immediate allergic reactions after their second vaccination (absolute risk, 0.16% [95% CI, 0.01%-2.94%]), 232 developed mild symptoms (13.65% [95% CI, 7.76%-22.9%]), and, conversely, 1360 tolerated the dose (99.84% [95% CI, 97.09%-99.99%]). Among 78 persons with severe immediate allergic reactions to their first SARS-CoV-2 mRNA vaccination, 4 people (4.94% [95% CI, 0.93%-22.28%]) had a second severe immediate reaction, and 15 had nonsevere symptoms (9.54% [95% CI, 2.18%-33.34%]). There were no deaths. Graded vaccine dosing, skin testing, and premedication as risk-stratification strategies did not alter the findings. Certainty of evidence was moderate for those with any allergic reaction to the first dose and low for those with severe allergic reactions to the first dose.

CONCLUSIONS AND RELEVANCE In this systematic review and meta-analysis of case studies and case reports, the risk of immediate allergic reactions and severe immediate reactions or anaphylaxis associated with a second dose of an SARS-CoV-2 mRNA vaccine was low among persons who experienced an immediate allergic reaction to their first dose. These findings suggest that revaccination of individuals with an immediate allergic reaction to a first SARS-CoV-2 mRNA vaccine dose in a supervised setting equipped to manage severe allergic reactions can be safe.

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Supplemental content

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SARS-CoV-2 vaccination effectively reduces the risk of infection and severe COVID-19 outcomes. With more than 8.6 billion doses administered worldwide, immunization is a global priority to stem the count of the approximately 274 million infected and 5.3 million dead.[1] Factors associated with facilitating vaccination include increasing vaccine mandates and supply, whereas factors associated with barriers to vaccination include vaccine inequity, hesitancy, disinformation and misinformation, and rare adverse effects, such as severe allergic reactions (which occur in 7.9 per 1 million vaccinations[2]). Early in the global vaccine rollout, December 9, 2020,[3] rare cases of allergic reactions to mRNA vaccines rapidly led to recommendations stating that persons with an immediate allergic reaction to the first dose of an mRNA COVID-19 vaccine should not receive additional doses of either of the mRNA COVID-19 vaccines.[3-5] This contraindication is inconsistent with allergy specialist practice parameters, which do not contraindicate readministration of non-COVID vaccines to those with prior vaccine allergic reactions.[6]

The immunology of allergic reactions is commonly understood to imply that, once an initial reaction occurs, repeated exposures reproducibly lead to acute and potentially life-threatening reactions (eg, anaphylaxis to food in those with a food allergy). Although this paradigm has been assumed regarding COVID vaccination, its evidence base has not been critically appraised. We systematically reviewed the literature on the risk of a second severe allergic reaction after SARS-CoV-2 vaccination.

Key Points

Question What is the risk of an immediate severe allergic reaction to a second dose of a SARS-CoV-2 mRNA vaccine among individuals who had an immediate allergic reaction of any severity to their first dose?

Findings In this systematic review and meta-analysis of 22 studies including 1366 patients revaccinated under the supervision of an allergist, there was a low incidence (0.16%) of immediate severe allergic reactions associated with receiving a second dose of SARS-CoV-2 mRNA vaccine among individuals who had an immediate allergic reaction to their first dose. There were no deaths.

Meaning This study suggests that there is a low risk of a severe immediate allergic reaction associated with a second SARS-CoV-2 mRNA vaccine dose among persons who had an immediate allergic reaction to their first dose.

Methods

We searched MEDLINE, Embase, and the World Health Organization Global Coronavirus database (a database aggregating published and preprint COVID-19 reports daily from 112 other literature databases), from inception through October 4, 2021, for studies of any design addressing the risk of a second allergic reaction to SARS-CoV-2 vaccines of any severity among individuals who had a prior allergic reaction to a SARS-CoV-2 vaccine (eMethods in the Supplement). We additionally searched Web of Science (all databases) using forward and backward citation analysis to identify any additional relevant records. Studies that detailed delayed (>4 hours after vaccine) reactions or involved SARS-CoV-2 revaccination but did not address individuals with prior allergic reactions were excluded. Three reviewers (D.K.C., M.S., and M.G.) independently and in duplicate screened records using Covidence (Veritas Health Innovation), and 4 reviewers (E.M.A., D.B.K.G., M.S., and M.G.) independently and in duplicate extracted data. **Figure 1** details the PRISMA diagram for the literature search and final study selection. Consensus among the reviewers was used to resolve conflicts. We extracted the total number of second dose revaccinations in individuals with an immediate first dose SARS-CoV-2 vaccine allergic reaction, the number of revaccinations tolerated (as indicated by the investigator; this was defined as mild or self-limiting subjective or objective symptoms that either spontaneously resolved or resolved with antihistamine treatment), the number of revaccinations resulting in a severe allergic reaction (eg, described in the studies as either anaphylaxis or as requiring injectable epinephrine administration), and reactions stratified by the severity of initial reaction (anaphylaxis or not). Reaction severity was defined at the study level by the reporting investigator, using Brighton Collaboration criteria,[7] classification by Ring and Messmer,[8] World Allergy Organization criteria,[9] or National Institute of Allergy and Infectious Diseases criteria.[10] Study authors were contacted individually to verify final data extraction, if any cases were duplicated, if the author group had multiple included publications, and to clarify any study design questions. Pooled data were analyzed using random-effects generalized linear models (binomial family, logit link) using Stata, version 14.3 (StataCorp LLC). The primary outcome was the incidence of severe allergic reactions (eg, anaphylaxis) after second vaccination, with 95% exact (Clopper-Pearson) CIs. The secondary outcome included the rate of any

Figure 1. PRISMA Diagram for Study Selection

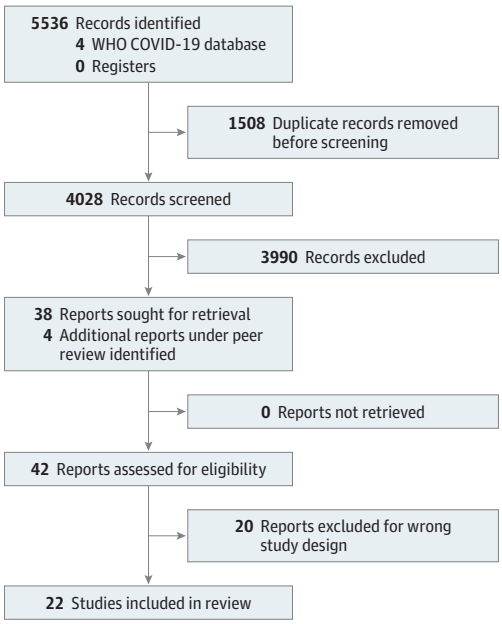


Table 1. Characteristics of the Included Studies

Source and country	Design	Female, %	Median or mean age, y	Total second doses			Total No. of patients			Included patients with anaphyl to first dose	Graded dosing	Skin testing used	Premedication allowed	Total second doses deferred	Comments
				Administered	With nonsevere symptoms	With anaphyl	Anaphyl after first dose and received a second dose	Anaphyl after both first and second dose	Anaphyl after first dose and deferred second dose						
Tuong et al,[14] 2021; US	Case series	100	42.8 (range, 21-64)	15	6	2	1	0	0	Yes	Yes	Yes	No	0	Both cases of anaphyl occurred on the last step of a multidose desensitization; 1 of these patients had positive Moderna vaccine testing results indicating allergy, with negative excipient testing results indicating no allergy
Krantz et al,[15] 2021; US and Denmark	Case series	100	44.8 (range, 29-54)	4[a]	0	0	4	0	0	Yes	No	Yes	Yes	0	After verification with the authors, the US numbers represented their initial patients, who were included with additional patients who became part of a larger multicenter report in the study by Krantz et al[17]; therefore, these reflect only the Danish patients
Rasmussen et al,[16] 2021; Denmark	Case series	88.5	46 (range, 18-88)	30	0	0	4	0	0	Yes	No	Yes	No	1	25 Patients received the AstraZeneca vaccine with their first dose and tolerated an mRNA vaccine with their second dose
Krantz et al,[17] 2021; US	Case series	86	43 (SD, 14)	159	32	0	19	0	13	Yes	No	Yes	Yes	30	Included 8 patients from the Krantz et al[15] study and 11 patients from the Wolfson et al[18] study; per discussion with the authors, no adjustments to these totals were made; potentially duplicated cases were adjusted in the data from the other articles
Wolfson et al,[18] 2021; US	Case series	89	40.9 (SD, 13.6)	58[b]	15	3	3	3	2	Yes	No	Yes	Yes	7	The 3 patients with anaphyl had anaphyl to the first dose, but had negative skin testing results; 1 of the patients had a grade 2 reaction but did not seek care or treatment; 11 patients had Ring and Messmer grade 2 reactions, but only 6 were treated with epinephrine initially; there were 56 patients in this report, including 8 patients with first dose anaphyl, who were also part of the Krantz et al study[17]; we accounted for duplication among the patients with anaphyl but not the other patients; we present the primary estimates based on excluding only the unique patients (which were only those with anaphyl) from the Wolfson et al study,[18] but did perform sensitivity analysis that included them

(continued)

Table 1. Characteristics of the Included Studies (continued)

Source and country	Design	Female, %	Median or mean age, y	Total second doses			Total No. of patients			Included patients with anaphyl to first dose	Graded dosing	Skin testing used	Premedication allowed	Total second doses deferred	Comments
				Administered	With nonsevere symptoms	With anaphyl	Anaphyl after first dose and received a second dose	Anaphyl after both first and second dose	Anaphyl after first dose and deferred second dose						
Kessel et al,[19] 2021; Israel	Case series	77.8	54.3 (range, 23-75)	18	4	0	7	0	0	Yes	No	Yes	Yes	0	NA
Kelso,[20] 2021; US	Case report	100	48.6 (range, 43-56)	3	0	0	3	0	1	Yes	No	Yes	No	1	NA
Mustafa et al,[21] 2021; US	Case report	100	64 and 39	2	0	0	0	0	0	Yes	Yes	Yes	No	0	NA
Vanijcharoenkarn et al,[22] 2021; US	Case series	92	Not specified	73	5	0	4	0	3	Yes	Mixed	Yes	No	15	NA
Robinson et al,[23] 2021; US	Case series	78	Mean age range, 41-43	860	146	0	3	0	3	Yes	No	NS	No	43	There were 358 persons receiving a second dose in this study who did not fill out a postvaccination symptom survey; the authors consider the nonresponders to be missing data; the study was not designed to investigate outcomes of a second dose
Eastman et al,[24] 2021; US	Case series	84.8	42 (range, 19-69)	53	17	0	2	0	0	Yes	Mixed	Yes	No	13	NA
Park et al,[25] 2021; US	Case report	100	34	1	0	0	1	0	0	Yes	No	Yes	No	0	NA
Arroliga et al,[26] 2021; US	Case series	86	39 (range, 23-61)	6	0	0	0	0	2	No	No	No	No	13	There were 8 patients lost to follow-up, and 5 patients deferred receiving a second dose
Loli-Ausejo et al,[27] 2021; Spain	Case series	81.8	39 (range, 29.5-56.5)	10	5	0	0	0	0	No	Yes	Yes	Yes	1	NA
Pitlick et al,[28] 2021; US	Case series	80	48 (range, 20-90)	44	7	0	4	0	3	Yes	Yes	Yes	No	11	This report includes 8 patients who were initially included as part of an early published case series, but have been included in a single large series of 55 patients
Yacoub et al,[29] 2021; Italy	Case series	85.7	47.6 (range, 38-55)	8	3	0	0	0	1	No	No	No	Yes	4	NA
Shavit et al,[30] 2021; Israel	Case series	70.9	52 (SD, 16)	6	3	0	0	0	3	No	No	No	Yes	Not specified	NA

(*continued*)

Table 1. Characteristics of the Included Studies (continued)

Source and country	Design	Female, %	Median or mean age, y	Total second doses			Total No. of patients			Included patients with anaphyl to first dose	Graded dosing	Skin testing used	Premedication allowed	Total second doses deferred	Comments
				Administered	With nonsevere symptoms	With anaphyl	Anaphyl after first dose and received a second dose	Anaphyl after both first and second dose	Anaphyl after first dose and deferred second dose						
Kohli-Pamnani et al,[31] 2021; US	Case series	87	56 (SD, 16)	16	3	0	1	0	0	Yes	No	Yes	Yes	2	2 Patients had anaphyl to the first dose, one of whom received a second mRNA vaccine dose, but the other opted for the Janssen vaccine for their second dose; both tolerated the second dose
Inoue et al,[32] 2021; Japan	Case report	67.1	20 to ≥60	2	0	0	0	0	0	No	No	No	No	Not specified	NA
Warren et al,[33] 2021; US	Case series	91	40.9 (SD, 10.3)	22	0	1	17	1	0	Yes	No	Yes	No	0	This study was not originally intended to investigate revaccination; at the time of publication, only 1 patient received a second dose, and had repeated anaphyl; after discussion with the authors, they reported that the other 20 persons were revaccinated as part of California's vaccine mandate, with no further severe reactions
Carpenter et al,[34] 2021; US	Case report	100	60	1	1	0	0	0	0	No	No	Yes	No	1	NA
Kaplan et al,[35] 2021; US	Case series	86.7	48 (range, 19-89)	30	30	0	5	0	0	Yes	Yes	Yes	Yes	8	NA

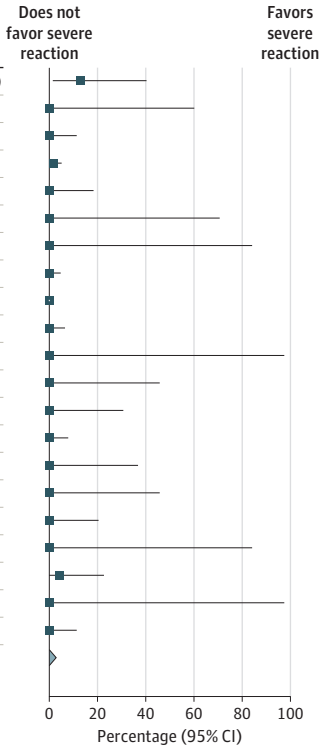
Abbreviations: Anaphyl, anaphylaxis; NA, not applicable.

[a] This study includes patients who were also reported by Krantz et al.[17] All duplicates have been accounted for, and the unique patients are presented here.

[b] This study includes patients who were also reported by Krantz et al.[17] All duplicate cases of anaphylaxis have been accounted for, with only the unique patients presented here. After discussion with the authors, we were unable to account for all duplicate patients in the denominator of all second doses administered. Thus, for the primary analysis, only the 3 unique patients with anaphylaxis were included as the study denominator. In the sensitivity analysis, this is reported as shown here, which includes the case number as originally published, including potential duplicates.

Figure 2. Pooled Incidence of Immediate Severe Allergic Reactions to a Second SARS-CoV-2 mRNA Dose Among Persons Who Had an Immediate Allergic Reaction to Their First SARS-CoV-2 mRNA Vaccine Dose

Source	Second doses administered	Second dose anaphylaxis	Percentage (95% CI)
Tuong et al,[14] 2021	15	2	13.33 (1.66-40.46)
Krantz et al,[15] 2021	4	0	0.00 (0.00-60.24)
Rasmussen et al,[16] 2021	30	0	0.00 (0.00-11.57)
Krantz et al,[17] 2021	162	3	1.85 (0.38-5.32)
Kessel et al,[19] 2021	18	0	0.00 (0.00-18.53)
Kelso,[20] 2021	3	0	0.00 (0.00-70.76)
Mustafa et al,[21] 2021	2	0	0.00 (0.00-84.19)
Vanijcharoenkarn et al,[22] 2021	73	0	0.00 (0.00-4.93)
Robinson et al,[23] 2021	860	0	0.00 (0.00-0.43)
Eastman et al,[24] 2021	53	0	0.00 (0.00-6.72)
Park et al,[25] 2021	1	0	0.00 (0.00-97.50)
Arroliga et al,[26] 2021	6	0	0.00 (0.00-45.93)
Loli-Ausejo et al,[27] 2021	10	0	0.00 (0.00-30.85)
Pitlick et al,[28] 2021	44	0	0.00 (0.00-8.04)
Yacoub et al,[29] 2021	8	0	0.00 (0.00-36.94)
Shavit et al,[30] 2021	6	0	0.00 (0.00-45.93)
Kohli-Pamnani et al,[31] 2021	16	0	0.00 (0.00-20.59)
Inoue et al,[32] 2021	2	0	0.00 (0.00-84.19)
Warren et al,[33] 2021	22	1	4.55 (0.12-22.84)
Carpenter et al,[34] 2021	1	0	0.00 (0.00-97.50)
Kaplan et al,[35] 2021	30	0	0.00 (0.00-11.57)
Overall: I^2 = 0.3%	1366	6 (1360 successes)	0.16 (0.01-2.94)



[a] For analysis purposes, this study by Krantz et al[17] was combined with the 3 cases (all anaphylaxis) from Wolfson et al[18] given that these 2 studies had overlap of cases.

immediate nonsevere symptoms occurring (defined in the studies as mild or self-limiting symptoms that were either subjective or objective). Sensitivity analyses included modeling the rate of tolerated vaccine administrations, excluding case reports, plausible assumptions to address missing outcome data or potential overlapping studies, using a fixed-effect model with a bayesian framework (mininimally informative priors: main effect [N(0, 10)], between-study variance [inverse gamma (0.001, 0.001)]). Prespecified subgroup analyses were by risk of bias, graded dosing, skin testing, and premedication. The Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) approach[11,12] provided assessment of the quality of the body of the evidence, and the Joanna Briggs Institute tool[13] provided the framework for assessment of risk of bias (eTable 1 in the Supplement). Publication bias was assessed through GRADE, assessment of the search comprehensiveness, and inspection of funnel plots for small effects. Heterogeneity was assessed using methods recommended by GRADE involving consistency of the point estimates and overlap of 95% CIs given evidence that I^2 could be misleading in this type of analysis.[11,12] A 2-sided $P < .05$ was considered statistically significant.

Results

Twenty-two studies (single-group cohorts, case series, and case reports) detailing second-dose SARS-CoV-2 mRNA vaccination for 1366 individuals (87.8% women; mean age, 46.1 years) with a known or suspected prior immediate allergic reaction to a SARS-CoV-2 mRNA vaccine, including 78 persons with prior severe immediate allergic reactions (eg, anaphylaxis) to a SARS-CoV-2 mRNA vaccine, were included.[14-35] **Table 1**[14-35] details the study characteristics. All revaccinations were administered to adults under the guidance of an allergy specialist and used mRNA vaccines. A total of 6 severe reactions occurred (absolute risk, 0.16% [95% CI, 0.01%-2.94%]; pooled random-effects model; moderate-certainty evidence; **Figure 2**); 1360 patients tolerated the dose (99.84% [95% CI, 97.09%-99.99%]; pooled random-effects model). Although 4 of the cases of severe immediate allergic reactions occurred in persons who had severe allergic reactions with their first dose (absolute risk, 4.94% [95% CI, 0.93%-22.28%]; pooled random-effects model; low-certainty evidence; eFigure 1 in the Supplement), none of the other 74 patients with severe immediate allergic reactions to the first dose experienced severe immediate allergic reactions to the second dose. None of the 6 patients with severe immediate allergic reactions died, and 5 recovered rapidly after receiving intramuscular epinephrine (the sixth patient did not seek or receive treatment, despite experiencing a reaction consistent with moderately severe anaphylaxis, and recovered). A total of 232 persons (13.65% [95% CI, 7.76%-22.9%]; pooled random-effects model; moderate-certainty evidence) experienced mild immediate nonsevere symptoms with their second dose (eFigure 2 in the Supplement). Of the 78 persons who had an immediate severe reaction with the first dose, 15 (9.54% [95% CI, 2.18%-33.34%]; pooled random-effects model) experienced mild

Table 2. GRADE Evidence Profile Table

Outcome	No. of studies	Certainty assessment						Effect			Certainty[b]
		Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of events	No. of individuals[a]	Rate, % (95% CI)	
Incidence of anaphylaxis to a second dose of the SARS-CoV-2 mRNA vaccine in persons who had an allergic reaction to their first dose	22	Case studies and case reports	Not serious[c]	Not serious	Not serious	Not serious	Large effect of tolerating and residual confounding would suggest an effect of reacting when none was detected[d]	6	1366	0.16 (0.01-2.94)	+++ (Moderate)
Incidence of anaphylaxis to a second dose of the SARS-CoV-2 mRNA vaccine in persons who had anaphylaxis to their first dose	17	Case studies and case reports	Not serious[c]	Not serious	Not serious	Not serious[e]	Large effect of tolerating and residual confounding would suggest an effect of reacting when none was detected[d,e]	4	78	4.94 (0.93-22.28)	++ (Low)
Incidence of mild allergic symptoms to a second dose of the SARS-CoV-2 mRNA vaccine in persons who had an allergic reaction to their first dose	22	Case studies and case reports	Not serious[c]	Not serious	Not serious	Not serious	Large effect of tolerating and residual confounding would suggest an effect of reacting when none was detected[d]	232	1366	13.65 (7.76-22.9)	+++ (Moderate)

Abbreviation: GRADE, Grading of Recommendation, Assessment, Development, and Evaluation.

[a] Patient or population: patients receiving second mRNA COVID vaccination after a previous allergic reaction to a mRNA COVID vaccine dose.

[b] GRADE Working Group grades of evidence: high certainty, we are very confident that the true effect lies close to that of the estimate of effect; moderate certainty, we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different; low certainty, our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect; and very low certainty, we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. The number of plus symbols indicates the degree of certainty, where more plus symbols indicate a higher degree of certainty.

[c] Risk of bias addressed in subgroup and sensitivity analyses.

[d] A history of allergic reaction to previous COVID vaccination was a priori thought to guarantee a reaction to repeated doses, but far fewer than all individuals who received the second dose had an allergic reaction or anaphylaxis. Furthermore, those receiving a second dose of the vaccine, after an initial allergic reaction, would be at higher likelihood to be intensely monitored for any possible allergic reaction, whereas those without any history of an allergic reaction would not be intensely monitored.

[e] Imprecision in width of 95% CIs and total sample size sufficient to prevent rating up certainty for considerations of residual confounding, but not to rate down; the qualitative effect of the incidence of repeated anaphylaxis being not very high (eg, 100%) is more certain than the quantitative estimate of a mean of 4.9%.

immediate nonsevere symptoms with their second dose (eFigure 3 in the Supplement). Sensitivity and subgroup analyses, including accounting for studies that permitted the use of graded dosing, premedication, or skin testing, and risk of bias, did not alter the main findings (eTable 2 in the Supplement). **Table 2** details the GRADE evidence profile.

Discussion

This systematic review and meta-analysis found moderate-certainty evidence of a low incidence of severe immediate allergic reactions associated with the second dose of a SARS-CoV-2 mRNA vaccine among individuals with a history of an allergic reaction of any severity to their first mRNA vaccine dose. Revaccination of such persons led to no repeated reactions in most individuals and to nonsevere immediate symptoms in approximately 13.65% individuals.

These findings contradict the common assumption that a history of immediate reaction, including severe immediate allergic reactions, to a prior SARS-CoV-2 mRNA vaccine guarantees another reaction after revaccination. Immunoglobulin E (IgE) can be responsible for such stereotypically reproducible allergic responses—as in the case of allergic reactions to foods—but anaphylaxis can also occur idiosyncratically and nonspecifically owing to non-IgE-dependent mechanisms. Our findings therefore suggest that SARS-CoV-2 mRNA vaccine-induced anaphylaxis may not occur via an IgE-dependent mechanism, something that is also consistent with mechanistic data,[27] the lack of any consistent and verifiable specific allergen within SARS-CoV-2 mRNA vaccines,[33] the inability of skin testing of the ingredients of the vaccine to predict immediate allergic reactions to vaccination,[18] and the overall very rare baseline incidence of severe immediate allergic reactions to SARS-CoV-2 vaccines.[2]

These data should prompt reconsideration of a history of allergic reaction to a prior dose of SARS-CoV-2 mRNA vaccine as a contraindication to a second dose of the vaccine.[36] Supervision of second vaccination in a medical setting equipped to manage a severe immediate allergic reaction (as opposed to vaccination occurring in a retail pharmacy or nonmedical-based setting) may be appropriate instead.[2] Consultation with an allergist prior to the second vaccination, when possible, might be beneficial. Removing barriers to vaccination is paramount to maximizing immunity and thereby protecting individuals and societies against COVID-19.

Limitations

This study has some limitations. First, the data address second-dose SARS-CoV-2 mRNA vaccinations, whereas other vaccine platforms and doses beyond the second dose require further study. Second, there is a risk of imprecision given the limited study numbers and patient numbers detailing these patient outcomes, albeit the absence of reactions in the situation of allergy can be considered as successes, and sensitivity analyses accounting for this led to findings consistent with the main analyses. We speculate that prior work calculating a very low event rate of severe reactions to the first dose (7.9 events per 1 000 000 vaccine doses)[2] and a contraindication against provision of additional doses to persons with an immediate allergic reaction to a first dose both may explain why there were not more studies available to include in this systematic review and meta-analysis. However, we hope that our analysis provides reassurance that, when immediate reactions to the first dose do occur, it is safe to give second doses in this context and that this would lead to more published research becoming available because this is planned as a living systematic review. Third, while there may be potential overlap of cases between included reports, we resolved cases through correspondence with primary study authors and use of sensitivity analyses. Fourth, some of the component studies were subject to risk of selection bias, but this was mitigated by the findings being consistent in subgroup and sensitivity analyses and for patients with a history of anaphylaxis, for which this might have been less of a concern. Fifth, severe reactions were partly defined as requiring injectable epinephrine, and while other potential definitions could apply, this severity definition is an accepted standard within the allergy field.[37] Sixth, all included studies were conducted with allergy specialist guidance, which could limit generalizability.

Conclusions

In this systematic review and meta-analysis of 22 case studies and case reports, the risk of repeated immediate allergic reactions and severe immediate allergic reactions or anaphylaxis associated with a second SARS-CoV-2 mRNA vaccination was low among persons who experienced an allergic reaction to their first dose, although 1 in 7 may have experienced mild symptoms. Although further research is warranted, these findings support the safe revaccination of individuals with an allergic reaction to a first SARS-CoV-2 mRNA vaccine dose in a setting equipped to manage severe allergic reactions, if they were to occur.

ARTICLE INFORMATION

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Author Contributions: Drs Chu and Greenhawt had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Chu, Abrams, Stone, Krantz, Shaker, Greenhawt.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Chu, Abrams, Golden, Stone, Krantz, Shaker, Greenhawt.
Critical revision of the manuscript for important intellectual content: Chu, Abrams, Golden, Blumenthal, Wolfson, Krantz, Shaker, Greenhawt.
Statistical analysis: Chu, Abrams, Greenhawt.
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