Supplementary Online Content

Chu DK, Abrams EM, Golden DBK, et al. Risk of second allergic reaction to SARS-CoV-2 vaccines: a systematic review and meta-analysis. *JAMA Intern Med.* Published online February 21, 2022. doi:10.1001/jamainternmed.2021.8515

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Risk of Bias Ratings for Included Studies

For Case Series	Tuong et al[e1]	Krantz et al[e2]	Rassumssen et al[e3]	Krantz et al[e4]	Wolfson et al[e5]	Kessel et al[e6]	Pitlick et al[e7]	Vanijcharoenkarn et al [e8]	Robinson et al[e9]	Eastman et al[e10]	Arroliga et al[e11]	Loli-Asseio et al[e12]	Yacoub et al[e13]	Shavit et al[e14]	Kohli-Pamnani et al[e15]	Inoue et al[e16]	Kaplan et al[e17]
Were there clear criteria for inclusion in the case series?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Were valid methods used for identification of the condition for all participants included in the case series?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the case series have consecutive inclusion of participants?	No	Yes	Yes	Unclear	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Did the case series have complete inclusion of participants?	Unclear	Yes	Yes	Unclear	No	Yes	Unclear	No	No	Yes	No	Yes	Yes	Yes	Unclear	Yes	Unclear
Was there clear reporting of the demographics of the participants in the study?	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was there clear reporting of clinical information of the participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the outcomes or follow up results of cases clearly reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Was statistical analysis appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Overall Appraisal	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**	**Include**
For Case Reports	**Park et al[e18]**	**Mustafa et al[e19]**	**Kelso et al[e20]**	**Warren et al[e21]**	**Carpenter et al[e22]**												
Were patient's demographic characteristics clearly described?	Yes	No	No	Yes	Yes												
Was the patient's history clearly described and presented as a timeline?	Yes	Yes	Yes	Yes	No												
Was the current clinical condition of the patient on presentation clearly described?	Yes	Yes	Yes	No	Yes												
Were diagnostic tests or assessment methods and the results clearly described?	Yes	Yes	Yes	Yes	Yes												
Was the intervention(s) or treatment procedure(s) clearly described?	Yes	Yes	Yes	Yes	Yes												
Was the post-intervention clinical condition clearly described?	Yes	Yes	Yes	No	Yes												
Were adverse events (harms) or unanticipated events identified and described?	Yes	Yes	Yes	Yes	Yes												
Does the case report provide takeaway lessons?	Yes	Yes	Yes	Yes	Yes												
Overall Appraisal	**Include**	**Include**	**Include**	**Include**	Include												

Some elements of the JBI tool address reporting quality rather than risk of bias. Only the risk of bias domains were considered in judgements regarding risk of bias.

E References

E1.Tuong LAC, Capucilli P, Staicu M, Ramsey A, Walsth E, Mustafa SS. Graded Administration of Second Dose of Moderna and Pfizer-BioNTech COVID-19mRNA Vaccine in Patients with Hypersensitivity to First Dose. Open Forum Infectious Diseases 2021; In Press.

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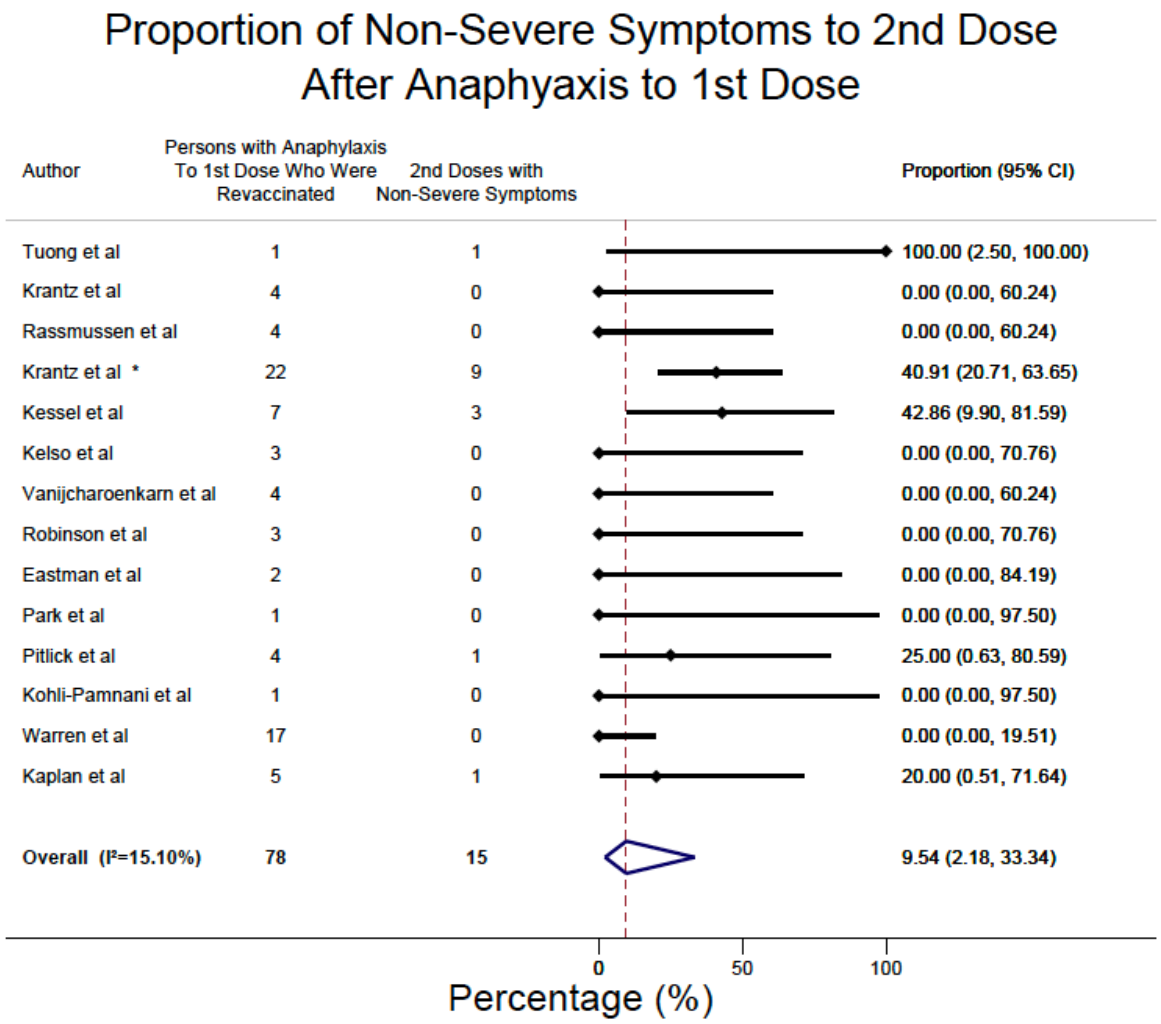
eTable 2. Additional Sensitivity Analyses

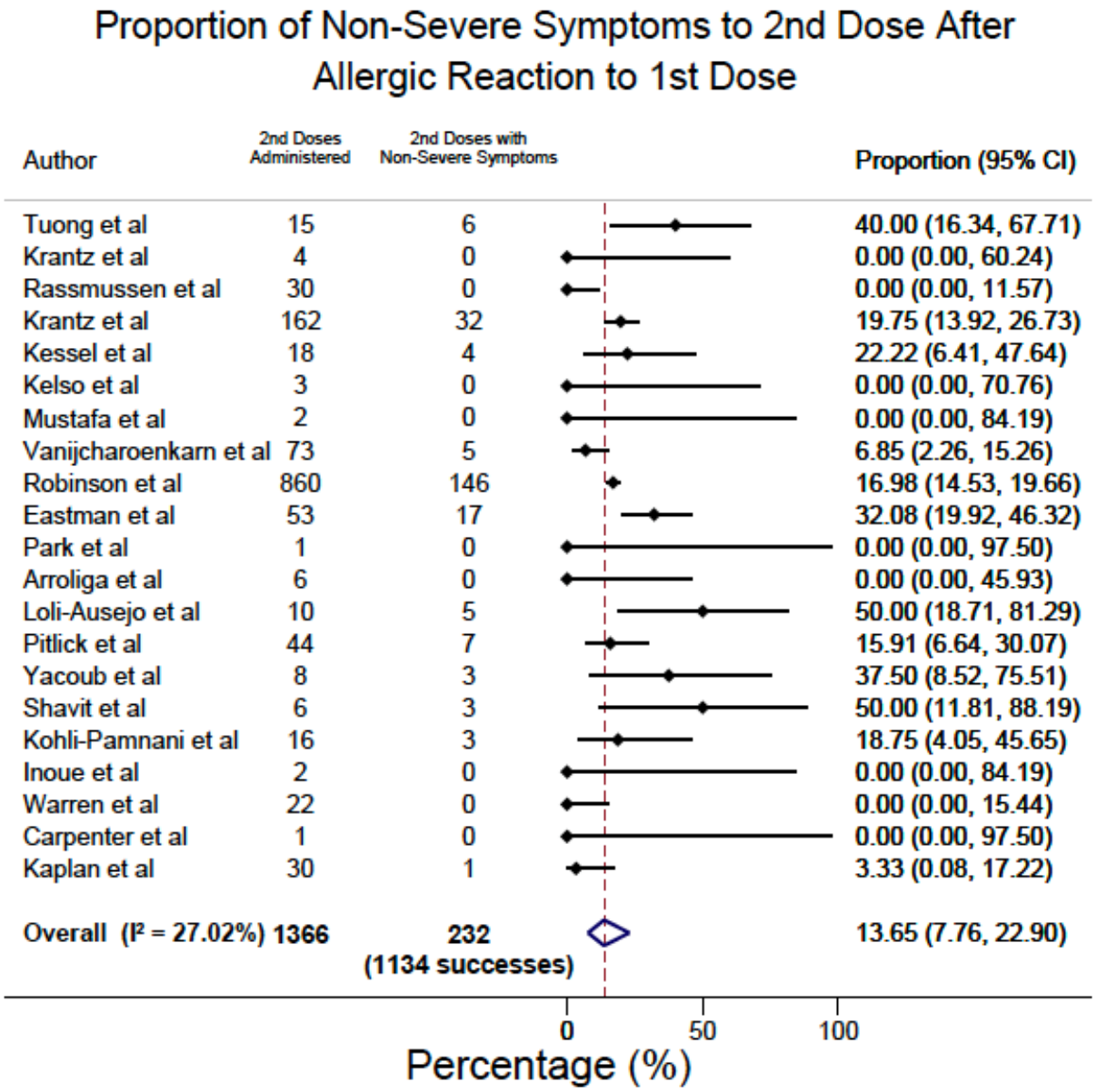
	Anaphylaxis after 2nd in those with reaction to first, % (95%CI or CrI)	Mild symptoms after 2nd dose in those with reaction to first, % (95%CI or CrI)	Anaphylaxis after 2nd in those with anaphylaxis to first, % (95%CI or CrI)
Subgroup analyses			
Risk of Bias			
High	0 (0, 100)	15.84 (9.76, 24.65)	5.04 (0.96, 22.57)
Low	1.06 (0.40, 2.79)	12.44 (5.31, 26.46)	6.56 (2.48, 16.21)
Interaction	p=1.00	p=0.95	p=0.99
Graded dosing			
Yes	1.29 (0.02, 40.98)	18.91 (6.83, 42.57)	0 (0, 100)
No	0.23 (0.02, 3.12)	13.39 (6.93, 24.32)	6.56 (2.48, 16.21)
Mixed	0 (0, 100)	17.46 (11.78, 25.10)	0 (0, 100)
Interaction	p=1.00	p=0.99	p=1.00
Premedication			
Yes	1.18 (0.38, 3.58)	10.12 (4.27, 22.11)	2.63 (0.37, 16.46)
No	0.09 (0.00, 6.05)	21.17 (12.23, 34.10)	7.69 (2.50, 21.30)
Interaction	p=1.00	p=0.98	p=0.97
Skin testing			
Yes	0.72 (0.10, 5.05)	12.68 (6.80, 22.40)	n/a
No	No repeat anaphylaxis	24.43 (6.90, 58.51)	n/a
Interaction	n/a	p=0.99	n/a
Sensitivity analyses			
Model number tolerated as events since allergy should guarantee repeat reactions	99.84 (97.07-99.99)% tolerated	n/a	91.70 (65.32, 98.48)% tolerated
Exclude case reports	0.16 (0.01, 3.02)	14.87 (9.09, 23.37)	5.63 (2.13, 14.07)
Wolfson, (partial duplication with Krantz)			
Include as published (ignores duplication)	0.31 (0.03, 2.76)	15.39 (9.87, 23.21)	Frequentist does not converge Bayesian: 2.58 (0.003, 11.94)
Fixed effect	0.44 (0.20, 0.97)	17.04 (15.14, 19.13)	5.56 (2.1, 13.89)
Bayesian Random	0.21 (0.0002, 0.90)	14.33 (7.25, 22.04)	4.93 (0.74, 10.38)
Assume any who deferred had 2x anaphylaxis rate	0.12 (0.003, 4.25)	n/a	1.20 (0.14, 9.85)
Assume any who deferred had 5x anaphylaxis rate	0.08 (0.001,5.40)	n/a	3.86 (1.4, 10.21)

eFigure 1. Incidence of Repeat Anaphylaxis to SARS-CoV-2 mRNA Vaccination



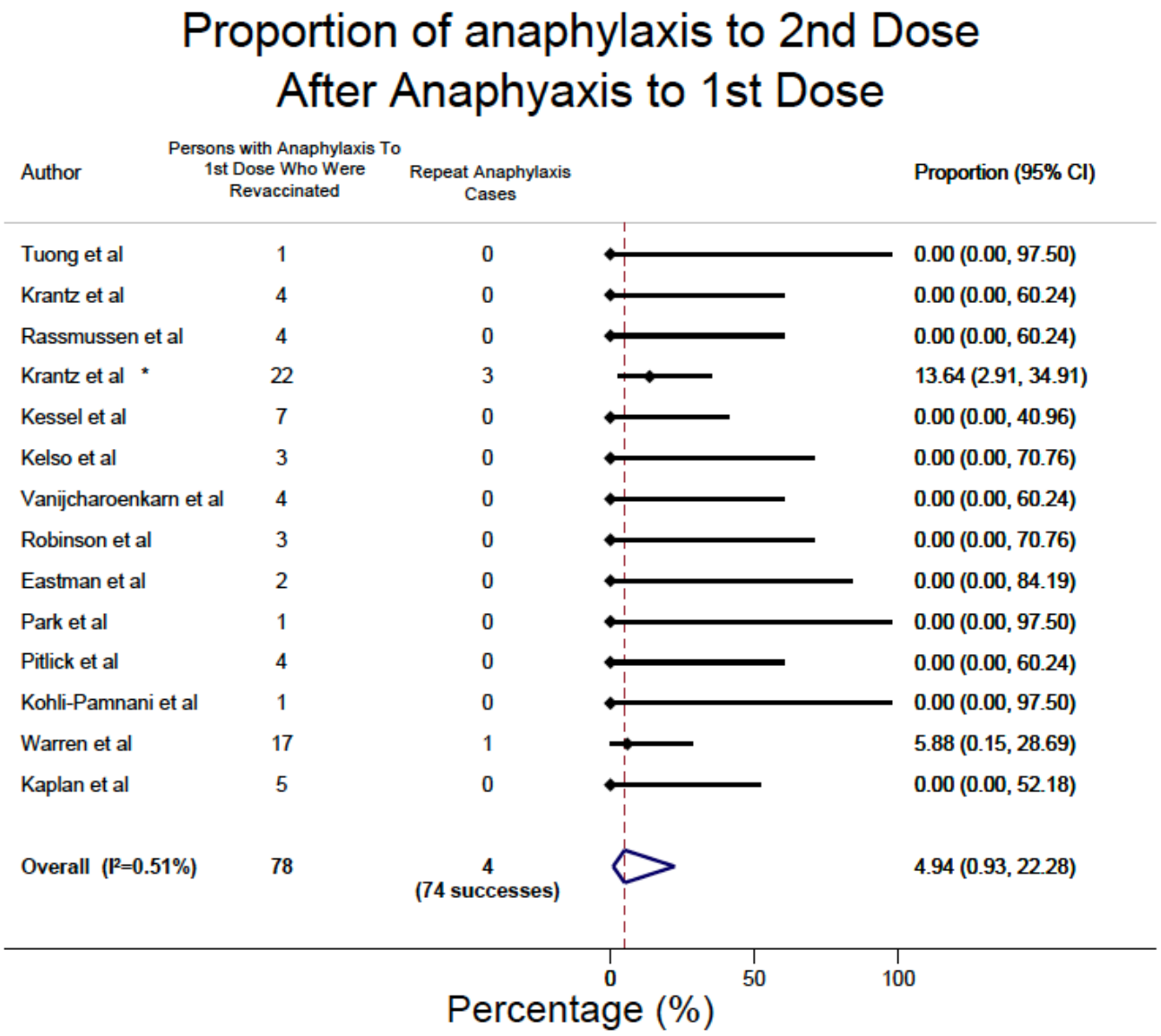
[*] **For statistical reporting purposes, 3 cases of anaphylaxis reported in Wolfson et al (reference e5) were combined with the cases in Krantz et al (reference e4). These studies had overlap of non-severe cases.**

eFigure 2. Incidence of Non-Severe Symptoms With 2nd Dose SARS-CoV-2 mRNA Vaccination



[*] **For statistical reporting purposes, 3 cases of anaphylaxis reported in Wolfson et al (reference e5) were combined with the cases in Krantz et al (reference e4). These studies had overlap of non-severe cases.**

eFigure 3. Incidence of Non-Severe Symptoms After Anaphylaxis to mRNA COVID-19 Vaccination



[*] For statistical reporting purposes, 3 cases of anaphylaxis reported in Wolfson et al (reference e5) were combined with the cases in Krantz et al (reference e4). These studies had overlap of non-severe cases.

eMethods. Registered Systematic Review Protocol

Repeat Allergic Reactions to SARS-CoV2 Vaccines in Patients Who Have Experienced an Allergic Reaction to a Prior Dose of a SARS-CoV2 Vaccine

Matthew Greenhawt, Marcus Shaker, David Golden, Elissa Abrams, Derek Chu

Start Date: August 20, 2021
Anticipated Completion Date: October 1, 2021

Question Development

In the spring of 2021, we previously performed a systematic review and meta-analysis detailing the risk of allergic reactions occurring after initial SARS-CoV-2 vaccination, inclusive of the following questions:

1) What is the risk of a severe allergic reaction, including anaphylaxis, to a SARS-CoV-2 vaccine in a patient with no history of a severe allergic reaction to a SARS-CoV-2 vaccine or its excipients?
2) In patients without a history of a severe allergic reaction, including anaphylaxis, to a SARS-CoV-2 vaccine or its excipients, should allergy skin testing to SARS-CoV-2 vaccines or its excipients be performed?
3) In patients with a history of a severe allergic reaction, including anaphylaxis, to a SARS-CoV-2 vaccine or its excipients, should allergy skin testing to SARS-CoV-2 vaccines or its excipients be performed to determine if vaccine withholding is needed?

A 4th question was formulated within the PICO search for question 3, but not addressed at that time. This was based on investigators' pre-specified determination that this literature was still too early and evolving at the time the search was initiated, and the impression that insufficient data was available to answer this question existed.

4) Should SARS-CoV-2 mRNA or adenovirus vector vaccines be administered to an individual who had an immediate allergic reaction to the first dose of the vaccine (defined as a generalized, systemic allergic reaction with acute onset occurring within 4 hours of vaccine administration), or given as a first dose to an individual who is suspected to have reacted previously to an excipient ingredient that is also present in the SARS-CoV-2 mRNA or adenovirus vector vaccines?

This initial meta-analysis and GRADE document was published in June 2021 (Greenhawt M, 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 Jun 18:S2213-2198(21)00671-1. doi: 10.1016/j.jaip.2021.06.006.) and immediately informed the public health sector regarding such risks and proposed methods of risk assessment and mitigation. However, we were unable to address a 4th and fundamental question at the time, regarding outcomes related to re-vaccination, as there were no data available (we had identified 3 small reports of a total of 15 patients, which we narratively described in our paper as having successfully received their second dose). Given a fluid, evolving interim situation since this publication regarding understanding of the likely mechanisms explaining allergic reactions to the vaccine, and emergence of multiple additional case series documenting re-vaccination outcomes within this population, this investigative group feels this question can now be systematically reviewed and meta-analyzed. Such data are urgently needed given contraindications to additional vaccination specifically based on a prior SARS-CoV-2 vaccine allergic reaction, and this systematic review will provide an urgent update to the knowledge on this subject, with high

likelihood of impacting public health policy internationally. This is particularly germane given shifts in policy in multiple countries, recommending additional boosters beyond the initially recommended series.

Prior to initiating this systematic review, a single pre-specified question was formulated for search, using the PICO (Population, Intervention, Comparator, Outcomes) format. The populations for study included published data regarding patients with known allergic reaction to a SARS-CoV-2 vaccine, who are seeking an additional dose of the vaccine. The following question was developed:

What is the risk of a severe allergic reaction (including anaphylaxis), to a SARS-CoV-2 vaccine in patients with a history of an allergic reaction of any reported severity to a prior SARS-CoV-2 vaccine dose?

Population: Patients with a known prior history of SARS-CoV-2 vaccine reaction of any severity, who are seeking an additional SARS-CoV-2 vaccine dose
Intervention: Those receiving an additional SARS-CoV-2 vaccination dose
Comparator: No subsequent vaccination
Outcome: Allergic reaction to a SARS-CoV-2 vaccine

Protocol
Protocol version 2021-08-20

Review question

What is the risk of an allergic reaction of any severity to SARS-CoV2 vaccination in persons who experienced an allergic reaction of any severity to a prior dose of SARS-CoV-2 vaccine?

Searches

The following databases will be searched since inception (date of search, 20 Aug, 2021)
1. MEDLINE
2. Embase
3. WHO Global Coronavirus database

We will also use Web of Science (all databases) forward and backward citation analysis of any relevant study. There will not be restrictions on language and period. Prior to submission of the manuscript, we will update the search.

Types of study to be included

For risk of an allergic reaction, including anaphylaxis, to a second vaccine dose:

RCTs, observational studies, and case reports

Condition or domain being studied

People at risk for a repeat allergic reaction to SARS-CoV2 vaccination

Participants/population

Individuals who experienced an allergic reaction to a previous dose of a SARS-CoV-2 vaccine

Intervention(s), exposure(s)

SARS-CoV2 vaccine

Comparator(s)/control

Those not receiving a second SARS-CoV2 vaccine, though we anticipate that the majority of the data to answer this question optimally will come from observational studies and case-series, which do not have a control arm.

Context

Worldwide

Main outcome(s)

1. Risk of vaccine induced anaphylaxis occurring with repeat vaccination dose.
    --Defined as investigator reported cases of anaphylaxis, severe allergic reactions, or reactions requiring injected epinephrine for treatment.

Measures of effect

Absolute measures of risk, incidence rate of anaphylaxis per 100,000 vaccinations

Additional outcome(s)

2. Risk of any allergic symptoms developing after repeat vaccination dose.
    --Defined as investigator reported cases of doses tolerated without severe symptoms. This would be inclusive of doses where mild symptoms--defined as no more than mild or self-limiting subjective or objective symptoms, which either spontaneously resolved or resolved with anti-histamine treatment--were reported by the investigator to have occurred.

This is additionally inclusive of any case reported as “tolerated” per investigator description or that were not classified as a severe reaction or anaphylaxis.

Measures of effect

None

Data extraction (selection and coding)

Screening and Selection of studies
Title and abstract screening, selection of full texts, data extraction and risk of bias assessments will be performed independently in duplicate. All conflicts will be resolved by discussion and if cannot be resolved by discussion with a third reviewer. We will use Covidence for screening.

Data extraction
Data extraction will occur independently and in duplicate by a minimum of 2 authors. Any disagreement will be resolved by discussion, and if needed, a third author. We will extract, apart from the outcome measures, study characteristics including Author, year, country, study design, vaccine type (mRNA vs. adenovirus-vector), dose deferrals, subgroups of persons with anaphylaxis to their first dose, use of premedication, use of graded dosing protocols, assessment by skin testing prior to vaccination, and study quality. In case of multiple publications of the same population, we will use all available information to analyze the multiple records as a single study as the unit of analysis. If this is not possible, and over 70% of the population is likely overlapping, we will use the largest study.

Risk of bias (quality) assessment

Randomized trials, which we do not anticipate to find, will be assessed using the Cochrane Risk of Bias version 2 tool. Nonrandomized comparative studies will be assessed using the ROBINS-I tool. Case series (those without a comparator group as per ACCP 2008 and JBI definition) and case reports will be evaluated using the JBI risk of bias tools for case series and case report studies, respectively. The domains relating to risk of bias, rather than reporting quality, will be used in judgements regarding high, probably high, probably low, or low risk of bias.

Strategy for data synthesis

Given that we anticipate the events to be rare and of risks, we will meta-analyze proportions in single arm studies by logistic-normal random effects, and in comparative studies by risk difference using DerSimonian and Laird random effects models. Sensitivity analyses will be done using the inverse outcome – eg. if anaphylaxis is too rare for models to estimate, we will analyze the proportion of individuals that tolerate receiving the vaccine. Statistical heterogeneity will be assessed using the GRADE approach, as I^2 will likely be misleading in pooling observational studies. Analysis will be done using Stata 14.3. We will use the GRADE approach to rate the overall quality of evidence.

Analysis of subgroups or subsets

1. High versus low risk of bias, , anticipating lower rates of allergic reactions among those with higher risk of bias.
2. Adjudicated versus non adjudicated anaphylaxis, anticipating higher rates of allergic reactions in non-adjudicated reports.

3. Precautionary measures such as a graded dose administration or premedication before immunization with antihistamines versus no such precautionary measures, hypothesizing that those with precautionary measures might report lower rates of allergic reactions
4. Risk of repeat anaphylaxis in persons experiencing anaphylaxis to a prior dose, hypothesizing that those with a previous history of anaphylaxis would have a higher risk of a anaphylaxis to repeat exposure.

Type and method of review

Meta-analysis, Systematic review

Anticipated or actual start date

20 August 2021

Anticipated completion date

30 September 2021

Funding sources/sponsors

None

Literature Selection and Search Strategy

Five reviewers will screen records independently and in duplicate using Covidence, for initial inclusion, full text inclusion, and final inclusion for data extraction. A total of two reviewers will be minimally required to render a decision for any abstract, and a threshold of 2 votes to include or exclude a particular abstract will be used. Conflicts will be resolved by direct discussion between the conflicting reviewers. Search terms were generated by DC previously per the first report. Inclusion criteria included human studies only, any study reporting re-administration of SARS-CoV-2 vaccines to persons who reported possible or probable allergic reactions (including anaphylaxis) related to a prior dose of SARS-CoV-2 vaccine. Exclusion criteria will be studies that did not address allergic outcomes. In cases of unclear reporting or data we will attempt to contact authors for clarification. Only published studies were used for this analysis.

Search Terms:

Incidence of repeat allergic reactions to SARS-CoV-2 vaccine upon re-vaccination

We searched the global coronavirus database: ((tw:(allerg*)) OR (tw:(anaphyl*))) AND (tw:(vaccin*))