Updated Guidance Regarding The Risk ofAllergic Reactions to COVID-19 Vaccines and Recommended Evaluation and Management: A GRADE Assessment, and International Consensus Approach

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Special Article: Updated Guidance Regarding The Risk of Allergic Reaction to COVID-19 Vaccines and Recommended Evaluation and Management: A GRADE Assessment, and International Consensus Approach

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Abbreviations: Coronavirus disease 2019(COVID-19), Vaccine Adverse Event Reaction System (VAERS), vaccine safety datalink (VSD) skin testing (ST), Grading of Recommendation, Assessment, Development, and Evaluation (GRADE), Research Electronic Data Capture (REDcap), National Institutes of Allergy and Infectious Diseases (NIAID), polyethylene glycol (PEG), polysorbate 80 (PS), Complement Activation-Related Pseudoallergy (CARPA), Immune Stress Response Reaction (ISRR), Canadian Society of Allergy and Clinical Immunology (CSACI), Credibility Interval (CrI), Confidence Interval (CI)

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Abstract: In mid-2021, a multi-disciplinary group of international experts developed 11 recommendations for 4 GRADE questions regarding immediate presumed allergic reactions following mRNA COVID-19 vaccines. Questions concerning diagnostic accuracy of vaccine/excipient skin testing to determine re-vaccination outcomes or risk of re-vaccinating individuals with 1st dose allergic reactions lacked evidence-based answers at the time , but can now be addressed, in an updated guidance with 7 GRADE questions and 8 recommendations. Following a 1st dose immediate allergic vaccine reaction, the overall risk of an immediate allergic reaction to the 2nd dose is 0.16% (95%CI 0.01% to 2.94%, moderate certainty evidence). In individuals with a severe 1st dose reaction (e.g., anaphylaxis), the risk for non-severe immediate allergic symptoms is 13.6% (95%CI 7.76%-22.9%, moderate certainty evidence), and the risk of repeat anaphylaxis is 4.94% (95%CI, 0.93%-22.28%, low certainty evidence). In evaluating 2nd dose reactions, skin testing sensitivity to either mRNA vaccine (BNT162b2 or mRNA-1273) was 0.2 (95%CrI 0.01-0.52) and specificity 0.97 (95%CrI 0.9-1). Polyethylene glycol (any molecular weight) test sensitivity was 0.02 (95%CrI 0.00-0.07) and specificity 0.99 (95%CrI 0.96-1). Polysorbate (any polyoxyethylene group number) test sensitivity was 0.03 (95%CrI 0.00-0.0.11) and specificity 0.97 (95%CrI 0.91-1). Combined for both either vaccine and either excipient, test sensitivity was 0.03 (95%CrI 0.00-0.08) and specificity was 0.98 (95%CrI 0.95-1.00, moderate certainty of evidence). We recommend re-vaccination after a 1st dose immediate allergic reaction over no re-vaccination for persons desiring additional vaccination. We recommend against greater than standard post-vaccination observation time (e.g., 15 minutes). We recommend against skin testing to the mRNA COVID-19 vaccine or vaccine excipients to assess the risk of a 2nd dose allergic reaction among persons with 1st dose reactions. We suggest persons with a history of an immediate allergic reaction to the mRNA vaccine or vaccine excipients be vaccinated under the supervision of an allergy specialist, or other person with expertise in managing vaccine allergy, in a properly equipped setting. Pre-medication, graded-dose challenges, or special precautions for persons with a comorbid allergic history are not suggested or required for initial or subsequent vaccination.

Introduction:

Through January 2023, the novel SARS-CoV-2 coronavirus and subsequent COVID-19 (Coronavirus disease 2019) global pandemic has caused over 671 million infections and 6.8 million fatalities.[1] Multiple efficacious COVID-19 vaccines have been available since December 2020.[2] The rare occurence of severe allergic reactions to these vaccines raised initial concern about the role of vaccine excipients polyethylene glycol (PEG) in the mRNA vaccines and polysorbate 80 (PS) in the viral vector vaccines.[3-7] In mid-2021, a meta-analysis and systematic review was performed, which formulated preliminary (given limited data) GRADE based consensus recommendations regarding presumed allergic reactions following the mRNA COVID-19 vaccines (BNT162b2 or mRNA-1273). This calculated the incidence of immediate (e.g., occurring within 4 hours of administration as per the 2007 Brighton Collaboration Criteria [BCC] definition), severe (e.g. anaphylaxis) 1st dose reactions to be 7.91 per million vaccinations, and the incidence of PEG allergy to be 0.15 cases per million person years in the United States and Canada, and found poor test sensitivity for using PEG as a testing reagent for suspected non-COVID-19 vaccine and medication allergy.[5] At the time, there were scant data to analyze the risk of severe 2nd dose allergic reactions when re-vaccinating individuals with 1st dose reactions, and the precision of vaccine or vaccine excipient skin testing to predict this risk.

Though immediate, severe COVID-19 vaccine allergic reactions occur rarely, many global health authorities have contraindicated vaccination in persons with a history of allergy to the vaccine or a vaccine excipient.[5] However, withholding doses based on allergic risk may not be necessary. Additional data have emerged since the June 2021 publication, and our experiences with COVID have shown that healthcare policies should change rapidly as the evidence evolves, and that the urgent recommendations made early in the pandemic can become outdated. This updated guidance specifically focuses on comprehensive recommendations for the approach to assessing a patient who has an immediate presumed allergic reaction to their 1st dose of a mRNA COVID-19 vaccine, in determining if a 2nd dose should be given, or for those concerned about risk of an immediate allergic reaction to a first vaccination, for those seeking vaccination. This document does not address non-immediate adverse reactions to vaccination.

Methods:
Following previously published methodology,[5] we reconvened an ad hoc international panel of clinical experts from Australia, Canada, Europe, Japan, South Africa, the UK, and the US to evaluate the current evidence regarding the risk and benefit of re-vaccination, and the utility of skin testing in persons with an immediate, presumed allergic reaction to mRNA COVID-19 vaccination from a societal perspective. While it is recognized that delayed, primarily cutaneous reactions (>4 hours post- mRNA COVID-19 vaccination) have been reported,[8] this document exclusively focuses on immediate (and potentially life-threatening) presumed allergic reactions to the vaccine and vaccine excipients, which have been specified as a reason for additional doses to be contraindicated.[9] The panel was chosen based on expertise in allergic reaction and anaphylaxis diagnosis, management, and policy; published expertise in COVID-19 vaccine allergy; as well as persons with expertise in advocacy, emergency medicine, infectious diseases, primary care, and public health to provide broad potential stakeholder impact of the evidence and recommendations. All members of the initial 2021 publication were invited as authors. While panel members with direct financial or industry conflicts of interests related to COVID-19 vaccine development or clinical trials were excluded, those with industry involvement in unrelated areas of allergy (e.g., asthma, allergic rhinitis, atopic dermatitis, etc.) were permitted to participate as long as their involvement was disclosed and specified. The development of this guidance did not include any industry input, funding, or financial or non-financial contribution. No member of the guidance panel received honoraria or remuneration for any role in the guidance development process.

Where possible, data to inform recommendations were taken from published focused systematic reviews and meta-analyses (through the fall of 2022), which were available for assessing a) the risk of severe allergic reactions to initial COVID-19 vaccine doses,[5] b) diagnostic accuracy of COVID-19 vaccine excipient testing in persons with suspected vaccine excipient allergy,[5] c) risk of a severe allergic reaction to administration of a 2nd dose of the vaccine in an individual with a prior history of a 1st dose immediate allergic reaction of any severity to the vaccine,[10] and d) the diagnostic accuracy of allergy testing to the vaccine and vaccine excipients prior to providing the 2nd dose of the vaccine in individuals with a 1st dose allergic reaction.[10,11] Reaction severity was defined at the individual study level, as indicated by the investigator in the included study, with non-severe allergic reactions defined as mild or self-limiting subjective or objective symptoms that either spontaneously resolved or resolved with anti-histamine treatment, and severe allergic reaction as either anaphylaxis (using BCC,[12] Ring and Messmer classification,[13] World Allergy Organization criteria,[7] or National Institutes of Allergy and Infectious Diseases criteria[14]) or a reaction requiring injectable epinephrine administration.[10,11] Additional published sources of data (original works and non-systematic reviews) were also considered. A primary draft, inclusive of 7 focused questions, was developed by the senior authors (MG, MS, EA, DG, DC) using the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) format for evidence synthesis from an individual perspective with secondary consideration for the healthcare perspective. GRADE methodology is explained in detail elsewhere.[15-18] This draft was circulated and revised iteratively by the workgroup, and a modified Delphi panel among the members was used to rate agreement and consensus with the final recommendations. A REDCap survey (Research Electronic Data Capture, Nashville, TN) was sent to the 94 voting panel members who were asked to rate their level of agreement with recommendations (1=strongly disagree, 2= disagree, 3=neutral, 4=agree, 5=strongly agree), using methodology and

threshold/consensus procedure as previously described.[5,19] One author (TD) participated only in the capacity as the Delphi methodologists and did not vote. We used the European Commission Guidance for Industry of Adverse Drug Reactions threshold for what was considered a rare event as between 1 case per 1,000-10,000 individuals, and very rare as < 1 case per 10,000 individuals.[20] Threshold for poor diagnostic test sensitivity or specificity was set at 0.5.[21]

The guideline statements and recommendations are presented in Table 1. The wording "we recommend" is used for strong recommendations and "we suggest" for conditional recommendations.[15] (Table E1) Though a conditional recommendation itself may direct the clinician toward a particular management pathway, the evidence-synthesis supporting the recommendation lacks a high certainty of evidence for a definitive course of action in all contexts. Instead, this indicates an area that is preference-sensitive, with the decision to follow the recommendation subject to shared decision-making and dependent on the pateint's values and preferences. The GRADE strength and certainty of evidence are summarized in Tables 2 and 3, and the risk of bias assessment in Table E2 (the risk of bias for any meta-analysis was included as it was originally published). Higher certainty of evidence implies that further research is unlikely to change the confidence in the estimated effect, whereas lower certainty of evidence implies further research would be more likely to change the confidence in the estimated effect. The final list of recommendations was developed by panel discussion and consensus. The Evidence to Decision Framework supplement provides a summary reflection of the evidence in the context of the clinical recommendation. The results of the modified Delphi panel for each recommendation are shown in the Table E3.

All questions addressed in this document are posed under the presumption that the patient is seeking either initial mRNA-COVID-19 vaccination or subsequent vaccination after having either an immediate presumed allergic reaction to their initial vaccination or a known allergy to one of the vaccine excipients, and that there is a medical professional willing to provide this vaccination depending on the strength and direction of the evidence.

Results:

Question 1: What is the risk of COVID-19 vaccine anaphylaxis in a patient with no history of anaphylaxis to a COVID-19 vaccine or its excipients?

Recommendation 1a: For patients with no history of a previous allergic reaction to a COVID-19 vaccine or its excipients, the risk of first-dose COVID-19 vaccine-induced anaphylaxis is exceptionally low, and we recommend vaccination over either no vaccination or vaccine deferral.
Strong Recommendation; High Certainty of Evidence

Recommendation 1b: For patients with a history of a severe allergic reaction, including anaphylaxis, unrelated to a mRNA COVID-19 vaccine or vaccine excipient, we suggest against additional post-vaccination observation beyond standard wait time (e.g., 15 minutes).
Conditional Recommendation; Low Certainty of Evidence

Question 2: In a patient without a history of anaphylaxis to a mRNA COVID-19 vaccine or its excipients, should allergy skin testing to mRNA COVID-19 vaccines or its excipients be performed prior to initial mRNA COVID-19 vaccination?

Recommendation 2: For patients with no history of a previous allergic reaction of any severity, including anaphylaxis, following a mRNA COVID-19 vaccine or related vaccine excipient, we recommend against vaccine or vaccine excipient testing prior to initial mRNA COVID-19 vaccination in an attempt to predict the rare individual who will have a severe allergic reaction to an initial vaccine dose.
Strong Recommendation; Low Certainty of Evidence

For patients who have never received a mRNA COVID-19 vaccine, the risk of a severe immediate allergic reaction to a mRNA COVID-19 vaccine is very low and no special precautions such as skin testing or prolonged wait times after vaccination are needed for patients, including those with other co-morbid allergic diseases, to prevent immediate allergic reactions.[5,10]

Evidence Summary: Questions 1 and 2, and recommendations 1a, 1b and 2 are similar as previously published in the 2021 guidance. A 2021 systematic review and meta-analysis searched the World Health Organization (WHO) Global Coronavirus database, the COVID vaccine RCT living evidence map, government websites, medical literature, and press releases for all estimates of anaphylaxis induced by COVID-19 vaccines up to March 19, 2021 to assess the risk of first dose severe allergic reactions (including anaphylaxis).[5] Using a random-effects model, this found a meta-analyzed incidence rate of 7.91 (95%CI 4.02-15.59) cases of adjudicated COVID-19 vaccine anaphylaxis per million (using the BCC), with no anaphylaxis-related fatalities, among 26 reports involving reported cases adjudicated to meet (original) BCC for anaphylaxis with a sample size of at least 20,000 doses.[5] (Figure 1) A meta-regression comparing adjudicated vs. non-adjudicated cases found higher odds of reported anaphylaxis in non-adjudicated reports (OR 5.53, 95%CI 4.01-7.61) as well as lower rates of anaphylaxis associated with vaccines using adenoviral-vector vaccines (OR 0.47, 95%CI 0.33-0.68) and

inactivated virus (OR 0.31, 95%CI 0.18-0.53) vs. mRNA vaccines, among 46 reports.[5] Table 2 details the certainty of evidence for this estimate, and Table E2 the risk of bias assessment.

PEG is the main excipient in the mRNA COVID-19 vaccines and has been suspected as a potential triggering agent for mRNA COVID-19 vaccine reactions.[3,4] In the BNT162b2 vaccine, this is present in a concentration of 0.05mg PEG2000 per dose, but PEG2000 content in the mRNA-1273 vaccine is not specified. In the aforementioned 2021 systematic review, the calculated incidence of PEG allergy was 0.15 cases per million person-years in the US and Canada, based on reporting to a Canadian national physician-reported drug allergy database entries from 2015-2018 and the FDA Adverse Event Reporting System (FAERS) database from 1989 through 2017.[5,22,23] For persons without prior suspicion of PEG allergy, no data are available regarding pre-emptive PEG skin testing prior to an initial PEG-containing mRNA vaccination to help predict the risk of allergic reactions mRNA vaccines. In the 2021 systematic review, the pooled sensitivity and specificity for the use of prick or intradermal PEG skin testing (any molecular weight, calculated in persons with suspected PEG allergy), as the next-best surrogate measure for predicting a reaction to an initial mRNA COVID-19 vaccine in patients without a history of mRNA COVID-19 vaccine allergy, were 0.59 (95%CI 0.44-0.72) and 0.99 (95%CI 0.98-0.99), respectively. Not all patients included in this meta-analysis who were tested to PEG for a suspected reaction underwent confirmatory oral PEG challenge, which further limits the precision of such testing.[5] While strong GRADE recommendations with low certainty of evidence are uncommon, the recommendation strength had a low certainty because it was downgraded due to risk of bias secondary to the lack of oral challenge gold standard and indirectness given studies involved PEG containing medications and vaccines, but not specifically COVID-19 vaccines because these were conducted prior to the pandemic. Table 3 details the certainty of evidence for this estimate and Table E2 the risk of bias assessment.

Persons with a personal history of allergic disease (e.g., asthma, food allergy, drug allergy, non-COVID vaccine or non-COVID vaccine-excipient allergy) are not at increased risk of having a severe allergic reaction, including anaphylaxis, to an initial dose of a mRNA COVID-19 vaccine.[5,8,9,24-27] These patients do not require any special precautions to receive these vaccines (e.g., vaccine or excipient skin testing prior to the dose, allergist supervision, or prolonged post-vaccination observation), and can be vaccinated in a routine setting (e.g. primary care office, vaccine center, public health center, pharmacy, etc).

Discussion: Compared to historical rates of vaccine-associated anaphylaxis (1.3-17 events per million doses), global adjudicated rates of mRNA COVID-19 vaccine anaphylaxis may be slightly higher than other agents but are still overall rare.[28-31] To date, no fatalities related to mRNA-COVID-19 vaccine anaphylaxis have been published in the medical liteature. With COVID-19 vaccination, the 2007 BCC vaccine anaphylaxis definition has led to higher estimates of anaphylaxis than when using the World Allergy Organization or the National Institutes of Allergy and Infectious Diseases anaphylaxis criteria.[32] The BCC have been updated in 2022 in light of these incongruences reported with the mRNA-COVID-19 vaccine anaphylaxis experience.[33] To date, while PEG has been speculated as the provoking excipient most likely responsible for mRNA COVID-19 vaccine allergic reactions (with potential that PS allergic individuals cross-react to PEG), this has not been proven, nor have mRNA COVID-19 vaccine reactions proven to be IgE mediated.[8,34,35] Given a very low baseline population prevalence of

PEG allergy, the very rare rate of first dose mRNA COVID-19 severe allergic reactions, poor sensitivity of PEG skin testing, and lack of evidence supporting mRNA-COVID-19 vaccine reactions as IgE mediated, no evidence supports a population screening approach to detect pre-existing specific-IgE against PEG or PS as a means to predict the risk of a severe allergic reaction to an initial dose of a mRNA COVID-19 vaccine.[5]

Threshold agreement was achieved for the voting on these 3 recommendations in the 1st round of voting, with 97% (recommendation 1a), 88% (recommendation 1b), and 96.7% (recommendation 2) agreement (with 2.2%, 5.4%, and 2.2% disagreement) among 92 voting authors (2 authors did not record a vote). (Table E2). Six authors communicated a preference for post-vaccination observation wait times ranging from 15-60 minutes as measures that were considered harmless, reassuring to nervous patients, and potentially able to capture more acute events. Such preferences are already reflected in the conditional, rather than strong, nature of recommendation 1b. Language suggesting that longer wait time could promote vaccine hesitancy was removed in the final iteration of the recommendation. Further explanation of the dissonance between the strength of recommendation 2 and its certainty of the evidence was added to the discussion section.

Question 3*:* Can additional supervised doses of mRNA COVID-19 vaccines be administered to a patient who had an immediate allergic reaction (defined as occurring within 4 hours of vaccine administration) of any severity following the 1st dose of the vaccine?

<u>Recommendation 3:</u> We recommend that individuals who had an immediate allergic reaction of any severity to the 1st dose mRNA COVID-19 vaccine can receive additional mRNA COVID-19 vaccine doses, and those who have a history of an allergic reaction of any severity to one of the vaccine excipients can receive either their initial or additional mRNA COVID-19 vaccine doses.
Strong Recommendation; Moderate Certainty of Evidence

For patients with a history of a previous immediate allergic reaction to a mRNA COVID-19 vaccine or vaccine excipient of any severity, the risk of either a severe immediate reaction or repeat severe immediate allergic reaction to a mRNA COVID-19 vaccine is very low.[5,10]

Evidence Summary: A published systematic review and meta-analysis using a pooled random-effects model showed that from among 22 reports of 1366 individuals with an immediate allergic reaction of any severity to a first mRNA COVID-19 vaccine, the absolute risk of a 2nd dose severe reaction to the same mRNA COVID-19 vaccine is 0.16% (95%CI 0.01%-2.94%, 6 reactions in 1366 patients, moderate certainty evidence), and the risk of any non-severe immediate allergic symptoms is 13.65% (95%CI 7.76%-22.9%, 232 reactions in 1337 patients, moderate certainty evidence). [34,36-56] In individuals with a severe immediate allergic reaction to a first mRNA COVID-19 vaccine, the risk of any non-severe immediate allergic symptoms is 9.54% (95%CI, 2.18%-33.34%, 15 reactions in 78 patients, low certainty evidence), and the

absolute risk of a repeat severe reaction with a 2nd dose of the same vaccine is 4.94% (95%CI, 0.93%-22.28%, 4 reactions in 78 patients, low certainty evidence). (Figure 2a-c) There were no fatalities related to allergic reactions from mRNA COVID-19 re-vaccination.[10] Several case series have demonstrated that children allergic to PEGylated medication (specifically PEG-aspargase) tolerate their initial dose of mRNA COVID-19 vaccination.[57-60] More robust experience in administering the initial mRNA COVID-19 vaccine to individuals with known or suspected PEG allergy is needed; published evidence to date has shown no vaccine reactions in these cases.[60,61] In these included studies, all re-vaccination occurred under the supervision of an allergy specialist, in a setting equipped to treat anaphylaxis. Table 2 details the certainty of evidence for this estimate, and Table E2 the risk of bias assessment. Figure E1 helps provide a practical translation for the testing precision.

Discussion: While allergy specialist guidance for non-COVID-19 vaccines recommend against withholding vaccination for vaccine or excipient allergic individuals, COVID-19 vaccine guidance has followed some general public health authority recommendations to not vaccinate such individuals.[9,25-27] While this potentially limited the available evidence base for the meta-analysis of 2nd dose reactions, there were still 22 studies of 1366 particpants included in the meta-analysis, which found a 0.16% rate of repeat severe reactions.[10]

Severe allergic reactions occur very rarely with either initial or subsequent doses of mRNA COVID-19 vaccination.[5,10] This very low rate of reaction should not preclude re-vaccinating someone with an mRNA COVID-19 vaccine who reacted to their initial dose (or administering the initial vaccine for someone with an allergy to one of the vaccine excipients), within the context of a shared decision-making approach of considering an alternative vaccine platform or deferring additional doses. There are data from small case series of persons with known PEG allergy who have been administered and tolerated initial doses of mRNA COVID-19 vaccines, and it has been demonstrated that mRNA COVID-19 vaccine reactions are unlikely to result from IgE mediated reactions to PEG.[57-62]

The very low rate of repeat immediate severe allergic reactions upon re-vaccination may be explainable by two hypotheses. First, there is evidence that reactions may be mediated through an anti-PEG IgG mechanism [eg. Complement Activation-Related Pseudoallergy (CARPA)]. Second, the phenomenon of Immune Stress Response Reaction (ISRR), a benign phenomenon mimicking an allergic reaction, which can manifest as anxiety or stress-induced symptoms (e.g. flushing, urticaria, dyspnea), vasovagal reactions, or dissociative neurologic symptoms, has been identified as a common cause of adverse reactions after COVID-19 vaccination (Table E3)[35,63] Given no data that PEG anti-IgE is mediating mRNA vaccine reactions, both of the above are plausible hypotheses which likely indicate there is a low probability that mRNA vaccine allergic reactions are IgE mediated, explaining their lack of repoducibility.[8,10,11,34]

In formulating this recommendation, we weighed the potential benefits and harms of vaccination, an allergic reaction, and disease exposure against each other, along with consideration of patient values, preferences, and cost. A shared decision-making approach may be considered for individual contexts and circumstances, though the evidence supports a strong recommendation that the vaccine should not be withheld in such individuals who are desiring vaccination. Some patients may wish to change to a different brand of mRNA vaccine than the one they initially

reacted to, which, while not explicitly studied, is not felt to represent any additional risk, and this is a preference-sensitive option to explore. Recommendations 4 and 5 provide further explanation and context regarding further risk assessment and supervision for repeat vaccination after an initial reaction (or initial vaccination in the excipient allergic).

Threshold agreement was achieved for the voting on this recommendation in the 1st round of voting, with 85.9% agreement (6.5% disagreement) among 92 voting authors (2 authors did not record a vote). (Table E3) There were 11 authors suggesting that the recommendation have added context regarding the assessment and supervision of such pateints, which is more specifically addressed in recommendations 4 and 5. Five authors suggested language stratifying the handling of persons with severe reactions from non-severe reactions. The recommendation was slightly reworded to better clarify those with reactions to their initial vaccine from those with allergy to the vaccine excipient who may be receiving their initial vaccine dose. The word "severe" was removed prior to "history of allergic reactions" from the initial wording. Language was added better specifying the population as "desiring additional vaccination" after two authors mentioned consideration for a shifting landscape of additional vaccination efficacy against newer variants and lower consquences of natural disease after having received at least one dose of vaccine in terms of risk to benefit of additional doses after an allergic reaction.

Question 4: **In a patient with a history of an immediate allergic reaction of any severity to a previous mRNA COVID-19 vaccine or its excipients, should allergy skin testing to mRNA COVID-19 vaccines or their excipients be performed to determine if a future dose of vaccine should be withheld?**

<u>Recommendation 4:</u> For individuals with a history of an immediate allergic reaction to a mRNA COVID-19 vaccine or its excipients, we recommend against performing skin testing using any mRNA-COVID-19 vaccine or its excipients for the purpose of risk assessment to determine if they should receive a vaccine dose. Strong recommendation; Moderate Certainty of Evidence

mRNA COVID-19 vaccine and vaccine excipient allergy testing has poor sensitivity though high specificity in predicting repeat immediate allergic reactions of any severity to mRNA-COVID-19 vaccination in persons with a history of an immediate allergic reaction to the vaccine or vaccine excipient.[11]

Evidence Summary: A systematic review and meta-analysis detailed 20 studies among 317 individuals with 1st dose immediate allergic reactions to the vaccine who underwent 578 skin tests to any one or combination of either mRNA COVID-19 vaccine, PEG, and PS, for risk stratification assessment prior to receiving a 2nd vaccine dose, and were then re-vaccinated with the same vaccine provoking the initial reaction.[11,34,36-38,40-44,47,49,50,53,55,56,61,64-67] Test sensitivity for either mRNA vaccine was 0.2 (95%CrI 0.01-0.52) and specificity 0.97 (95%CrI 0.9-1). PEG test sensitivity was 0.02 (95%CrI 0.00-0.07) and specificity 0.99 (95%CrI 0.96-1). PS test sensitivity was 0.03 (95%CrI 0.00-0.0.11) and specificity 0.97 (95%CrI 0.91-1).[11] Combined for use of any of the 3 testing agents, sensitivity was 0.03 (95%CrI 0.00-0.08) and specificity was 0.98 (95%CrI 0.95-1.00) (Figures 3 and 4). Multiple sensitivity analyses accounting for studies that permitted use of graded dosing (n=9 studies), premedication (n=8 studies), or patients with

1st dose anaphylaxis (n=17 studies) did not alter the main findings though sensitivity was increased for specific sensitivity analyses for use of the individual vaccines in predicting severe second dose reactions (6 total severe second dose reactions occurred, 4 in persons with no detectable sensitization). Sensitivity analysis was also performed to account for persons with 1st dose reactions who deferred evaluation or a 2nd dose in the studies. This presumed that 25% or 50% of the total number of patients deferring evaluation or a 2nd dose across all studies underwent full evaluation and were considered as true positive cases, which improved sensitivity to 0.22 (any test), 0.32 (PEG), and 0.48 (any vaccine).[11] One study included in the meta-analysis noted that use of Refresh Tears for PS testing led to an irritant response, resulting in false positive responses in 12/25 non-allergic control subjects tested.[40] Table 3 details the certainty of evidence for this estimate, and Table E2 the risk of bias assessment.

Discussion: Vaccine excipient allergy is a very rare but acknowledged possible cause of allergic reactions to vaccines.[24,28] mRNA COVID-19 vaccines contain PEG 2000 as their major excipient, in addition to lipids and cholesterol, which is different than traditional vaccines that use food derivatives, preservatives, and antibiotics.[7,24,28] Despite no definitive evidence that PEG 2000 is a provoking allergen in mRNA COVID-19 vaccine reactions or that such reactions involve anti-PEG IgE,[8,24] the vaccine remains largely contraindicated by health authorities in persons with known or suspected PEG allergy.[9,26,27] The baseline incidence of PEG allergy is very low within the US and Canada and PEG skin testing in non-COVID-19 vaccine settings has low sensitivity.[5] Some groups advocate use of a specific PEG testing algorithm, which includes testing to very high MW PEG.[68] Skin testing to both PEG (as well as PS, considered potentially cross-reactive with PEG) and the mRNA vaccine was initially proposed to assess vaccine-related immediate allergic reactions, following recommendations in the most recent vaccine allergy practice parameters.[4] In the context of persons with 1st dose mRNA COVID-19 reactions, the meta-analysis found very poor sensitivity for skin testing to either the vaccine, PEG, or PS in predicting repeat immediate allergic reactions of any severity, and concluded that skin testing had limited utility for this purpose.[11] The very low rate of repeat immediate severe allergic reactions upon re-vaccination (0.16%), poor test sensitivity with the mRNA vaccine or vaccine excipient testing (0.03), and speculation that reactions may be mediated through an anti-PEG IgG mechanism [eg. Complement Activation-Related Pseudoallergy (CARPA)] or represent ISRR, indicate a low probability that mRNA vaccine allergic reactions are IgE mediated.[8,10,11,34] Moreover, in the setting of such low test sensitivity and without evidence that these reactions are IgE mediated, the high specificity of vaccine or vaccine excipient testing does not infer a high accuracy in identifying persons who are not allergic to the vaccine or excipient, and this more likely indicates testing with non-relevant components which also are not irritant.[11] Therefore, we recommend against skin testing to PEG, PS or to the mRNA COVID-19 vaccine itself as a means to predict risk of a severe allergic reaction to a COVID-19 vaccine.[11] This approach is independent of the incidental finding in the setting of evaluating a mRNA COVID-19 vaccine reaction that a patient history indicates a strong likelihood of prior PEG allergy. In that context, the clinician may wish to consider PEG testing or PEG oral challenge as part of the workup to confirm PEG allergy for other decision-making purposes, apart from the mRNA COVID-19 vaccine-related issue.[23,69,70] One paper suggests that there is differing allergenicity between PEGylated liposomes (e.g. the PEG content in vaccines) and unmodified PEG polymer (e.g. PEG in medications).[71]

Threshold agreement was achieved for the voting on this recommendation on the 1st round of voting, with 83.7% agreement (8.7% disagreement) amond 92 voting authors (2 authors did not record a vote). (Table E2) There were 10 authors who disagreed with the recommendation and findings of the supporting published meta-analysis, who felt that skin testing still may have some utility in particular shared decision-making contexts with certain patients. One author voiced concern that the meta-analysis conclusion was potentially biased based on lack of randomized controlled trials of skin testing, and that the included studies were case series of varying size and conduct, which are of much lower quality. One author commented that the skin testing sensitivity did increase in the sensitivity analysis, and that these may have more utility than perceived. One author also commented that the recommendation against skin testing contradicted the general approach outlined in the 2012 Allergy Joint Task Force Vaccine Allergy practice parameter, despite the findings of the meta-analysis; however, the 2012 practice parameter does not recommended skin testing for the purpose of vaccine deferral. Three authors offered suggestion of additional references regarding excipient skin testing, some of which were added. One author questioned if sensitivity and specificity for the testing could be truly defined if there is no proven IgE-mediated mechanism of reaction.

Question 5: In a patient with a history of an immediate allergic reaction of any severity to a previous mRNA COVID-19 vaccine or its excipients, what is the most appropriate setting for these individuals to receive their vaccination?

<u>Recommendation 5:</u> We recommend referral to an allergist (or other clinician with expertise in the management of vaccine allergy and allergic reactions) for assessment and supervised vaccination of such individuals for their initial dose, or for the subsequent dose after a reaction to a prior dose.

Strong Recommendation, Moderate Certainty Evidence

Patients with a history of an allergic reaction of any severity to an mRNA-COVID-19 vaccine or vaccine excipient should receive either their initial mRNA COVID-19 vaccine dose (excipient allergy) or the dose immediately following a suspected reaction (mRNA-COVID-19 vaccine allergy) under the supervision of an allergy specialist, or other person with expertise in managing severe allergic reactions, including anaphylaxis.

Evidence Summary: The meta-analyzed data demonstrating both the low risk of repeat severe reactions and the poor utility in skin testing to vaccine and vaccine excipients to predict the risk of a recurrent reaction were all from studies performed under allergist guidance.[10,11] Similarly, studies of PEG or PS allergic individuals who were vaccinated to mRNA COVID-19 vaccines were also performed under allergist guidance.

Discussion: The panel recognizes vaccination or re-vaccination of patients with a history of an allergic reaction to the vaccine or to the vaccine excipients most likely lies outside the expertise of most general vaccine clinics.[5] Furthermore, because health authority policy has generally recommended against vaccinating such individuals, most general vaccination settings have had limited experience in managing patients with these risks.[5] The panel recognizes that it may be difficult for non-hospital based allergy practices to have access to mRNA COVID-19 vaccine,

given supply issues and storage requirements, complicating matters for patients seeking vaccination. Despite a very low risk of reaction, these patients should ideally be vaccinated under the supervision of a clinician (ideally a physician specialist) trained in recognizing and managing anaphylaxis, in a setting equipped to manage such reactions, and not in a general, non-medical setting (e.g. a pharmacy). Difficulty in specialists in the non-hospital setting being able to obtain vaccine for such administration could hinder this recommendation. Skin testing to vaccine or vaccine excipient is also not recommended as a means of risk assessment for either an initial or a repeat reaction. Once the initial vaccination in the excipient allergic individual, or the 2nd dose in person with suspected immediate allergic reaction to their 1st mRNA COVID-19 vaccine dose is tolerated, additional doses can be done in standard fashion (e.g., without allergy specialist supervision), similar to recommendations for patients who have no prior history of mRNA COVID-19 vaccine or excipient allergy.[28] Withholding vaccination is unnecessary based on these data.[10] However, many decisions may still be preference-sensitive, and this guidance relies on the willingness of those within the field to implement the recommendations (e.g., allergists, vaccinators, and referring clinicians), and the affected patients to seek care.[5] We caution that this recommendation is formulated within the first 2 years of the experience with mRNA COVID-19 vaccine reactions, and future published evidence may evolve.

Threshold agreement was achieved for the voting on this recommendation on the 1st round of voting with 94.6% agreement (3.3% disagreement) among 92 voting authors (2 authors did not record a vote). (Table E3). There was concern raised by 7 authors in specifically recommending that the clinician to whom such indivuduals are referred needs to be an allergy specialist, as opposed to any clinician with expertise in the diagnosis and management of severe allergic reactions (including anaphylaxis). It was voiced by several authors that access to an allergy specialist in some parts of the world is not always practical or feasible. Wording in this section and in the recommendations was changed in response. Six authors suggested that only persons with severe immediate allergic reactions (including anaphylaxis) required supervision by an allergist or other physician with training and experience in managing severe allergic reactions, whereas persons with non-severe immediate initial reactions could be supervised by any physician (e.g. a generalist). Several authors commented regarding both ongoing difficulties in obtaining vaccine for ambulatory offices that are not part of a large academic medical center and that many patients may want to be vaccinated in retail pharmacy settings; and one author voiced concern that allergy specialists in smaller private practices may be more reluctant to follow these recommendations.

Question 6: Should a patient with a history of an immediate allergic reaction to the vaccine or vaccine excipient be pre-medicated prior to receiving their vaccine to prevent a severe allergic reaction?

<u>Recommendation 6:</u> We suggest against routine H1-antihistamine or systemic corticosteroid pre-medication prior to vaccination to prevent anaphylaxis. Conditional Recommendation, low certainty of evidence

Question 7: Should a patient with a history of an immediate allergic reaction to the vaccine or vaccine excipient receive their vaccine as a graded dose rather than a single dose?

<u>Recommendation 7:</u> We suggest against graded dosing or stepwise desensitization compared to a single dose.
Conditional Recommendation, low certainty of evidence

Neither pre-medication with anti-histamine or steroid, nor graded (e.g., split) dosing is recommended or required for persons with a history of an immediate allergic reaction to the vaccine or vaccine excipient prior to receiving any dose of their mRNA-COVID-19 vaccine series.

Evidence Summary: These recommendations are similar to previously published guidance, but updated with additional evidence from meta-analysis of second dose reactions and skin testing to predict second dose reactions.[5,10,11] There is no evidence demonstrating benefit or necessity for either premedication or graded dosing. In both meta-analyses of the risk of 2nd dose reactions, when stratifying by studies that permitted pre-medication vs. not, or graded dose challenges vs. single dose, there was no difference in outcomes seen.[10,11] However, none of the included studies were specifically designed or powered to assess these questions. It is not advised that persons who take daily or frequent antihistamines or glucocorticoseroids for the management of other conditions should discontinue taking these on the day of receiving their mRNA COVID-19 vaccine. Rather, this recommends against specific use (or requirement) of pre-medication for the purposes of reducing the occurrence or severity of a vaccine-associated allergic reaction. A possible exception to this may be in the case of a patient with systemic mastocytosis receiving mRNA COVID-19 vaccination. The European Competence Network on Mastocytosis has recommended antihistamine pre-medication as a general consensus best practice for persons with mastocytosis considered at high risk for anaphylaxis, though this group acknowledged no data to support that antihistamine premediction provides protection against vaccine reactions in this population, and that systemic mastocytosis patients have been reported to have no increased risk for a mRNA COVID-19 vaccine reaction.[72] While a shared decision-making approach can be considered for those who may otherwise be hesitant to receive initial or subsequent mRNA COVID-19 vaccination without premedication or graded dosing (or who have systemic mastocytosis and are considered at high general risk for anaphylaxis), neither are necessary nor required for safe vaccination in the patient with mRNA COVID-19 excipient allergy or a history of a reaction to a prior vaccine dose.

Discussion: While graded dosing (or stepwise desensitization) and pre-medication with either antihistamine or glucocorticosteroids are considered safe approaches, neither are required nor have been proven necessary compared to no pre-medication and/or administering a single vaccine dose in persons with a history of reaction to the vaccine or vaccine excipient.[28] At best this remains a highly conservative option, which is consistent with past vaccine allergy practice parameters and both may be strongly preferred steps by some patients and administering clinicians.[5] A 2-step graded challenge (and in older practice parameters, multi-step desensitization) in individuals with previous immediate allergic reactions to the vaccine has been the customary management step for non-COVID-19 vaccine allergy, despite a lack of research establishing that this provides a definitive safety benefit, or is necessary (as opposed to an accommodation that makes either the patient or clinician more comfortable).[28] While no RCT comparing single vs. 2-step graded challenges for mRNA COVID-19 vaccination has been performed, one was performed for influenza vaccine that showed no difference in outcome between the approaches.[65,73] It is reasonable to expect that this finding would generalize to other vaccines. There is no evidence to suggest that split dosing results in a different immune response than a single dose.[65] Similarly, many allergists have considered antihistamine (with or without glucocorticosteroid) pre-medication for such patients, as is customary in allergen immunotherapy patients experiencing frequent local or even prior systemic reactions, but again this has been previously recommended in the absence of evidence that it results in a safety benefit or is necessary.[74] The 2020 Anaphylaxis GRADE guideline from the Joint Task Force of Allergy Practice Parameters has noted limited value and potential harm for use of glucocorticoid premedication in the context of anaphylaxis prevention in most, but not all, settings. [75] With mRNA COVID-19 vaccination, there is an additional concern that glucocorticosteroid premedication could potentially inhibit immune response to the vaccine.[5] Previous COVID-19 vaccination recommendations lacked data regarding re-vaccination outcomes and relied heavily upon expert opinon to create a bridge policy to help patients. The approach was also contextual, to maximize the number of feasible and mutually acceptable approaches (to patient and clinician) in order to enable vaccination while evidence evolved. [5] More data (from 2 large meta-analyses of 2nd dose reactions) are now available to supplement this evidence base.[10,11] The panel recognizes there is an important role for shared decision-making in discussing risk and benefits of vaccination, and a more conservative versus more aggressive approach to re-vaccination, particularly in someone with prior severe anaphylaxis to an initial mRNA-COVID-19 vaccination (or prior ISRR with COVID vaccination), who may be reluctant to be re-vaccinated. Consultation with a clinician trained in the management of adverse reactions to vaccines, such as a board certified allergist, can be of considerable benefit in helping to assess and manage such patients. This clinician's highest value can be in helping determine the likelihood that a prior reaction was allergic versus some other mechanism of an adverse reaction, including to be able to differentiate between anaphylaxis or truly immune-mediated reaction and an ISRR,[35,63] and to help reduce anxiety levels among patients and staff regarding possible vaccine-related allergic reactions.

Threshold agreement was achieved for the voting on these recommendations on the 1st round of voting, with 81.7% (recommendation 6) and 84.9% (recommendation 7) agreement (6.5% disagreement with each) among 93 voting authors (1 author did not record a vote) (Table E3). There were 13 authors who voiced concern that there was relatively low harm and likely potential benefit in using anti-histamine pre-treatment, and felt that such pre-treatment could be

advisable and reassuring for certain patients under a shared decision-making context, including one author highlighting these as particulary important to reassure patients who may have had 1st dose anaphylaxis. Eleven authors felt that there was a role for graded-dosing, which could be advisable and reassuring for certain patients under a shared decision-making context. One author also commented that the conditional recommendation against graded dosing contradicted the approach outlined in the 2012 Allergy Joint Task Force Vaccine Allergy practice parameter. One author disagreed with both recommendations on the basis that no studies have been specifically designed to show that pre-treatment or graded dosing are unnecessary from a safety perspective. However, while additional points of discussion were added, no changes to the recommendations were made given these preferences are reflected in the conditional, rather than strong, nature of recommendation.

Special Circumstances

Are patients with allergic co-morbidities more likely to have mRNA COVID-19 Vaccine Reactions?

For persons with co-morbid allergic disease (including mast cell disorders or prior anaphylaxis to any food, medication, or vaccine) apart from a PEG/PS or prior mRNA COVID-19 vaccine reaction, we suggest against special precautions for mRNA COVID-19 vaccination, including needing specialist supervision.[72] Evidence is lacking to confirm such individuals are at elevated risk for a severe COVID-19 vaccine reaction compared to the general population. Multiple studies have observed that a high percentage of reported/self-reported allergic reactions to the mRNA COVID-19 vaccines occur in females and/or persons reporting a history of one or more allergic conditions, including both food and medication/vaccine reactions.[39,76-80] These have included data from passive reporting systems (e.g., the Vaccine Adverse Event Reaction System [VAERS], vaccine safety datalink [VSD]) that captured only data on persons with reported reactions (and no comparative data regarding rates of similar allergic co-morbidity among persons tolerating vaccination), and two observational cohorts from large healthcare systems where significantly higher rates of these underlying allergic conditions were seen among those reacting to vaccine vs. non-reactors.[52,76-78,80-82] However across all such reports, the overall rate of initial or second dose reactions is still very low. No published studies have been powered or designed to prospectively evaluate if allergic co-morbidity is a risk factor, though a National Institutes of Allergy and Infectious Diseases (NIAID) sponsored multi-centered randomized placebo parellel assignment trial that has now completed could provide additional data regarding such potetial risk factors. (www.clinicaltrials.gov, NCT04761822). Retrospective and observational data suggest that women and those with past allergic history in particular may be at risk for reactions to the first and subsequent doses of COVID-19 vaccines.[79-81] Allergic conditions are common in the general population, and self-reported allergy occurs at higher rates than may actually be confirmed by a specialist. Given both a high rate of allergic co-morbidity and a very low overall rate of immediate allergic reactions to these vaccines in the general population, it is very likely that the overwhelming majority of individuals with underlying allergic co-morbidities have tolerated mRNA COVID-19 vaccines without issue.[5] Therefore, co-morbid allergic history is likely a negligible risk, pending systematic evidence synthesis to evaluate whether these individuals have a greater reaction risk than the general population, and such patients do not require any special precautions. These patients can be vaccinated in primary care offices, pharmacies, community vaccination clinics, and other venues where vaccinations are provided.

How Should Patients with a History of an Allergic Reaction to a mRNA-COVID-19 Vaccine or Vaccine Excipient be Managed in Resource Limited Settings Where Allergy Consultation Is Not Available?

In resource limited settings where allergy specialist referral is not readily available, alternative care models may be presented in a shared decision-making context to patients with a history of mRNA COVID-19 vaccine or excipient allergy in order to provide assessment and opportunity for vaccination by remote consultation, use of alternative vaccine products, or vaccination in any setting where patients can be monitored and treated for anaphylaxis to help avoid delay in vaccination.

How Should Concerns About the Bivalent mRNA COVID-19 Vaccine, or Initial Reactions Occuring on Booster Doses be Managed?

It is possible that someone may initially tolerate their first mRNA COVID-19 vaccine dose or doses and react to a subsequent dose. While first dose reactions and repeat reactions to a second dose are the scenarios which have been robustly studied, the panel recommends no change in the approach outlined herein when dealing with reactions with other doses (e.g., non-first dose reactions). Thus, these scenarios and rates of reaction detailed herein would apply to the risk of reaction to any next dose if there is no history of reaction to any prior dose, and the risk of reaction to a subsequent dose if there is a reaction to the prior dose (e.g., the risk is likely similar for dose 3 if dose 1 and 2 were tolerated as it would be for receiving dose 1; and the risk is also approximate for dose 2 after reacting to dose 1 as it would be for dose 3 if the reaction was to dose 2 and the patient tolerated dose 1). In the fall of 2022, bivalent mRNA COVID-19 vaccines became available, which are more specifically tailored towards Omicron strain variants. Like seasonal influenza vaccines, which have a common base but use different virion particles to match circulating strains, these are not considered distinct vaccines for allergenicity purposes, and the approach for receiving a bivalent dose would not vary from non-bivalent doses.

Limitations

This document has several limitations. First, this guidance is limited to immediate allergic reactions occurring within the first four hours of mRNA COVID-19 vaccination. There are a several delayed-onset symptoms that have been reported post-mRNA COVID-19 vaccination, including "Moderna Arm", and unmasking or worsening of chronic urticaria.[83-86] These have been excluded from analysis and discussion in this guidance, as they fall outside the scope of the immediate post-vaccination period. Second, experience with vaccination/re-vaccination in persons with excipient allergy or a 1st dose reaction is limited, as is experience in skin testing to the vaccine and vaccine excipients. The skin testing meta-analysis included only 317 patients, and there was heterogeneity in the methods that the groups used in testing to the vaccine and excipients, both of which could have influenced the low pooled test sensitivity estimates. Both of the published systematic reviews and meta-analyses are planned as living systematic reviews, and will be updated as additional data emerge. Third, these recommendations remain limited to the populations that have been studied. It is likely that some patients with first dose reactions opted to not receive a second dose, or were not studied, and there could be differences between the groups that pursued second dose vaccination and those who did not. The data from which the recommendations were formulated have come largely from US studies, performed under allergist

supervision, and we acknowledge an information gap in managing these issues in low to middle income or resource-limited areas. The studies included in the meta-analyses are largely from tertiary care centers, and some were rated high risk of bias.[5,10,11] It is possible that recommendations may be made by an allergy specialist to direct another care provider who is actually administering the vaccine, which may not be acceptable to the vaccinating clinician with either less experience in treating anaphylaxis or vaccinating someone with a prior vaccine-associated presumed allergic reaction. These factors may therefore result in modification to the stated recommendations in clinical practice. As such, this document provides evidence-based recommendations to the clinician, who will ultimately make their own decision on how to proceed with such patients. The Evidence to Decision Framework supplement provides a summary reflection of the evidence in the context of the clinical recommendation and helps balance the recommendations in light of these limitations and contexts where the options are highly preference-sensitive. Fourth, we re-emphasize some recommendations are not intended to be carried out in ***routine medical settings (e.g., non-allergy specialist setting such as a pharmacy or community vaccination center).*** The approaches outlined for individuals with prior vaccine or vaccine excipient reactions are intended to be performed in facilities staffed with personnel skilled and trained to be able to assess and treat an allergic reaction (e.g., epinephrine is available and staff are trained to use this), and where it is possible to provide direct post-vaccination observation of patients for 15 minutes. Fifth, data on mRNA and non-mRNA COVID-19 vaccination continue to evolve, at times rapidly. We realize that there still are remaining questions and unmet needs that could not be answered in this document or at this time. These are summarized in table 4. Lastly, this document follows the Institute of Medicine standards for trustworthy clinical practice guidelines[87] (Table E4) with the exception of patient stakeholder and public involvement, given this was not an officially sponsored professional society document or practice parameter, but rather a broad medical expert consensus statement regarding an evidenced-based practice. The document was created by clinicians who have incorporated their experiences in managing such patients, which was felt to reflect the input and preferences of those patients.

The recommendations contained herein are based on high-quality evidence where possible, including several meta-analyses, and where this is not possible, are based on expert opinion achieved through a large consensus of international experts. All recommendations must always be considered and adapted within the context of patient care, which can be very individualized based on particular circumstances. Both the patient and the vaccinating clinician may have preferences for a particular vaccination related practice or a precaution that, in the course of this evidenced review, may have a recommendation or suggestion against doing so. Practice variation at the clinician level in allergy is common and part of the fabric of the specialty, in particular when such variation is applied in the context of the needs of an individual patient and situation. This differs, however, from the evidence-based conclusions of a GRADE guidance document aimed to apply across a specialty or several specialties at a level to broadly inform policy, formulated from multiple meta-analyses on the subject, and further solidified through using a modified Delphi panel. Therefore, while the panel feels that the recommendations or suggestions in this guidance are based on the most up-to-date and comprehensive evidence synthesis, there may be individual situations or patients where, under a shared decision-making paradigm, and based on mutual preference after explaining the evidence and the risks and

benefits of potential deviation from the recommended approach, the clinician may choose an alternative practice than outlined in this guidance.

Conclusion

There is very rare occurrence of allergic reactions, including anaphylaxis, to both 1st and 2nd doses of the vaccine. The vaccine should not be withheld in persons with a history of an allergic reaction (of any severity) to the vaccine or the vaccine excipient. Testing to the vaccine or vaccine excipient does not appear to assist in clinical decision making due to poor test accuracy, and is not recommended. There is no clear evidence that these vaccine reactions occur through IgE mediated pathways. This document provides an updated evidence-based expert international consensus stressing a patient-centered approach involving consideration of the risks and benefits of receiving mRNA COVID-19 vaccination, applicable to initial doses and any subsequent booster doses. This will continue to be a living document that will require periodic updating due to still emerging needs assessment, including further research data on the nature of vaccine-associated reactions and the necessity of potential risk-assessment measures.

Figures and Legends

Figure 1: Incidence of Adjudicated Anaphylaxis Reported in Association with COVID-19 Vaccination

Legend: Internationally reported adjudicated rates of anaphylaxis to initial doses of mRNA COVID-19 vaccines

Figure 2: Pooled incidence of immediate allergic reactions of any severity to a 2nd mRNA COVID-19 vaccine dose among persons who had an immediate allergic reaction to their 1st mRNA COVID-19 vaccine dose.

Legend: Pooled incidence for (A) severe 2nd dose reactions; (B) non-severe 2nd dose reactions; and (C) repeat severe reactions

Figure 3: Sensitivity and Specificity of mRNA COVID-19 Vaccine or Vaccine Excipient Skin Testing to Evaluate the Risk of a Second Dose Reaction

Legend: Forrest plot of the sensitivity and specificity for (A) the combined analysis of skin testing to polyethylene glycol, polysorbate, or either mRNA COVID-19 vaccine; (B) skin testing to either mRNA COVID-19 vaccine

Figure 4: Sensitivity and Specificity of mRNA COVID-19 Vaccine Excipient Skin Testing to Evaluate the Risk of a Second Dose Reaction

Legend: Forrest plot of the sensitivity and specificity for the (A) polyethylene glycol or (B) polysorbate in predicting the risk of a 2nd dose immediate allergic reaction to a mRNA COVID-19 vaccine

References

1. Johns Hopkins University Coronavirus Resource Center Accessed October 28, 2022 Available from: https://coronavirusjhuedu/maphtml
2. https://extranet.who.int/pqweb/sites/default/files/documents/Status_COVID_VAX_02April2022.pdf. Accessed April 13, 2022.
3. Banerji A, Wolfson AR, Wickner PG, et al. COVID-19 Vaccination in Patients with Reported Allergic Reactions: Updated Evidence and Suggested Approach. J Allergy Clin Immunol Pract 2021;9(6):2135-2138. DOI: 10.1016/j.jaip.2021.03.053.
4. Banerji A, Wickner PG, Saff R, et al. mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current Evidence and Suggested Approach. J Allergy Clin Immunol Pract 2021;9(4):1423-1437. DOI: 10.1016/j.jaip.2020.12.047.
5. Greenhawt M, Abrams EM, Shaker 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;9(10):3546-3567. DOI: 10.1016/j.jaip.2021.06.006.
6. Klimek L, Jutel M, Akdis CA, et al. ARIA-EAACI statement on severe allergic reactions to COVID-19 vaccines - An EAACI-ARIA Position Paper. Allergy 2021;76(6):1624-1628. DOI: 10.1111/all.14726.
7. Cardona V, Ansotegui IJ, Ebisawa M, et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J 2020;13(10):100472. DOI: 10.1016/j.waojou.2020.100472.
8. Copaescu AM, Rosa Duque JS, Phillips EJ. What have we learned about the allergenicity and adverse reactions associated with the severe acute respiratory syndrome coronavirus 2 vaccines: One year later. Ann Allergy Asthma Immunol 2022;129(1):40-51. DOI: 10.1016/j.anai.2022.03.030.
9. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#contraindications. Accessed April 13, 2022.
10. 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 2022;182(4):376-385. DOI: 10.1001/jamainternmed.2021.8515.
11. Greenhawt M, Shaker M, Golden DBK, et al. Diagnostic accuracy of vaccine and vaccine excipient testing in the setting of allergic reactions to COVID-19 vaccines: A systematic review and meta-analysis. Allergy 2023;78(1):71-83. DOI: 10.1111/all.15571.
12. Ruggeberg JU, Gold MS, Bayas JM, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007;25(31):5675-84. DOI: 10.1016/j.vaccine.2007.02.064.
13. Ring J, Laubenthal H, Messmer K. Incidence and classification of adverse reactions to plasma substitutes. Klin Wochenschr 1982;60(17):997-1002. DOI: 10.1007/BF01716961.
14. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117(2):391-7. DOI: 10.1016/j.jaci.2005.12.1303.

15. Chu DK, Golden DBK, Guyatt GH. Translating Evidence to Optimize Patient Care Using GRADE. J Allergy Clin Immunol Pract 2021;9(12):4221-4230. DOI: 10.1016/j.jaip.2021.09.035.
16. Brozek JL, Akl EA, Alonso-Coello P, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy 2009;64(5):669-77. DOI: 10.1111/j.1398-9995.2009.01973.x.
17. Brozek JL, Akl EA, Jaeschke R, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines: Part 2 of 3. The GRADE approach to grading quality of evidence about diagnostic tests and strategies. Allergy 2009;64(8):1109-16. DOI: 10.1111/j.1398-9995.2009.02083.x.
18. Brozek JL, Akl EA, Compalati E, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines part 3 of 3. The GRADE approach to developing recommendations. Allergy 2011;66(5):588-95. DOI: 10.1111/j.1398-9995.2010.02530.x.
19. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377-81. DOI: 10.1016/j.jbi.2008.08.010.
20. Cornelius VR, Liu K, Peacock J, Sauzet O. Variation in adverse drug reactions listed in product information for antidepressants and anticonvulsants, between the USA and Europe: a comparison review of paired regulatory documents. BMJ Open 2016;6(3):e010599. DOI: 10.1136/bmjopen-2015-010599.
21. Power M, Fell G, Wright M. Principles for high-quality, high-value testing. Evid Based Med 2013;18(1):5-10. DOI: 10.1136/eb-2012-100645.
22. Abrams EM, Greenhawt M, Shaker M, Kosowan L, Singer AG. Primary care provider-reported prevalence of vaccine and polyethylene glycol allergy in Canada. Ann Allergy Asthma Immunol 2021;127(4):446-450 e1. DOI: 10.1016/j.anai.2021.05.011.
23. Stone CA, Jr., Liu Y, Relling MV, et al. Immediate Hypersensitivity to Polyethylene Glycols and Polysorbates: More Common Than We Have Recognized. J Allergy Clin Immunol Pract 2019;7(5):1533-1540 e8. DOI: 10.1016/j.jaip.2018.12.003.
24. Kelso JM. The adverse reactions to vaccines practice parameter 10 years on-what have we learned? Ann Allergy Asthma Immunol 2022;129(1):35-39. DOI: 10.1016/j.anai.2022.01.026.
25. https://www.csaci.ca/wp-content/uploads/2021/11/2021-11-15-UPDATE-COVID-19-Vaccine-Testing-Administration-Guidance.pdf. Accessed December 10, 2021.
26. https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting. Accessed March 3, 2021.
27. https://www.allergy.org.au/hp/papers/ascia-hp-position-statement-covid-19-vaccination. Accessed April 13, 2022.
28. Kelso JM, Greenhawt MJ, Li JT, et al. Adverse reactions to vaccines practice parameter 2012 update. J Allergy Clin Immunol 2012;130(1):25-43. DOI: 10.1016/j.jaci.2012.04.003.

29. McNeil MM, Weintraub ES, Duffy J, et al. Risk of anaphylaxis after vaccination in children and adults. J Allergy Clin Immunol 2016;137(3):868-78. DOI: 10.1016/j.jaci.2015.07.048.
30. Dreskin SC, Halsey NA, Kelso JM, et al. International Consensus (ICON): allergic reactions to vaccines. World Allergy Organ J 2016;9(1):32. DOI: 10.1186/s40413-016-0120-5.
31. Su JR, Moro PL, Ng CS, Lewis PW, Said MA, Cano MV. Anaphylaxis after vaccination reported to the Vaccine Adverse Event Reporting System, 1990-2016. J Allergy Clin Immunol 2019;143(4):1465-1473. DOI: 10.1016/j.jaci.2018.12.1003.
32. Hourihane JO, Byrne AM, Blumchen K, Turner PJ, Greenhawt M. Ascertainment Bias in Anaphylaxis Safety Data of COVID-19 Vaccines. J Allergy Clin Immunol Pract 2021;9(7):2562-2566. DOI: 10.1016/j.jaip.2021.04.025.
33. Gold MS, Amarasinghe A, Greenhawt M, et al. Anaphylaxis: Revision of the Brighton collaboration case definition. Vaccine 2022. DOI: 10.1016/j.vaccine.2022.11.027.
34. Warren CM, Snow TT, Lee AS, et al. Assessment of Allergic and Anaphylactic Reactions to mRNA COVID-19 Vaccines With Confirmatory Testing in a US Regional Health System. JAMA Netw Open 2021;4(9):e2125524. DOI: 10.1001/jamanetworkopen.2021.25524.
35. Picard M, Stone CA, Jr., Greenhawt M. Management of patients with immediate reactions to COVID-19 vaccines. J Allergy Clin Immunol 2023;151(2):413-415. DOI: 10.1016/j.jaci.2022.09.003.
36. Tuong LAC, Capucilli P, Staicu M, Ramsey A, Walsth E, Mustafa SS. Graded Administration of Second Dose of Moderna and Pfizer-BioNTech COVID-19
mRNA Vaccine in Patients with Hypersensitivity to First Dose. Open Forum Infect Dis. 2021 Oct 6;8(12):ofab507.
37. Krantz MS, Bruusgaard-Mouritsen MA, Koo G, Phillips EJ, Stone CA, Jr., Garvey LH. Anaphylaxis to the first dose of mRNA SARS-CoV-2 vaccines: Don't give up on the second dose! Allergy 2021;76(9):2916-2920. DOI: 10.1111/all.14958.
38. Rasmussen TH, Mortz CG, Georgsen TK, Rasmussen HM, Kjaer HF, Bindslev-Jensen C. Patients with suspected allergic reactions to COVID-19 vaccines can be safely revaccinated after diagnostic work-up. Clin Transl Allergy 2021;11(5):e12044. DOI: 10.1002/clt2.12044.
39. Krantz MS, Kwah JH, Stone CA, Jr., et al. Safety Evaluation of the Second Dose of Messenger RNA COVID-19 Vaccines in Patients With Immediate Reactions to the First Dose. JAMA Intern Med 2021;181(11):1530-1533. DOI: 10.1001/jamainternmed.2021.3779.
40. Wolfson AR, Robinson LB, Li L, et al. First-Dose mRNA COVID-19 Vaccine Allergic Reactions: Limited Role for Excipient Skin Testing. J Allergy Clin Immunol Pract 2021;9(9):3308-3320 e3. DOI: 10.1016/j.jaip.2021.06.010.
41. Kessel A, Bamberger E, Nachshon L, Rosman Y, Confino-Cohen R, Elizur A. Safe administration of the Pfizer-BioNtTech COVID-19 vaccine following an immediate reaction to the first dose. Allergy 2021;76(11):3538-3540. DOI: 10.1111/all.15038.
42. Kelso JM. Misdiagnosis of systemic allergic reactions to mRNA COVID-19 vaccines. Ann Allergy Asthma Immunol 2021;127(1):133-134. DOI: 10.1016/j.anai.2021.03.024.
43. Mustafa SS, Ramsey A, Staicu ML. Administration of a Second Dose of the Moderna COVID-19 Vaccine After an Immediate Hypersensitivity Reaction With the First Dose: Two Case Reports. Ann Intern Med 2021;174(8):1177-1178. DOI: 10.7326/L21-0104.

44. Vanijcharoenkarn K, Lee FE, Martin L, Shih J, Sexton ME, Kuruvilla ME. Immediate Reactions After the First Dose of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Messenger RNA Vaccines Do Not Preclude Second-Dose Administration. Clin Infect Dis 2021;73(11):2108-2111. DOI: 10.1093/cid/ciab448.
45. Robinson LB, Landman AB, Shenoy ES, et al. Allergic symptoms after mRNA COVID-19 vaccination and risk of incomplete vaccination. J Allergy Clin Immunol Pract 2021;9(8):3200-3202 e1. DOI: 10.1016/j.jaip.2021.05.031.
46. Eastman J, Holsworth A, Kelbel T, Pebbles T, Hartog N. Cohort experience of 2nd mRNA vaccine dose tolerance after an initial dose reaction. Ann Allergy Asthma Immunol. 2022;128:217-218.
47. Park HJ, Montgomery JR, Boggs NA. Anaphylaxis After the Covid-19 Vaccine in a Patient With Cholinergic Urticaria. Mil Med 2022;187(9):e1556-e1558. DOI: 10.1093/milmed/usab138.
48. Arroliga ME, Dhanani K, Arroliga AC, et al. Allergic reactions and adverse events associated with administration of mRNA-based vaccines. A health-care system experience. Allergy Asthma Proc 2021;42(5):395-399. DOI: 10.2500/aap.2021.42.210069.
49. Loli-Ausejo D, Gonzalez de Abreu JM, Fiandor A, et al. Allergic reactions after administration of pfizer-biontech covid-19 vaccine to healthcare workers at a tertiary hospital. J Investig Allergol Clin Immunol 2021:0. DOI: 10.18176/jiaci.0751.
50. Pitlick MM, Sitek AN, Kinate SA, Joshi AY, Park MA. Polyethylene glycol and polysorbate skin testing in the evaluation of coronavirus disease 2019 vaccine reactions: Early report. Ann Allergy Asthma Immunol 2021;126(6):735-738. DOI: 10.1016/j.anai.2021.03.012.
51. Yacoub MR, Cucca V, Asperti C, et al. Efficacy of a rational algorithm to assess allergy risk in patients receiving the BNT162b2 vaccine. Vaccine 2021;39(44):6464-6469. DOI: 10.1016/j.vaccine.2021.09.048.
52. Shavit R, Maoz-Segal R, Iancovici-Kidon M, et al. Prevalence of Allergic Reactions After Pfizer-BioNTech COVID-19 Vaccination Among Adults With High Allergy Risk. JAMA Netw Open 2021;4(8):e2122255. DOI: 10.1001/jamanetworkopen.2021.22255.
53. Kohli-Pamnani A, Zapata K, Gibson T, Kwittken PL. Coronavirus disease 2019 vaccine hypersensitivity evaluated with vaccine and excipient allergy skin testing. Ann Allergy Asthma Immunol 2022;128(1):97-98. DOI: 10.1016/j.anai.2021.08.417.
54. Inoue S, Igarashi A, Morikane K, et al. Adverse reactions to BNT162b2 mRNA COVID-19 vaccine in medical staffs with a history of allergy. medRxiv 2021:2021.09.13.21263473. DOI: 10.1101/2021.09.13.21263473.
55. Carpenter T, Konig J, Hochfelder J, Siegel S, Gans M. Polyethylene glycol and polysorbate testing in 12 patients before or after coronavirus disease 2019 vaccine administration. Ann Allergy Asthma Immunol 2022;128(1):99-101. DOI: 10.1016/j.anai.2021.10.009.
56. Kaplan B, Farzan S, Coscia G, et al. Allergic reactions to coronavirus disease 2019 vaccines and addressing vaccine hesitancy: Northwell Health experience. Ann Allergy Asthma Immunol 2022;128(2):161-168 e1. DOI: 10.1016/j.anai.2021.10.019.
57. Rush C, Faulk KE, Bradley ZK, Turner A, Krumins M, Greenhawt M. The safety of SARS-CoV-2 vaccines in persons with a known history of pegaspargase allergy: A single

institution experience. J Allergy Clin Immunol Pract 2022;10(2):630-632. DOI: 10.1016/j.jaip.2021.11.025.
58. Koo G, Anvari S, Friedman DL, et al. mRNA COVID-19 vaccine safety in patients with previous immediate hypersensitivity to pegaspargase. J Allergy Clin Immunol Pract 2022;10(1):322-325. DOI: 10.1016/j.jaip.2021.09.051.
59. Mark C, Gupta S, Punnett A, et al. Safety of administration of BNT162b2 mRNA (Pfizer-BioNTech) COVID-19 vaccine in youths and young adults with a history of acute lymphoblastic leukemia and allergy to PEG-asparaginase. Pediatr Blood Cancer 2021;68(11):e29295. DOI: 10.1002/pbc.29295.
60. Picard M, Drolet JP, Masse MS, et al. Safety of COVID-19 vaccination in patients with polyethylene glycol allergy: A case series. J Allergy Clin Immunol Pract 2022;10(2):620-625 e1. DOI: 10.1016/j.jaip.2021.11.021.
61. Otani IM, Tsao LR, Tang M. Coronavirus disease 2019 vaccine administration in patients with reported reactions to polyethylene glycol- and polysorbate-containing therapeutics. Ann Allergy Asthma Immunol 2022;129(1):88-94 e1. DOI: 10.1016/j.anai.2022.03.006.
62. Mortz CG, Kjaer HF, Rasmussen TH, Rasmussen HM, Garvey LH, Bindslev-Jensen C. Allergy to polyethylene glycol and polysorbates in a patient cohort: Diagnostic work-up and decision points for vaccination during the COVID-19 pandemic. Clin Transl Allergy 2022;12(1):e12111. DOI: 10.1002/clt2.12111.
63. Immunization stress-related response. A manual for program managers and health professionals to prevent, identify and respond to stress- related responses following immunization. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO. https://appswhoint/iris/bitstream/handle/10665/330277/9789241515948-engpdf.
64. F AL, Fein M, Gabrielli S, et al. Allergic reactions to the coronavirus disease 2019 vaccine (ARCOV) study: The McGill University Health Centre experience. Ann Allergy Asthma Immunol 2022;129(2):182-188 e1. DOI: 10.1016/j.anai.2022.05.014.
65. Van Meerbeke SW, Fajt ML, Marini RV, Domsic RT, Petrov AA. Antibody response to graded dosing of coronavirus disease 2019 messenger RNA vaccines after allergic reaction to first dose. Ann Allergy Asthma Immunol 2022;129(3):373-374. DOI: 10.1016/j.anai.2022.05.004.
66. Csuth A, Nopp A, Storsaeter J, Nilsson L, Jenmalm MC. COVID-19 vaccines and anaphylaxis-evaluation with skin prick testing, basophil activation test and Immunoglobulin E. Clin Exp Allergy 2022;52(6):812-819. DOI: 10.1111/cea.14143.
67. Cahill JA, Kan M. Successful administration of second dose of BNT162b2 COVID-19 vaccine in two patients with potential anaphylaxis to first dose. Allergy 2022;77(1):337-338. DOI: 10.1111/all.14996.
68. Bruusgaard-Mouritsen MA, Jensen BM, Poulsen LK, Duus Johansen J, Garvey LH. Optimizing investigation of suspected allergy to polyethylene glycols. J Allergy Clin Immunol 2022;149(1):168-175 e4. DOI: 10.1016/j.jaci.2021.05.020.
69. Zhou ZH, Stone CA, Jr., Jakubovic B, et al. Anti-PEG IgE in anaphylaxis associated with polyethylene glycol. J Allergy Clin Immunol Pract 2021;9(4):1731-1733 e3. DOI: 10.1016/j.jaip.2020.11.011.

70. Sellaturay P, Nasser S, Ewan P. Polyethylene Glycol-Induced Systemic Allergic Reactions (Anaphylaxis). J Allergy Clin Immunol Pract 2021;9(2):670-675. DOI: 10.1016/j.jaip.2020.09.029.
71. Troelnikov A, Perkins G, Yuson C, et al. Basophil reactivity to BNT162b2 is mediated by PEGylated lipid nanoparticles in patients with PEG allergy. J Allergy Clin Immunol 2021;148(1):91-95. DOI: 10.1016/j.jaci.2021.04.032.
72. Bonadonna P, Brockow K, Niedoszytko M, et al. COVID-19 Vaccination in Mastocytosis: Recommendations of the European Competence Network on Mastocytosis (ECNM) and American Initiative in Mast Cell Diseases (AIM). J Allergy Clin Immunol Pract 2021;9(6):2139-2144. DOI: 10.1016/j.jaip.2021.03.041.
73. Greenhawt MJ, Spergel JM, Rank MA, et al. Safe administration of the seasonal trivalent influenza vaccine to children with severe egg allergy. Ann Allergy Asthma Immunol 2012;109(6):426-30. DOI: 10.1016/j.anai.2012.09.011.
74. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011;127(1 Suppl):S1-55. DOI: 10.1016/j.jaci.2010.09.034.
75. Shaker MS, Wallace DV, Golden DBK, et al. Anaphylaxis-a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol 2020;145(4):1082-1123. DOI: 10.1016/j.jaci.2020.01.017.
76. Shimabukuro T, Nair N. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine. JAMA 2021;325(8):780-781. DOI: 10.1001/jama.2021.0600.
77. Shimabukuro TT, Cole M, Su JR. Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US-December 14, 2020-January 18, 2021. JAMA 2021;325(11):1101-1102. DOI: 10.1001/jama.2021.1967.
78. Team CC-R, Food, Drug A. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Moderna COVID-19 Vaccine - United States, December 21, 2020-January 10, 2021. MMWR Morb Mortal Wkly Rep 2021;70(4):125-129. DOI: 10.15585/mmwr.mm7004e1.
79. Blumenthal KG, Robinson LB, Camargo CA, Jr., et al. Acute Allergic Reactions to mRNA COVID-19 Vaccines. JAMA 2021;325(15):1562-1565. (In en). DOI: 10.1001/jama.2021.3976.
80. Li L, Robinson LB, Patel R, et al. Association of Self-reported High-Risk Allergy History With Allergy Symptoms After COVID-19 Vaccination. JAMA Netw Open 2021;4(10):e2131034. DOI: 10.1001/jamanetworkopen.2021.31034.
81. Macy E, Pandya S, Sheikh J, et al. Population-Based Incidence, Severity, and Risk Factors Associated with Treated Acute-Onset COVID-19 mRNA Vaccination-Associated Hypersensitivity Reactions. J Allergy Clin Immunol Pract 2022;10(3):827-836. DOI: 10.1016/j.jaip.2021.12.021.
82. Klein NP, Lewis N, Goddard K, et al. Surveillance for Adverse Events After COVID-19 mRNA Vaccination. JAMA 2021;326(14):1390-1399. DOI: 10.1001/jama.2021.15072.

83. McMahon DE, Amerson E, Rosenbach M, et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases. J Am Acad Dermatol 2021;85(1):46-55. DOI: 10.1016/j.jaad.2021.03.092.
84. Magen E, Yakov A, Green I, Israel A, Vinker S, Merzon E. Chronic spontaneous urticaria after BNT162b2 mRNA (Pfizer-BioNTech) vaccination against SARS-CoV-2. Allergy Asthma Proc 2022;43(1):30-36. DOI: 10.2500/aap.2022.43.210111.
85. Blumenthal KG, Ahola C, Anvari S, Samarakoon U, Freeman EE. Delayed large local reactions to Moderna COVID-19 vaccine: A follow-up report after booster vaccination. JAAD Int 2022;8:3-6. DOI: 10.1016/j.jdin.2022.03.017.
86. Blumenthal KG, Freeman EE, Saff RR, et al. Delayed Large Local Reactions to mRNA-1273 Vaccine against SARS-CoV-2. N Engl J Med 2021;384(13):1273-1277. DOI: 10.1056/NEJMc2102131.
87. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines; Graham R, Mancher M, Miller Wolman D, et al., editors. Clinical Practice Guidelines We Can Trust. Washington (DC): National Academies Press (US); 2011. Summary. Available from: https://www.ncbi.nlm.nih.gov/books/NBK209538/.

GRADE Evidence to Decision Framework

QUESTION

The Risk of Allergic Reaction to mRNA COVID-19 Vaccines and Recommended Evaluation and Management	
POPULATION:	Persons in need of COVID-19 vaccination, with and without a prior allergic reaction of any severity to the mRNA COVID-19 vaccine or a vaccine excipient
INTERVENTION:	Vaccination, including repeat vaccination after an immediate allergic reaction to the initial dose, without risk stratification
COMPARATOR	Vaccine Deferral or vaccination with risk stratification
OUTCOME:	Optimal patient and population health outcomes

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Through the winter of 2023, the novel SARS-CoV-2 coronavirus and subsequent COVID-19 (Coronavirus disease 2019) global pandemic has caused over 671 million infections and 6.8 million fatalities. Vaccines are considered the most effective strategy to end the pandemic. However, barriers to vaccination efforts include the rare occurrence of severe allergic reactions, which have been postulated to be related to the vaccine excipients polyethylene glycol (PEG) in the mRNA vaccines and polysorbate 80 (PS) in the viral vector vaccines	While interim GRADE-based guidance and multiple smaller studies have suggested that there is limited risk of either a 1st dose or a repeat allergic reaction to mRNA COVID-19 vaccines , and that skin testing to the vaccine and vaccine excipient are not helpful or necessary, most government health agencies have continued to recommend that individuals with a history of allergy to the vaccine or vaccine excipients not receive mRNA COVID-19 vaccination.

Testing accuracy for mRNA COVID-19 vaccine risk stratification

How accurate is performing a test to the vaccine excipients before vaccination, or to the vaccine or vaccine excipients in persons who had a 1st dose allergic reaction to determine the risk of reacting to a 2nd dose ?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very inaccurate ○ Inaccurate ○ Accurate ○ Very accurate ○ Varies ○ Don't know	Testing to vaccine excipient prior to initial vaccination: A systematic review identified 21 studies (case reports/series) that described skin testing (skin prick testing or intradermal testing) in 299 patients to either PEG of any molecular weight and/or polysorbate 80, where control subjects were also tested, to assess the baseline utility of PEG and polysorbate in the setting of suspected allergy to medication or non-COVID-19 vaccines containing these agents. For PEG, there were 15 reports detailing SPT and/or ID testing to varying agents and concentrations, which calculated a pooled sensitivity of 58.8% (30 true positive, 21 false negative) and specificity of 99.5% (247 true negative, 1 false positive). There was a total of 6 reports detailing 7 patients with suspected allergy to polysorbate that were tested (no false positives, and 57 controls tested that were non-reactive); the certainty of the accuracy of this testing was too low to report.	It is possible that some persons allergic to the vaccine and/or vaccine excipient, who had a first dose allergic reaction, may have deferred being tested for or receiving a second dose, which may bias the estimates. Study sizes were on the smaller side, and additional trials could shift the estimates. It is possible that some persons with a 1st dose reaction may only feel comfortable receiving a 2nd dose if they have undergone testing, despite how poor the testing performs in predicting risk of a 2nd reaction.

	Testing to the vaccine or vaccine excipients to assess risk of a 2nd dose reaction in persons with a 1st dose allergic reaction: A systematic review and meta-analysis detailed 16 studies among 423 individuals with 1st dose immediate allergic reactions to the vaccine who underwent 568 skin tests to any one or a combination of mRNA COVID-19 vaccine, PEG, and PS, for risk stratification assessment prior to receiving a 2nd vaccine dose, and were then re-vaccinated with the same vaccine that provoked the initial reaction. Test sensitivity for either mRNA vaccine was 0.19 (95%CrI 0.02-0.52) and specificity 0.96 (95%CrI 0.85-1). PEG test sensitivity was 0.02 (95%CrI 0.00-0.07) and specificity 0.99 (95%CrI 0.95-1). PS test sensitivity was 0.03 (95%CrI 0.00-0.0.11) and specificity 0.98 (95%CrI 0.91-1). Combined for use of any agent, test sensitivity was 0.03 (95%CrI 0.00-0.09) and specificity was 0.98 (95%CrI 0.95-1.00). One study included in the meta-analysis noted that use of Refresh Tears for PS testing produced an irritant effect, resulting in false positive responses in 12/25 non-allergic control subjects tested.	

Desirable effects of vaccination

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	The currently available mRNA COVID-19 vaccines have been shown in large RCTs to be very effective in reducing infection and severe complications of COVID-19 (high certainty evidence). At least 3 doses appear to be necessary to deliver such effects, and annual booster vaccination with variant-specific vaccine strains is recommended.	Efficacy against emerging variants remains unclear, though higher with at least 3 doses in all persons, and 4 doses in persons >50 years of age and with certain high-risk conditions. Vaccination on a population scale remains the best strategy against all strains. Variant-specific annual booster vaccination is proposed.

Undesirable effects of vaccination

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	Meta-analysis of randomized and observational data show with high certainty that the risk of anaphylaxis to a mRNA COVID-19 vaccine is very rare, either on a 1st dose, or to a 2nd dose in persons who had an immediate allergic reaction to a 1st dose. Testing to vaccine or vaccine excipients has very poor sensitivity and does not predict risk of a 1st dose or 2nd dose reaction. A verified or adjudicated fatality directly attributable to an allergic reaction to a mRNA COVID-19 vaccine has not been reported. Immediate allergic reactions are only a very small subset of possible vaccine related adverse events, which may include delayed reactions or other sequelae. All mRNA COVID-19 vaccines are administered in a healthcare setting (inclusive of retail pharmacy staffed by a registered nurse administering the vaccine) and with observation of at least 15 minutes, with both trained staff and epinephrine available to treat any rare anaphylactic reaction. To treat a reaction administration of epinephrine and supine positioning are the first steps, and if necessary, administration of intravenous fluids. Non-sedating,	Vaccine-related fatalities from allergic reactions are exceedingly rare, with no known rate, but that historically, vaccine-related anaphylaxis occurs at a rate of 1.3 anaphylaxis events per million vaccinations. By comparison, publications in the medical literature report that the rate for anaphylaxis to penicillin is 5-10 cases per million persons, and in the general population, the total occurrence of drug allergy fatalities is on the order of 0.1 to 1 event per 1,000,000 persons. Through early 2023, the current global estimated fatality rate from COVID-19 infection ranges 54.9-337/100,000 persons in countries represented by authors on this consensus document. To date, no allergic comorbidity has been identified as a definitive risk factor for having an immediate allergic reaction to a mRNA COVID-19 vaccine. Rare diseases are defined as conditions that affect less than 50 persons per 100, 000 population. The American orphan drug act from the year of 1983 defined rare diseases as disorders that affect less than 200, 000 persons in the country, which at that time corresponded to a prevalence of 86 per 100 000 population. Immediate allergic reactions to mRNA COVID-19 vaccines continue to meet criteria to be considered very rare effects.

	second generation antihistamines and/or inhaled beta-2-agonists can be used in addition after epinephrine administration for supportive treatment.	• Bruckner-Tuderman L. Epidemiology of rare diseases is important. J Eur Acad Dermatol Venereol. 2021 Apr;35(4):783-784. doi: 10.1111/jdv.17165.

Certainty of the evidence of testing for mRNA COVID-19 vaccine risk stratification

What is the overall certainty of the evidence of vaccine risk stratification?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Certainty of evidence of test accuracy O Very low O Low ● Moderate O High O No included studies Certainty of evidence of benefits and harms of vaccination: O Very low O Low O Moderate ● High O No included studies	<u>Testing to vaccine excipient prior to initial vaccination:</u> A systematic review identified 21 studies (case reports/series) that described skin testing (skin prick testing or intradermal testing) to either PEG of any MW and/or polysorbate 80, where control subjects were also tested, to assess the baseline utility of PEG and polysorbate in the setting of suspected allergy to medication or non-COVID-19 vaccines containing these agents. For PEG, there were 15 reports detailing SPT and/or ID testing to varying agents and concentrations, which calculated a pooled sensitivity of 58.8% (30 true positive, 21 false negative) and specificity of 99.5% (247 true negative, 1 false positive). There was a total of 6 reports detailing 7 patients with suspected allergy to polysorbate that were tested (no false positives, and 57 controls tested that were non-reactive), the certainty of the accuracy of this testing was too low to report. <u>Testing to the vaccine or vaccine excipients to assess risk of a 2nd dose reaction in persons with a 1st dose allergic reaction:</u> A systematic review and meta-analysis detailed 20 studies among 317 individuals with 1st dose immediate allergic reactions to the vaccine who underwent 578 skin tests to any one or combination of either mRNA COVID-19 vaccine, PEG, and PS, for risk stratification assessment prior to receiving a 2nd vaccine dose, and were then re-vaccinated with the same vaccine provoking the initial reaction. Test sensitivity for either mRNA vaccine was 0.2(95%CrI 0.01-0.52) and specificity 0.97(95%CrI 0.9-1). PEG test sensitivity was 0.02 (95%CrI 0.00-0.07) and specificity 0.99 (95%CrI 0.96-1). PS test sensitivity was 0.03 (95%CrI 0.00-0.0.11) and specificity 0.97 (95%CrI 0.91-1). Combined for use of any agent, test sensitivity was 0.03 (95%CrI 0.00-0.08) and specificity was 0.98 (95%CrI 0.95-1). One study included in the meta-analysis noted that use of Refresh Tears for PS testing was irritant, resulting in false positive responses in 12/25 non-allergic control subjects tested. <u>Use of pre-medication or graded dosing:</u> in the systematic review and meta analyses of 2nd dose reactions and skin testing to vaccine or vaccine excipient, stratification by use of single vs. graded	It is possible that some persons allergic to the vaccine and/or vaccine excipient, who had a first dose allergic reaction, may have deferred being tested for or receiving a second dose, which may bias the estimates. Study sizes were on the smaller side, and additional trials could shift the estimates. It is possible that some persons with a 1st dose reaction may only feel comfortable receiving a 2nd dose if they have undergone testing or receive it with either premedication or via a graded dose, despite no evidence these risk stratification measures improve outcomes.

	dosing or by premedication in either analysis did not alter the results.	

Certainty of the evidence of excipient testing to inform the risk of a mRNA COVID-19 vaccine reaction

What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of excipient testing?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Very low O Low ● Moderate O High O No included studies	While it has been speculated as a mechanism, there is no evidence that anti-PEG or anti-polysorbate IgE is responsible for immediate allergic reactions to mRNA COVID-19 vaccines. Testing for IgE to PEG, polysorbate, or the mRNA COVID-19 vaccine has shown very poor sensitivity, and 2nd dose immediate allergic reactions are rare, further questioning an IgE-mediated mechanism. There remains no evidence that immediate allergic reactions to mRNA COVID-19 vaccines are IgE mediated, and at least one study has speculated a non-IgE mechanism involving direct mast cell activation. • Warren CM, Snow TT, Lee AS, Shah MM, Heider A, Blomkalns A, et al. Assessment of Allergic and Anaphylactic Reactions to mRNA COVID-19 Vaccines With Confirmatory Testing in a US Regional Health System. JAMA Netw Open 2021;4:e2125524. • Chu DK, Abrams EM, Golden DBK, Blumenthal KG, Wolfson AR, Stone CA, Jr., et al. Risk of Second Allergic Reaction to SARS-CoV-2 Vaccines: A Systematic Review and Meta-analysis. JAMA Intern Med 2022;doi:10.1001/jamainternmed.2021.8515. • Greenhawt M, Shaker M, Golden DBK, Abrams EM, Blumenthal KG, Wolfson AR, et al. Diagnostic Accuracy of Vaccine and Vaccine Excipient Testing in the Setting of Allergic Reactions to COVID-19 Vaccines: A Systematic Review and Meta-analysis. Allergy 2022.	There is a very low prevalence of PEG or polysorbate allergy in the general population (0.12 cases per million person-years, and a low population incidence of reactions to COVID-19 vaccines (7.91 cases per million). There is a very low rate of 2nd dose immediate allergic reactions to mRNA COVID-19 vaccines, and no demonstration that this is mediated through anti-excipient or anti-vaccine IgE. Pre-emptive screening for PEG or polysorbate allergy prior to mRNA COVID-19 vaccination, or in response to a 1st dose reaction is not recommended due to low test sensitivity and question if the mechanism of reaction is IgE-mediated.

Certainty of the evidence of excipient testing's effects

What is the overall certainty of the evidence of effects of the management that is guided by the results of excipient testing?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Very low O Low ● Moderate O High O No included studies	Testing for IgE to PEG, polysorbate, or the mRNA COVID-19 vaccine has shown very poor sensitivity in predicting 2nd dose reactions, and testing to Refresh Tears as a surrogate for polysorbate 80 has shown this product to be an irritant. | Testing Reagent	TP	FP	FN	TN	Sensitivity	95% CrI	Specificity	95% CrI
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All agents, combined	5	27	88	458	0.03	0.00-0.08	0.98	0.95-1
Either mRNA vaccine agent	3	8	11	95	0.2	0.01-0.52	0.97	0.9-1
mRNA-1273 vaccine (Moderna)	2	6	1	27	0.59	0.08-0.98	0.76	0.01-1
BNT162b2 vaccine (Pfizer-BioNTech)	1	2	10	68	0.1	0.00-0.38	0.99	0.94-1
Polyethylene Glycol[a]	1	11	45	240	0.02	0.00-0.07	0.99	0.96-1
Polysorbate[b]	1	8	32	123	0.03	0.00-0.11	0.97	0.91-1
Sensitivity Analysis (all agents, combined)	**TP**	**FP**	**FN**	**TN**	**Sensitivity**	**95% CI**	**Specificity**	**95% CrI**
1st dose anaphylaxis patients included in the study	5	26	82	435	0.03	0.00-0.09	0.98	0.95-1
No 1st dose anaphylaxis patients included in the study	0	0	10	10	0.07	0.00-0.45	0.98	0.76-1
Graded Challenge allowed	4	15	45	197	0.08	0.01-0.23	0.97	0.9-1
No Graded Challenge allowed	1	11	47	248	0.01	0.00-0.06	0.99	0.96-1
Premedication Allowed	0	11	54	183	0.00	0.00-0.03	0.98	0.93-1
No Premedication Allowed	5	15	38	280	0.09	0.01-0.25	0.98	0.94-1
Predictive only of 2nd dose anaphylaxis	2	26	12	433	0.11	0.01-0.32	0.98	0.95-1

CrI=credible interval. TP=True Positive. FP=False Positive. FN=False Negative. TN=True negative. PLR=Positive likelih
Negative Likelihood Ratio.
[a] inclusive of any molecular weight polyethylene glycol tested
[b] inclusive of any polyoxyethylene group number tested

It is possible that some persons allergic to the vaccine and/or vaccine excipient, who had a first dose allergic reaction, may have deferred being tested for or receiving a second dose, which may bias the estimates. Study sizes were on the smaller side, and additional trials could shift the estimates. It is possible that some persons with a 1st dose reaction may only feel comfortable receiving a 2nd dose if they have undergone testing or receive it with either premedication or via a graded dose, despite no evidence these risk stratification measures improve outcomes.
Testing may have low sensitivity because there remains no proof that anti-PEG IgE is responsible for mRNA COVID-19 vaccine reactions, and this could be the wrong agent to test for, or the reactions may not be IgE mediated. While the analysis has demonstrated high test specificity, this may be misleading, and in light of poor sensitivity and limited proof of an IgE mediated mechanism, it does not infer high accuracy in identifying persons

	• Greenhawt M, Shaker M, Golden DBK, Abrams EM, Blumenthal KG, Wolfson AR, et al. Diagnostic Accuracy of Vaccine and Vaccine Excpient Testing in the Setting of Allergic Reactions to COVID-19 Vaccines: A Systematic Review and Meta-analysis. Allergy 2022.	who are not allergic to the vaccine or excipient, and likely just infers the testing is non-irritant. This approach is independent of the incidental finding in the setting of evaluating a mRNA COVID-19 vaccine reaction that a patient history indicates a strong likelihood of prior PEG allergy. In that context, the clinician may wish to consider PEG testing or PEG oral challenge as part of the workup to confirm PEG allergy for other decision-making purposes, apart from the COVID vaccine-related issue

Certainty of the evidence of excipient test result/management

How certain is the link between test results and management decisions?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Very low O Low ● Moderate O High O No included studies	It is unknown if PEG or polysorbate allergy is responsible for allergic reactions to mRNA COVID-19 vaccines. There remains no proof that these reactions are mediated through anti-PEG or anti-polysorbate IgE. Sensitivity of excipient testing before 1st vaccination, or testing to excipient or vaccine after a 1st dose immediate allergic reaction to predict the risk of a 2nd dose reaction has poor sensitivity.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
O Important uncertainty or variability ●Possibly important uncertainty or variability O Probably no important uncertainty or variability O No important uncertainty or variability		The global and uniform sentiment is a desire for rapid, comprehensive, and safe vaccination. While most individuals value optimal patient and population health outcomes, important variation may exist in the degree to which individuals are willing to accept risks of vaccine reactions to achieve timely immunity against COVID-19. This may in particular be the case given that individuals may not choose to receive additional booster shots given concerns about efficacy against emerging strains, and emerging evidence regarding immunity from natural infection augmenting immunity from a vaccine. This may prompt an individual who has reacted to a vaccine dose to feel the risks of their present immunity against further infection may outweigh the risk of potentially reacting to an additional dose of a vaccine. However, this opinion may differ for someone who has only received their initial dose, and has not had natural infection. Allergic reactions to mRNA COVID-19 vaccines are manageable events under the care of an allergy specialist, and persons with risk factors for a reaction or a history of a reaction can still be safely vaccinated in this setting. We recommend vaccination over no vaccination.

Balance of effects

Does the balance between desirable and undesirable effects favor vaccine deferral or vaccination?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Favors vaccination O Probably favors vaccination O Does not favor either the vaccination or vaccine deferral O Probably favors vaccine deferral O Favors vaccine deferral O Varies O Don't know	There is no evidence to date that conclusively shows PEG or polysorbate allergy is responsible for immediate allergic reactions to mRNA COVID-19 vaccines through an IgE mediated pathway, directed against PEG, polysorbate, or the vaccine itself. Skin testing to PEG has low sensitivity to predict a PEG allergy and low sensitivity to predict a reaction to a 2nd dose of a mRNA COVID-19 vaccine.	The risks of not being vaccinated and severe COVID-19 outcomes in the setting of a global pandemic outweighs the risks that someone who is allergic to the vaccine has a severe allergic reaction that could not be managed. The risk of a 1st or 2nd dose reaction are very low. Testing to excipients or the vaccine has very low sensitivity in predicting a reaction. Many government health authorities have recommended withholding mRNA COVID-19 vaccinations in persons with an allergy to the excipient or the vaccine, and have recommended alternative vaccine platforms as an option. However, there are considerable differences in efficacy of adenoviral vector vaccines in persons with mRNA vaccine reactions, which may reduce health equity.

Resources required for mRNA COVID-19 vaccine allergy testing risk stratification

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large costs O Moderate costs O Negligible costs and savings O Moderate savings O Large savings O Varies O Don't know	From a societal standpoint, the low sensitivity of excipient or vaccine testing in predicting mRNA COVID-19 vaccine reactions with the low prevalence of PEG/polysorbate allergy and/or low rate of initial or subsequent mRNA COVID-19 vaccine dose reactions strongly suggests against any population-based approach that would involve screening for pre-existing specific-IgE against PEG or polysorbate. The indirect costs of an allergy testing-based risk stratification approach may include delayed or deferred vaccination with increased risk of infection and hospitalization. Costs could be lowered if screening improved in sensitivity, and was tightly restricted to a very well-identified population deemed at very high-risk of a possible IgE mediated allergic reaction to the vaccine.	Recent systematic reviews and meta-analyses have shown that testing prior to initial vaccine dose or after an immediate allergic reaction to an initial dose to assess risk of a reaction to a 2nd dose has low sensitivity, and 2nd dose severe reactions are very rare. To test every individual who is perceived to have potential risk would require access to consultation with an experienced allergist, and the availability of testing materials. This is feasible in some contexts where there is ample access to such specialists, but in other areas (e.g., rural settings or low/middle income countries), access to a specialist may be more difficult. The indirect costs may include those associated with delayed or deferred vaccination, and with increased risk of infection and resulting hospitalization. Overall a testing approach is not supported by evidence that the testing is effective in determining risk, or that the rate of repeat reactions is high.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Evidence suggests the population risk of PEG and polysorbate anaphylaxis is very low. Similarly, severe immediate allergic reactions to 1st or 2nd doses of mRNA COVID-19 vaccines are very rare and allergy testing to the vaccine or vaccine excipient is of low utility. Performing allergy test-based risk stratification could have very high costs on a population level, though there are no studies that have explored the cost of such resource utilization.	

Cost effectiveness of testing

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Shaker et al modeled the cost-effectiveness of applying risk stratification and testing in the US, and the impact of extended wait time as a precaution. Using Markov modeling and microsimulation, universal vaccination was associated with a cost-savings of $503,596,316 and saved 7,607 lives vs. a risk-stratified approach until vaccine-associated anaphylaxis rates were >0.8%). Stratified post-vaccination extended observation time by anaphylaxis history was not cost-effective without >1% anaphylaxis case-fatality and >6% risk of vaccination-associated anaphylaxis. Furthermore, deferral of a second mRNA COVID-19 vaccine dose after a first reaction was not cost-effective unless first-dose protection was very high (meaning there was limited value of additional doses) and risk for vaccine-associated anaphylaxis with an additional dose was high. • Shaker M, Abrams EM, Greenhawt M. A Cost-Effectiveness Evaluation of Hospitalizations, Fatalities, and Economic Outcomes Associated with Universal Versus Anaphylaxis Risk-Stratified COVID-19 Vaccination Strategies. J Allergy Clin Immunol Pract. 2021 Jul;9(7):2658-2668.e3.	

Equity of testing

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Reduced ○ Probably reduced ○ Probably no impact	There is a low prevalence of allergy to PEG/Polysorbate or to the mRNA COVID-19 vaccines, and a high prevalence of COVID-19. Testing to the vaccine or vaccine excipient has been shown to have very low sensitivity in predicting risk of subsequent reactions, and testing to PEG outside of the context	While the evidence does not support that vaccine or vaccine excipient testing has good sensitivity and is of high utility, some allergists advocate there is benefit in performing skin testing as a way to reassure the patient, and that some patients would refuse re-vaccination without such testing.

○ Probably increased ○ Increased ○ Varies ○ Don't know	of mRNA COVID-19 vaccine reactions also has been shown to have poor sensitivity. To test every individual who is perceived to have potential risk would require access to consultation with an experienced allergist, and the availability of testing materials. This is feasible in some contexts where there is ample access to such specialists, but in other areas (e.g., rural settings or low/middle income countries), access to a specialist may be more difficult. The indirect costs may include those associated with delayed or deferred vaccination, and with increased risk of infection and resulting hospitalization.	

Acceptability of not testing

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Some clinicians and patients may be hesitant to proceed with vaccination if they perceive the risk of anaphylaxis to be elevated. Some may insist on testing to help hedge this risk. However, this concern may be overshadowed by the urgent need to vaccinate the population in both high and low risk groups, and evidence that the testing has poor sensitivity in determining risk of reaction.	Vaccines are acceptable to vast majority of individuals across societies and cultures. It is possible that some persons allergic to the vaccine and/or vaccine excipient, who had a first dose allergic reaction, may have deferred being tested for or receiving a second dose, which may bias the estimates. It is possible that some persons with a 1st dose reaction may only feel comfortable receiving a 2nd dose if they have undergone testing, despite no evidence this improves outcomes.

Feasibility of not testing

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There are now data from two meta-analysis that show poor sensitivity for skin testing to PEG, polysorbate, or the mRNA COVID-19 vaccine to predict risk of an immediate allergic reaction to a 1st dose of the vaccine or a repeat immediate allergic reaction. The overall rate of 1st dose or repeat immediate allergic reactions to the vaccine is very low and was not impacted by studies where testing was or was not performed.	Vaccination campaigns are feasible and are being implemented increasingly worldwide.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
TEST ACCURACY FOR SARS-COV-2 VACCINE RISK STRATIFICATION	**Very inaccurate**	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS OF VACCINATION	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS OF VACCINATION	Large	Moderate	Small	**Trivial**		Varies	Don't know

	JUDGEMENT						
CERTAINTY OF THE EVIDENCE OF TESTING FOR SARS-COV-2 VACCINE RISK STRATIFICATION	Very low	Low	**Moderate**	High			No included studies
CERTAINTY OF THE EVIDENCE OF EXCIPIENT TESTING TO INFORM THE RISK OF A SARS-COV-2 VACCINE REACTION	Very low	Low	**Moderate**	High			No included studies
CERTAINTY OF THE EVIDENCE OF EXCIPIENT TESTING'S EFFECTS	Very low	Low	**Moderate**	High			No included studies
CERTAINTY OF THE EVIDENCE OF EXCIPIENT TEST RESULT/MANAGEMENT	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	**Favors vaccination**	Probably favors vaccination	Does not favor either vaccination or vaccine deferral	Probably favors vaccine deferral	Favors vaccine deferral	Varies	Don't know
RESOURCES REQUIRED FOR SARS-COV-2 VACCINE ALLERGY TSTING RISK STRATIFICATION	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS OF TESTING	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY FROM TESTING	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY OF NOT TESTING	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY OF NOT TESTING	No	Probably no	Probably yes	**Yes**		Varies	Don't know

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
TEST ACCURACY FOR SARS-COV-2 VACCINE RISK STRATIFICATION	**Very inaccurate**	Inaccurate	Accurate	Very accurate		Varies	Don't know
DESIRABLE EFFECTS OF VACCINATION	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS OF VACCINATION	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF THE EVIDENCE OF TESTING FOR SARS-COV-2 VACCINE RISK STRATIFICATION	Very low	Low	**Moderate**	High			No included studies
CERTAINTY OF THE EVIDENCE OF EXCIPIENT TESTING TO INFORM THE RISK OF A SARS-COV-2 VACCINE REACTION	Very low	Low	**Moderate**	High			No included studies
CERTAINTY OF THE EVIDENCE OF EXCIPIENT TESTING'S EFFECTS	Very low	Low	**Moderate**	High			No included studies
CERTAINTY OF THE EVIDENCE OF EXCIPIENT TEST RESULT/MANAGEMENT	Very low	Low	**Moderate**	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	**Favors vaccination**	Probably favors vaccination	Does not favor either vaccination or vaccine deferral	Probably favors vaccine deferral	Favors vaccine deferral	Varies	Don't know
RESOURCES REQUIRED FOR SARS-COV-2 VACCINE ALLERGY TSTING RISK STRATIFICATION	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS OF TESTING	**Favors the comparison**	Probably favors the comparison	Does not favor either the intervention or	Probably favors the intervention	Favors the intervention	Varies	No included studies

	JUDGEMENT						
			the comparison				
EQUITY FROM TESTING	**Reduced**	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY OF NOT TESTING	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY OF NOT TESTING	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Table 1: Recommendations

Questions	Recommendation	Evidence Strength	Evidence Certainty
What is the risk of COVID-19 vaccine anaphylaxis in a patient with no history of anaphylaxis to a COVID-19 vaccine or its excipients?	For patients with no history of a previous allergic reaction to a mRNA COVID-19 vaccine or its excipients, the risk of first-dose mRNA COVID-19 vaccine-induced anaphylaxis is exceptionally low, and we recommend vaccination over either no vaccination or vaccine deferral.	Strong	High
	For patients with a history of a severe allergic reaction, including anaphylaxis, unrelated to a mRNA COVID-19 vaccine or vaccine excipient, we suggest against additional post-vaccination observation beyond standard wait time (e.g., 15 minutes).	Conditional	Low
In patients without a history of anaphylaxis to a mRNA COVID-19 vaccine or its excipients, should allergy skin testing to mRNA COVID-19 vaccines or its excipients be performed prior to initial mRNA COVID-19 vaccination?	For patients with no history of a previous allergic reaction of any severity, including anaphylaxis, following a mRNA COVID-19 vaccine or related vaccine excipient, we recommend against vaccine or vaccine excipient testing prior to initial mRNA COVID-19 vaccination in an attempt to predict the rare individual who will have a severe allergic reaction to an initial vaccine dose.	Strong	Low
Can additional supervised doses of mRNA COVID-19 vaccines be administered to a patient who had an immediate allergic reaction (defined as occurring within 4 hours of vaccine administration) of any severity following the 1st dose of the vaccine?	We recommend that individuals who had an immediate allergic reaction of any severity to the 1st dose mRNA COVID-19 vaccine can receive additional mRNA COVID-19 vaccine doses, and those who have a history of a severe allergic reaction to one of the vaccine excipients can receive either their initial or additional mRNA COVID-19 vaccine doses.	Strong	Moderate
In a patient with a history of an immediate allergic reaction of any severity to a previous mRNA COVID-19 vaccine or its excipients, should allergy skin testing to mRNA COVID-19 vaccines or their excipients be performed to determine if a future dose of vaccine should be withheld?	For individuals with a history of an immediate allergic reaction to a mRNA COVID-19 vaccine or its excipients, we recommend against performing skin testing using any mRNA-COVID-19 vaccine or its excipients for the purpose of risk assessment to determine if they should receive a vaccine dose.	Strong	Moderate
In a patient with a history of an immediate allergic reaction of any severity to a previous mRNA COVID-19 vaccine or its excipients, what is the most appropriate setting for these individuals to receive their vaccination?	We recommend referral to an allergist (or other clinician with expertise in the management of vaccine allergy and allergic reactions) for assessment and supervised vaccination of such individuals for their initial dose, or for the subsequent dose after a reaction to a prior dose.	Strong	Moderate
Should a patient with a history of an immediate allergic reaction to the vaccine or vaccine excipient be pre-medicated prior to receiving their vaccine to prevent a severe allergic reaction?	We suggest against routine H1-antihistamine or systemic corticosteroid pre-medication prior to vaccination to prevent anaphylaxis.	Conditional	Low
Should a patient with a history of an immediate allergic reaction to the vaccine or vaccine excipient receive their vaccine as a graded dose rather than a single dose?	We suggest against graded dosing or stepwise desensitization compared to a single dose.	Conditional	Low

Table 2: GRADE Certainty of Evidence Table for Questions Regarding Reaction Incidence

For Questions Related to Reaction Rates		Certainty assessment						Effect				
Question/Outcome Assessed	**№ of studies**	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**№ of events**	**№ of individuals**	**Rate (95% CI)**	**Certainty**	**Importance**
Question 1: What is the risk of COVID-19 vaccine anaphylaxis in a patient with no history of anaphylaxis to a COVID-19 vaccine or its excipients	47	observational studies and RCTs	Not serious	not serious [a,b]	not serious	not serious	none	674 (208)[c]	57,089,598 (41,018,326)[c]	event rate [c] 7.91 per 1,000,000 (4.02 to 15.59)	⊕⊕⊕⊕ HIGH	CRITICAL
Question 3: Can additional supervised doses of mRNA COVID-19 vaccines be administered to a patient who had an immediate allergic reaction (defined as occurring within 4 hours of vaccine administration) of any severity following the 1st dose of the vaccine?												
a) What is the incidence of anaphylaxis to a second SARS-CoV-2 vaccination in persons who had an allergic reaction to their first dose	22	Case studies and case reports	Not serious[d]	Not serious	Not serious	Not serious	Large effect of tolerating and Residual confounding would suggest an effect of reacting when none was detected[e]	6	1366	0.16% (0.01% to 2.91%)	⊕⊕⊕◯ MODERATE	CRITICAL
b) What is the incidence of anaphylaxis to a second SARS-CoV-2 vaccination in persons who had an anaphylaxis to their first dose	17	Case studies and case reports	Not serious[d]	Not serious	Not serious	Not serious[f]	Large effect of tolerating and Residual confounding would suggest an effect of reacting when none was detected[e,f]	4	78	4.94% (0.93% to 22.28%)	⊕⊕◯◯ LOW	CRITICAL
c) What is the incidence of mild allergic symptoms to a second SARS-CoV-2 vaccination in persons who had an allergic reaction to their first dose	22	Case studies and case reports	Not serious[d]	Not serious	Not serious	Not serious	Large effect of tolerating and Residual confounding would suggest an effect of reacting when none was detected[e]	232	1366	13.5% (7.66% to 22.27%)	⊕⊕⊕◯ MODERATE	CRITICAL

a. Non-adjudicated rates yield estimates that are higher than adjudicated ones by about 5-fold.

b. One adjudicated study yielded a markedly higher estimate than all others. It also was the only study that was not a national pharmacovigilance study. Though it contributed to some heterogeneity, it was not felt that this was so serious to rate down for inconsistency because the (1) estimate of effect was still rare, (2) excluding this study, yielding a pooled estimate of 6.43 (3.57-11.56) events per million doses was not importantly different in terms of rarity, (3) that this study was balanced by other studies with 0 events, and (4) visual inspection did not reveal serious inconsistency.

c. Values in parentheses are data restricted to studies with 20,000 or more doses.

d. Risk of bias addressed in subgroup and sensitivity analyses

e. 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 that received the second dose had an allergic reaction or anaphylaxis. Further, those being revaccinated, 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.

f. Imprecision in width of 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 repeat anaphylaxis being not very high (eg. 100%) is more certain than the quantitative estimate of a mean of 4.94%.

Table 3: Factors increasing certainty of evidence

For Questions Related to Diagnostic Testing Question/Outcome Assessed	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability 0.001%	pre-test probability 1%	pre-test probability 10%	
Question 2: In patients without a history of anaphylaxis to a mRNA COVID-19 vaccine or its excipients, should allergy skin testing to mRNA COVID-19 vaccines excipients be performed prior to initial mRNA vaccination? Sn: 0.59 (95%CI 0.44 to 0.72), Sp: 0.99 (95%CI 0.98 to 1.00) Prevalence : 0.001%, 1%, 10%											
True positives (patients with excipient allergy)	15 studies 296 patients	cohort & case-control type studies	serious [a]	serious [b]	Not serious [c]	Not serious [d]	Publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect	0 (0 to 0)	6 (1 to 8)	64 (5 to 76)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having excipient allergy)								0 (0 to 0)	4 (2 to 9)	36 (24 to 95)	
True negatives (patients without excipient allergy)								995 (977 to 999)	985 (967 to 989)	896 (879 to 899)	
False positives (patients incorrectly classified as having excipient allergy)								5 (1 to 23)	5 (1 to 23)	4 (1 to 21)	
Question 4: In a patient with a history of an immediate allergic reaction of any severity to a previous mRNA COVID-19 vaccine or its excipients, should allergy skin testing to mRNA COVID-19 vaccines or their excipients be performed to determine if a future dose of vaccine should be withheld? **For any testing agent, combined:** Sn: 0.03 (95%CI 0.00-0.08) Sp: 0.98 (95%CI 0.95 -1) Prevalence 2nd dose reaction: 0.16%								Pre-test probability 0.16%			
True positives (vaccine allergic)	20 studies 93 patients	cohort & case series	not serious	not serious	not serious	serious[e]	none	0 (0 to 0)			⊕⊕⊕◯ Moderate
False negatives (misclassified not allergic)								2 (2 to 2)			
True negatives (not vaccine allergic)	20 studies 485 patients	cohort & case series						976 (944 to 996)			
False positives (misclassified vaccine allergic)								22 (2 to 54)			
For either mRNA vaccine agent: Sn: 0.2(95%CI 0.01-0.52) Sp: 0.97(95%CI 0.9-1) Prevalence 2nd dose reactions: 0.16%								Pre-test probability 0.16%			
True positives (vaccine allergic)	14 studies 14 patients	cohort & case series	not serious	not serious	not serious	very serious[e]	none	0 (0 to 0)			⊕⊕◯◯ Low
False negatives (misclassified not allergic)								2 (2 to 2)			
True negatives (not vaccine allergic)	14 studies 103 patients	cohort & case series						964 (854 to 998) -			
False positives (misclassified vaccine allergic)								34 (0 to 144)			
For polyethylene glycol: Sn: 0.02 (95%CI 0-0.07) Sp: 0.99 (95%CI 0.95-1) Prevalence 2nd dose reactions: 0.16%								Pre-test probability 0.16%			
True positives (vaccine allergic)	19 studies 46 patients	cohort & case series	not serious	not serious	not serious	serious[e]	none	0 (0 to 0)			⊕⊕⊕◯ Moderate
False negatives (misclassified not allergic)								2 (2 to 2)			
True negatives (not vaccine allergic)	19 studies 251 patients	cohort & case series						985 (947 to 998)			
False positives (misclassified vaccine allergic)								13 (0 to 51)			
For polysorbate: Sn: 0.03 (95%CI 0-0.11) Sp: 0.97 (95%CI 0.91-1) Prevalence 2nd dose reactions: 0.16%								Pre-test probability 0.16%			
True positives (vaccine allergic)	13 studies 33 patients	cohort & case series	not serious	not serious	not serious	serious[e]	none	0 (0 to 0)			⊕⊕⊕◯ Moderate

For Questions Related to Diagnostic Testing Question/Outcome Assessed	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability 0.001%	pre-test probability 1%	pre-test probability 10%	
False negatives (misclassified not allergic)	13 studies 131 patients	cohort & case series						2 (2 to 2)			
True negatives (not vaccine allergic)								968 (914 to 998)			
False positives (misclassified vaccine allergic)								30 (0 to 84)			

Explanations: a. These were all case reports, with non-random selection of cases and controls; b. Challenges to the agents were not performed to confirm accuracy of the testing; c. Different agents and methods were used for testing and reported positives from these tests; d. Low numbers of cases were tested to derive these estimates. Bias is suspected as authors are more likely to report severe cases or cases with positive testing, whereas milder cases or cases with negative testing may not be reported; e. While heterogeneity among the studies is low, the n in many studies is low and may have a potential effect

Table 4: Prior Knowledge Gaps and Unmet Needs Regarding COVID-19 Vaccination and Risk of Allergic Reactions

Knowledge Gaps and Unmet Needs	
Knowledge Gaps	**Current Knowledge**
Definitive identification of an immunologic mechanism for reactions	Appears non-IgE mediated in most cases, and may involve Immune Stress Response Reactions (ISRR), though the precise mechanism remains unclear [63]
Determination of a known excipient(s) as an allergen	Unlikely to be anti-PEG and/or Polysorbate IgE in most cases [8, 11, 34]
Determination of risk for receiving COVID-19 vaccines containing an excipient to which a recipient is allergic	Likely low, based on study of PEG-aspargase allergic children, and documented PEG allergic individuals given polysorbate or PEG2000 containing vaccine
Determination of risk in receiving a 2nd dose of a COVID-19 vaccine after an allergic reaction to the 1st dose	Risk of a severe allergic reaction upon re-vaccination is 0.16%; risk of a repeat severe allergic reactions is 4.9%; risk of non-severe symptoms is 13%.[10]
Establish testing sensitivity, specificity, and reliability for use of the vaccine and/or vaccine excipients as a testing reagent	Meta-analysis of test sensitivity for PEG is 2%, for Polysorbate is 3%, for either mRNA vaccine is 19%, and combined for any agent is 3%[11]
Accurate determination of the incidence of allergic reactions, including anaphylaxis	Adjudicated severe allergic reaction rate is 7.91 reactions per million doses; this may be an overestimate as features of ISRR can be classified as anaphylaxis under Brighton criteria[5]
Identification of potential risk factors associated with immediate or delayed reactions	Studies in process which may better determine if allergic co-morbidity, atopy or underlying mast-cell disease increases risk, though the low overall baseline probability of anaphylaxis to the vaccine may complicate such efforts (www.clinicaltrials.gov, NCT04761822)
Effectiveness of testing or how test results influence vaccination hesitancy	Testing appears unnecessary and not predictive of vaccination outcomes or safety[11]
Effectiveness of single versus graded/split dosing for risk-assessment	From data of meta-analysis of 2nd dose reactions, there was no difference in 2nd dose outcomes if the 2nd dose was given as a single or a 2-step graded dose[10, 11]
Necessity of additional post-vaccination observation time for risk-assessment	For patients with a reaction history, a 30 minute observation time is recommended, but not been proven safer than standard wait times, and longer wait time is not cost-effective[5]
Efficacy of mixed vaccine platform schedule	Studies in process, but this regimen appears unnecessary based on allergic risk
Stability of graded /split dosing for mRNA vaccines	Stable for this purpose, but no difference in allergic outcomes if given as single or 2-step graded dose[10,11,64, 65]
Determination of durable immunity conferred by 1st dose of a vaccine to assist in determining risk/reward of additional doses	At least 3 doses are necessary for full immunity; yearly (or potentially more frequent) boosters being proposed. However, estimation of how effective subsequent doses are at providing protection against disease contraction and severe complications is evolving. No concern for immediate severe allergic safety signals have been noted with these additional doses after the primary series. (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/index.html)
Unmet Needs	**Progress to Date**
Consensus on reporting standards for anaphylaxis related to vaccines (Brighton Collaboration Criteria vs. NIAID or WAO criteria	Update to the Brighton Collaboration Criteria published in 2022 (33)
Development of an active surveillance system for vaccine reactions	No published progress
Preparedness and training of personnel at vaccination clinics to properly identify and treat potential anaphylaxis.	Anaphylaxis awareness efforts are ongoing

Consideration for use of placebo dosing, under a shared decision-making paradigm, for determining validity of a reaction in patients with underlying anxiety	Clinical trial underway. The AAAAI/ACAAI Allergy Joint Task Force 2022 Drug Allergy Practice Parameter discusses similar use of placebo dosing for administering drugs in which there is a reported past allergic reaction. (www.clinicaltrials.gov, NCT04761822)
Assessment of vaccine or excipient reactions in resource poor settings (e.g., rural, low/middle income countries)	No published progress. Knowledge gap as to what rate of reactions may be acceptable in such settings vs. what would be tolerated or handled in settings with better resources

Figure 1:

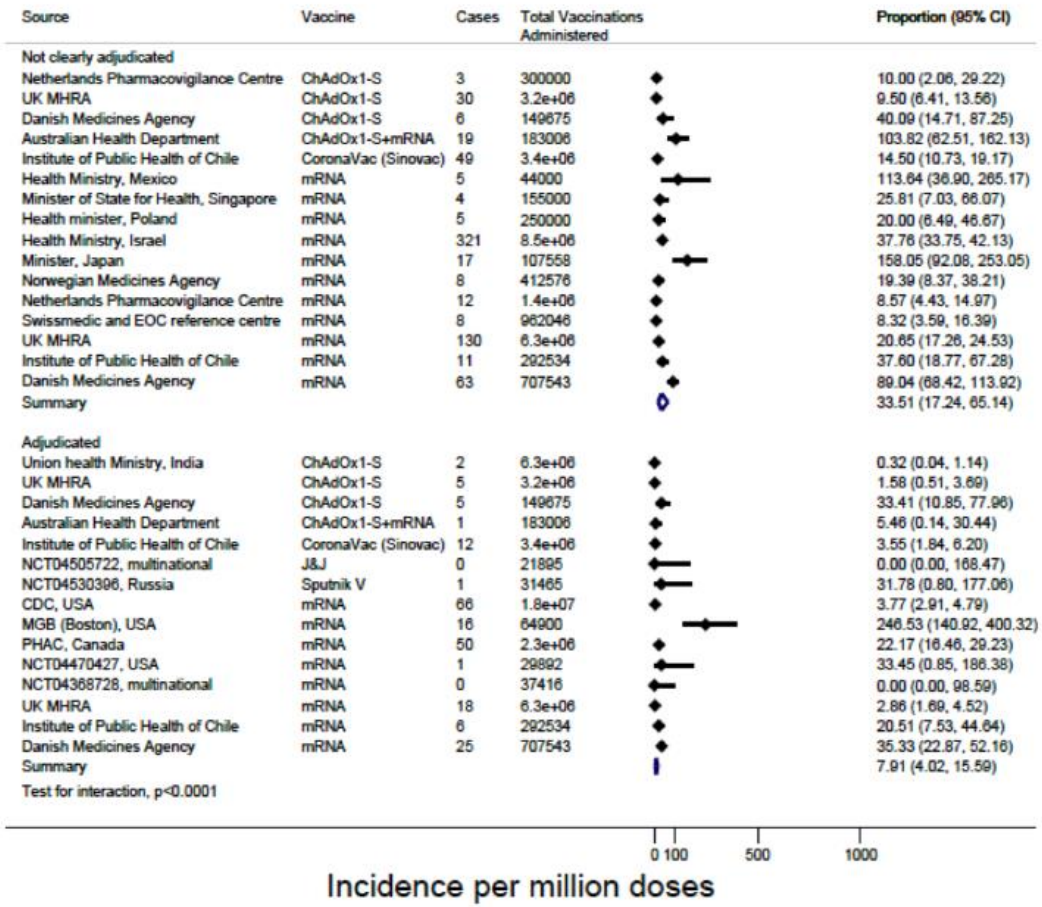

Source
Vaccine
Cases
Total Vaccinations Administered
Proportion (95% CI)
Not clearly adjudicated
Netherlands Pharmacovigilance Centre ChAdOx1-S 3 300000 10.00 (2.06, 29.22)
UK MHRA ChAdOx1-S 30 3.2e+06 9.50 (6.41, 13.56)
Danish Medicines Agency ChAdOx1-S 6 149675 40.09 (14.71, 87.25)
Australian Health Department ChAdOx1-S+mRNA 19 183006 103.82 (62.51, 162.13)
Institute of Public Health of Chile CoronaVac (Sinovac) 49 3.4e+06 14.50 (10.73, 19.17)
Health Ministry, Mexico mRNA 5 44000 113.64 (36.90, 265.17)
Minister of State for Health, Singapore mRNA 4 155000 25.81 (7.03, 66.07)
Health minister, Poland mRNA 5 250000 20.00 (6.49, 46.67)
Health Ministry, Israel mRNA 321 8.5e+06 37.76 (33.75, 42.13)
Minister, Japan mRNA 17 107558 158.05 (92.08, 253.05)
Norwegian Medicines Agency mRNA 8 412576 19.39 (8.37, 38.21)
Netherlands Pharmacovigilance Centre mRNA 12 1.4e+06 8.57 (4.43, 14.97)
Swissmedic and EOC reference centre mRNA 8 962046 8.32 (3.59, 16.39)
UK MHRA mRNA 130 6.3e+06 20.65 (17.26, 24.53)
Institute of Public Health of Chile mRNA 11 292534 37.60 (18.77, 67.28)
Danish Medicines Agency mRNA 63 707543 89.04 (68.42, 113.92)
Summary 33.51 (17.24, 65.14)
Adjudicated
Union health Ministry, India ChAdOx1-S 2 6.3e+06 0.32 (0.04, 1.14)
UK MHRA ChAdOx1-S 5 3.2e+06 1.58 (0.51, 3.69)
Danish Medicines Agency ChAdOx1-S 5 149675 33.41 (10.85, 77.96)
Australian Health Department ChAdOx1-S+mRNA 1 183006 5.46 (0.14, 30.44)
Institute of Public Health of Chile CoronaVac (Sinovac) 12 3.4e+06 3.55 (1.84, 6.20)
NCT04505722, multinational J&J 0 21895 0.00 (0.00, 168.47)
NCT04530396, Russia Sputnik V 1 31465 31.78 (0.80, 177.06)
CDC, USA mRNA 66 1.8e+07 3.77 (2.91, 4.79)
MGB (Boston), USA mRNA 16 64900 246.53 (140.92, 400.32)
PHAC, Canada mRNA 50 2.3e+06 22.17 (16.46, 29.23)
NCT04470427, USA mRNA 1 29892 33.45 (0.85, 186.38)
NCT04368728, multinational mRNA 0 37416 0.00 (0.00, 98.59)
UK MHRA mRNA 18 6.3e+06 2.86 (1.69, 4.52)
Institute of Public Health of Chile mRNA 6 292534 20.51 (7.53, 44.64)
Danish Medicines Agency mRNA 25 707543 35.33 (22.87, 52.16)
Summary 7.91 (4.02, 15.59)
Test for interaction, p<0.0001
0 100 500 1000
Incidence per million doses

Figure 2

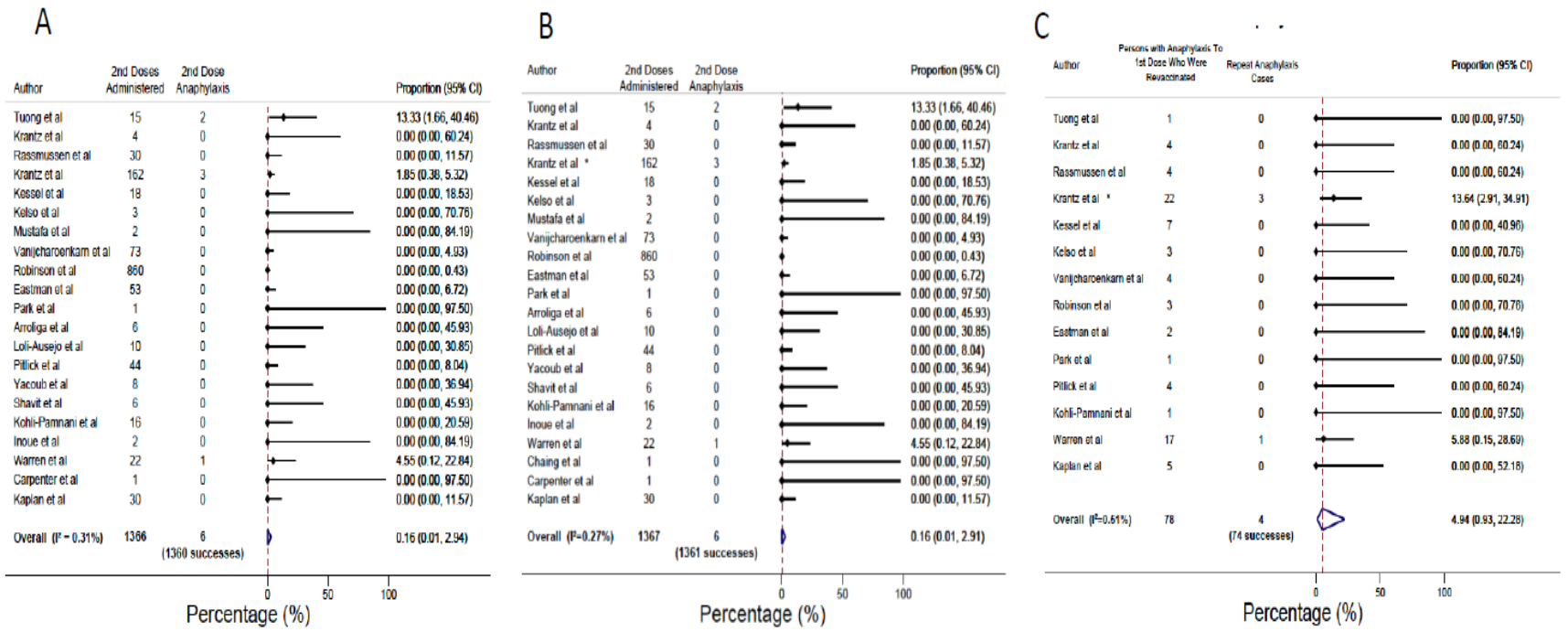
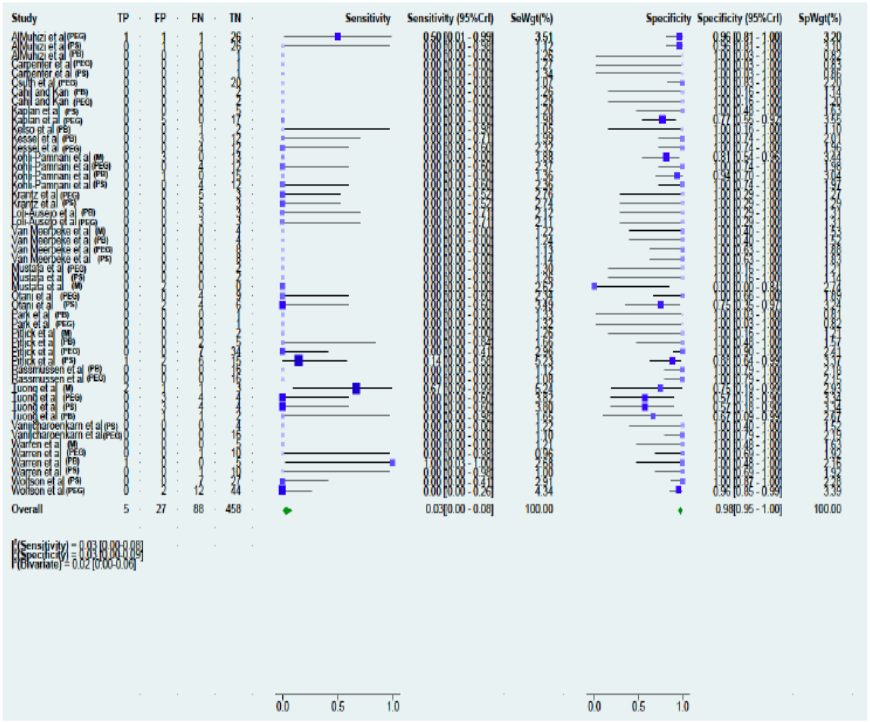
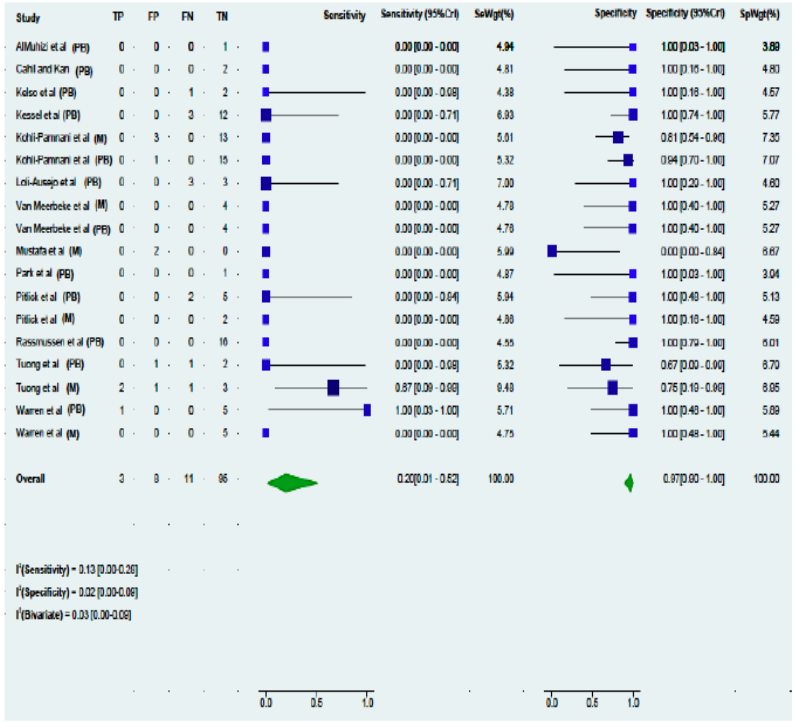

A
Author
2nd Doses Administered
2nd Dose Anaphylaxis
Proportion (95% CI)
Tuong et al 15 2 13.33 (1.66, 40.46)
Krantz et al 4 0 0.00 (0.00, 60.24)
Rassmussen et al 30 0 0.00 (0.00, 11.57)
Krantz et al 162 3 1.85 (0.38, 5.32)
Kessel et al 18 0 0.00 (0.00, 18.53)
Kelso et al 3 0 0.00 (0.00, 70.76)
Mustafa et al 2 0 0.00 (0.00, 84.19)
Vanijcharoenkarn et al 73 0 0.00 (0.00, 4.93)
Robinson et al 860 0 0.00 (0.00, 0.43)
Eastman et al 53 0 0.00 (0.00, 6.72)
Park et al 1 0 0.00 (0.00, 97.50)
Arroliga et al 6 0 0.00 (0.00, 45.93)
Loli-Ausejo et al 10 0 0.00 (0.00, 30.85)
Pitlick et al 44 0 0.00 (0.00, 8.04)
Yacoub et al 8 0 0.00 (0.00, 36.94)
Shavit et al 6 0 0.00 (0.00, 45.93)
Kohli-Pamnani et al 16 0 0.00 (0.00, 20.59)
Inoue et al 2 0 0.00 (0.00, 84.19)
Warren et al 22 1 4.55 (0.12, 22.84)
Carpenter et al 1 0 0.00 (0.00, 97.50)
Kaplan et al 30 0 0.00 (0.00, 11.57)
Overall (I² = 0.31%) 1366 6 (1360 successes) 0.16 (0.01, 2.94)
0 50 100
Percentage (%)
B
Author
2nd Doses Administered
2nd Dose Anaphylaxis
Proportion (95% CI)
Tuong et al 15 2 13.33 (1.66, 40.46)
Krantz et al 4 0 0.00 (0.00, 60.24)
Rassmussen et al 30 0 0.00 (0.00, 11.57)
Krantz et al * 162 3 1.85 (0.38, 5.32)
Kessel et al 18 0 0.00 (0.00, 18.53)
Kelso et al 3 0 0.00 (0.00, 70.76)
Mustafa et al 2 0 0.00 (0.00, 84.19)
Vanijcharoenkarn et al 73 0 0.00 (0.00, 4.93)
Robinson et al 860 0 0.00 (0.00, 0.43)
Eastman et al 53 0 0.00 (0.00, 6.72)
Park et al 1 0 0.00 (0.00, 97.50)
Arroliga et al 6 0 0.00 (0.00, 45.93)
Loli-Ausejo et al 10 0 0.00 (0.00, 30.85)
Pitlick et al 44 0 0.00 (0.00, 8.04)
Yacoub et al 8 0 0.00 (0.00, 36.94)
Shavit et al 6 0 0.00 (0.00, 45.93)
Kohli-Pamnani et al 16 0 0.00 (0.00, 20.59)
Inoue et al 2 0 0.00 (0.00, 84.19)
Warren et al 22 1 4.55 (0.12, 22.84)
Chaing et al 1 0 0.00 (0.00, 97.50)
Carpenter et al 1 0 0.00 (0.00, 97.50)
Kaplan et al 30 0 0.00 (0.00, 11.57)
Overall (I²=0.27%) 1367 6 (1361 successes) 0.16 (0.01, 2.91)
0 50 100
Percentage (%)
C
Author
Persons with Anaphylaxis To 1st Dose Who Were Revaccinated
Repeat Anaphylaxis Cases
Proportion (95% CI)
Tuong et al 1 0 0.00 (0.00, 97.50)
Krantz et al 4 0 0.00 (0.00, 60.24)
Rassmussen et al 4 0 0.00 (0.00, 60.24)
Krantz et al * 22 3 13.64 (2.91, 34.91)
Kessel et al 7 0 0.00 (0.00, 40.96)
Kelso et al 3 0 0.00 (0.00, 70.76)
Vanijcharoenkarn et al 4 0 0.00 (0.00, 60.24)
Robinson et al 3 0 0.00 (0.00, 70.76)
Eastman et al 2 0 0.00 (0.00, 84.19)
Park et al 1 0 0.00 (0.00, 97.50)
Pitlick et al 4 0 0.00 (0.00, 60.24)
Kohli-Pamnani et al 1 0 0.00 (0.00, 97.50)
Warren et al 17 1 5.88 (0.15, 28.69)
Kaplan et al 5 0 0.00 (0.00, 52.18)
Overall (I²=0.61%) 78 4 (74 successes) 4.94 (0.93, 22.28)
0 50 100
Percentage (%)

Figure 3

A



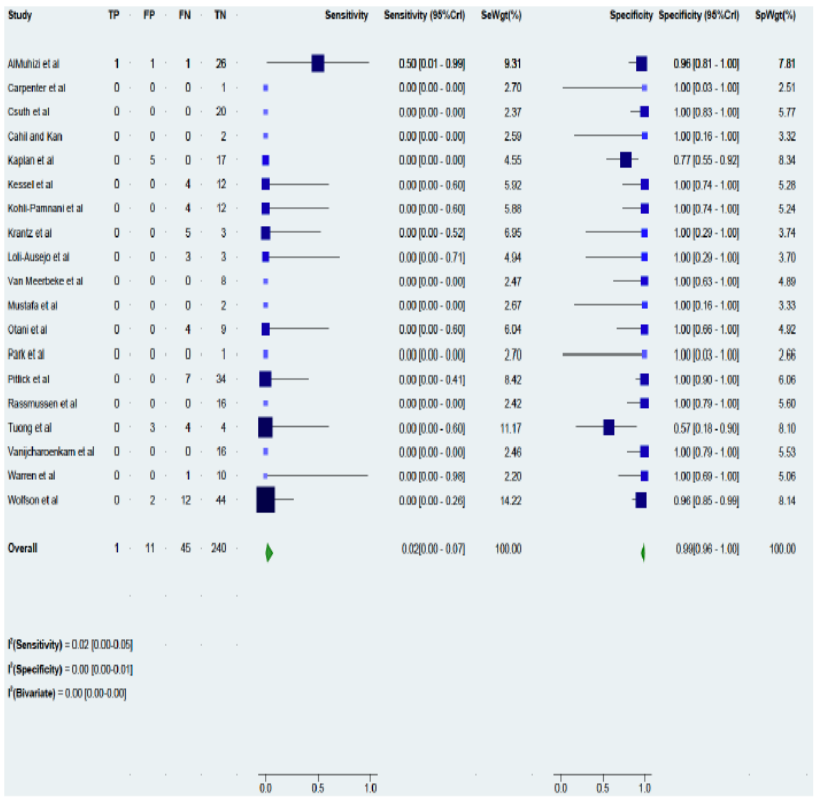
B



(I'm working on a higher resolution image for this)

Figure 4

A


Study TP FP FN TN Sensitivity Sensitivity (95%CrI) SeWgt(%) Specificity Specificity (95%CrI) SpWgt(%)
AlMuhizi et al 1 1 1 26 0.50 [0.01 - 0.99] 9.31 0.96 [0.81 - 1.00] 7.81
Carpenter et al 0 0 0 1 0.00 [0.00 - 0.00] 2.70 1.00 [0.03 - 1.00] 2.51
Csuth et al 0 0 0 20 0.00 [0.00 - 0.00] 2.37 1.00 [0.83 - 1.00] 5.77
Cahil and Kan 0 0 0 2 0.00 [0.00 - 0.00] 2.59 1.00 [0.16 - 1.00] 3.32
Kaplan et al 0 5 0 17 0.00 [0.00 - 0.00] 4.55 0.77 [0.55 - 0.92] 8.34
Kessel et al 0 0 4 12 0.00 [0.00 - 0.60] 5.92 1.00 [0.74 - 1.00] 5.28
Kohli-Pamnani et al 0 0 4 12 0.00 [0.00 - 0.60] 5.88 1.00 [0.74 - 1.00] 5.24
Krantz et al 0 0 5 3 0.00 [0.00 - 0.52] 6.95 1.00 [0.29 - 1.00] 3.74
Loli-Ausejo et al 0 0 3 3 0.00 [0.00 - 0.71] 4.94 1.00 [0.29 - 1.00] 3.70
Van Meerbeke et al 0 0 0 8 0.00 [0.00 - 0.00] 2.47 1.00 [0.63 - 1.00] 4.89
Mustafa et al 0 0 0 2 0.00 [0.00 - 0.00] 2.67 1.00 [0.16 - 1.00] 3.33
Otani et al 0 0 4 9 0.00 [0.00 - 0.60] 6.04 1.00 [0.66 - 1.00] 4.92
Park et al 0 0 0 1 0.00 [0.00 - 0.00] 2.70 1.00 [0.03 - 1.00] 2.66
Pitlick et al 0 0 7 34 0.00 [0.00 - 0.41] 8.42 1.00 [0.90 - 1.00] 6.06
Rassmussen et al 0 0 0 16 0.00 [0.00 - 0.00] 2.42 1.00 [0.79 - 1.00] 5.60
Tuong et al 0 3 4 4 0.00 [0.00 - 0.60] 11.17 0.57 [0.18 - 0.90] 8.10
Vanijcharoenkarn et al 0 0 0 16 0.00 [0.00 - 0.00] 2.46 1.00 [0.79 - 1.00] 5.53
Warren et al 0 0 1 10 0.00 [0.00 - 0.98] 2.20 1.00 [0.69 - 1.00] 5.06
Wolfson et al 0 2 12 44 0.00 [0.00 - 0.26] 14.22 0.96 [0.85 - 0.99] 8.14
Overall 1 11 45 240 0.02[0.00 - 0.07] 100.00 0.99[0.96 - 1.00] 100.00
I²(Sensitivity) = 0.02 [0.00-0.05]
I²(Specificity) = 0.00 [0.00-0.01]
I²(Bivariate) = 0.00 [0.00-0.00]
0.0 0.5 1.0
0.0 0.5 1.0

B

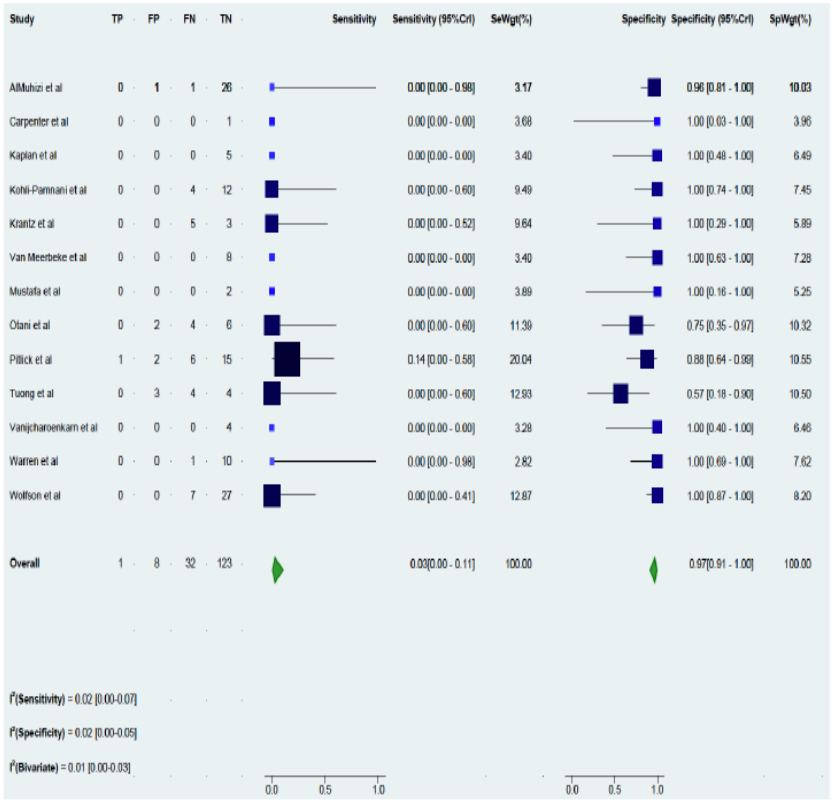

Study TP FP FN TN Sensitivity Sensitivity (95%CrI) SeWgt(%) Specificity Specificity (95%CrI) SpWgt(%)
AlMuhizi et al 0 1 1 26 0.00 [0.00 - 0.98] 3.17 0.96 [0.81 - 1.00] 10.03
Carpenter et al 0 0 0 1 0.00 [0.00 - 0.00] 3.68 1.00 [0.03 - 1.00] 3.96
Kaplan et al 0 0 0 5 0.00 [0.00 - 0.00] 3.40 1.00 [0.48 - 1.00] 6.49
Kohli-Pamnani et al 0 0 4 12 0.00 [0.00 - 0.60] 9.49 1.00 [0.74 - 1.00] 7.45
Krantz et al 0 0 5 3 0.00 [0.00 - 0.52] 9.64 1.00 [0.29 - 1.00] 5.89
Van Meerbeke et al 0 0 0 8 0.00 [0.00 - 0.00] 3.40 1.00 [0.63 - 1.00] 7.28
Mustafa et al 0 0 0 2 0.00 [0.00 - 0.00] 3.89 1.00 [0.16 - 1.00] 5.25
Otani et al 0 2 4 6 0.00 [0.00 - 0.60] 11.39 0.75 [0.35 - 0.97] 10.32
Pitlick et al 1 2 6 15 0.14 [0.00 - 0.58] 20.04 0.88 [0.64 - 0.99] 10.55
Tuong et al 0 3 4 4 0.00 [0.00 - 0.60] 12.93 0.57 [0.18 - 0.90] 10.50
Vanijcharoenkarn et al 0 0 0 4 0.00 [0.00 - 0.00] 3.28 1.00 [0.40 - 1.00] 6.46
Warren et al 0 0 1 10 0.00 [0.00 - 0.98] 2.82 1.00 [0.69 - 1.00] 7.62
Wolfson et al 0 0 7 27 0.00 [0.00 - 0.41] 12.87 1.00 [0.87 - 1.00] 8.20
Overall 1 8 32 123 0.03[0.00 - 0.11] 100.00 0.97[0.91 - 1.00] 100.00
I²(Sensitivity) = 0.02 [0.00-0.07]
I²(Specificity) = 0.02 [0.00-0.05]
I²(Bivariate) = 0.01 [0.00-0.03]
0.0 0.5 1.0
0.0 0.5 1.0

Table E1: The GRADE System of Recommendations and Evidence Certainty

Strength of Recommendation		
	For the Patient	For the Clinician
Strong	Most individuals in this situation would prefer the recommended course of action and only a small proportion would not.	The attending provider should strongly consider the recommended course of action as a first-line management. Formal decision aids may have less of a role to help individuals make decisions consistent with their values and preferences.
Conditional	The majority of individuals in this situation would prefer the suggested course of action, but many would not.	Different choices may be appropriate for different patients. Decision aids may be useful in helping individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
Certainty in estimates of effect / quality rating both for outcome and for an entire evidence base as it pertains to a PICO		
High	There is high confidence that the true effect lies close to that of the estimate of the effect.	
Moderate	There is moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	
Low	There is limited confidence in the effect estimate. The true effect may be substantially different from the estimate of the effect.	
Very Low	There is very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect	

E Table 1: Risk of Bias Ratings for Meta-Analyzed Questions

Question 1 (Joanna Briggs Institute Tool)

Study	Was the sample frame appropriate to address the target population?	Were study participants sampled in an appropriate way?	Was the sample size adequate?	Were the study subjects and the setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all participants?	Was there appropriate statistical analysis?	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Overall RoB
UK MHRA	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	No/probably no	Unclear	Yes/Probably yes	Yes/Probably yes	HIGH
UK MHRA	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	No/probably no	Unclear	Yes/Probably yes	Yes/Probably yes	HIGH
UK MHRA	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	LOW
UK MHRA	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	LOW
Institute of Public Health of Chile	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	LOW
Institute of Public Health of Chile	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	LOW
Institute of Public Health of Chile	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	No/probably no	Unclear	Yes/Probably yes	Yes/Probably yes	HIGH
Institute of Public Health of Chile	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	No/probably no	Unclear	Yes/Probably yes	Yes/Probably yes	HIGH
Australia Health Department	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	No/probably no	Unclear	Yes/Probably yes	Yes/Probably yes	HIGH
Australia Health Department	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	LOW
Mexico Heath Ministry	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	No/probably no	Unclear	Yes/Probably yes	Yes/Probably yes	HIGH
Singapore Health Ministry	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	No/probably no	Unclear	Yes/Probably yes	Yes/Probably yes	HIGH
USA CDC VAERS	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	LOW
MGB (Boston)	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	No/probably no	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	No/probably no	HIGH
India Health Ministry	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	LOW
Canada PHAC	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	LOW
Poland Health Minestry	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	No/probably no	Unclear	Yes/Probably yes	Yes/Probably yes	HIGH
USA NCT04405076	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
Australia and the United States NCT04368988	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
USA NCT04537208	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
South Africa NCT04444674	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
South Africa NCT04533399	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH

USA NCT04436276	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
USA NCT04470427	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	LOW
Australia NCT04495933	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
China NCT04412538	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
India NCT04471519	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
India NCT04471519	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
Multiple NCT04505722	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	LOW
Australia NCT04368988	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
Russia NCT04530396	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	LOW
Multiple NCT04368728	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	LOW
China NCT04412538	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
Australia NCT04405908	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
UK, Brazil and South Africa Multiple registrations	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
USA NCT04368728	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
USA NCT04368728	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
Canada NCT04450004	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
China NCT04383574	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
China ChiCTR2000032459	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
China ChiCTR2000031809	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
China NCT04466085	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
China NCT04445194	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
China NCT04352608	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
China NCT04341389	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	HIGH
Israel Health Minister	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	No/probably no	Unclear	Yes/Probably yes	Yes/Probably yes	HIGH
Japan Health Minister	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	No/probably no	Unclear	Yes/Probably yes	Yes/Probably yes	HIGH
Norwegian Medicines Agency	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	No/probably no	Unclear	Yes/Probably yes	Yes/Probably yes	HIGH
Romania	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	No/probably no	Unclear	Yes/Probably yes	Yes/Probably yes	HIGH
Romania	Yes/Probably yes	Yes/Probably yes	No/probably no	Not applicable	Yes/Probably yes	No/probably no	Unclear	Yes/Probably yes	Yes/Probably yes	HIGH
Netherlands Pharmacovigilance Centre	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	No/probably no	Unclear	Yes/Probably yes	Yes/Probably yes	HIGH
Netherlands Pharmacovigilance Centre	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	No/probably no	Unclear	Yes/Probably yes	Yes/Probably yes	HIGH

Swissmedic	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	No/probably no	Unclear	Yes/Probably yes	Yes/Probably yes	HIGH
Danish Medicines Agency	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	LOW
Danish Medicines Agency	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	LOW
Danish Medicines Agency	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	No/probably no	Unclear	Yes/Probably yes	Yes/Probably yes	HIGH
Danish	Yes/Probably yes	Yes/Probably yes	Yes/Probably yes	Not applicable	Yes/Probably yes	No/probably no	Unclear	Yes/Probably yes	Yes/Probably yes	HIGH

Question 2 (QADAS-2 tool)

Author	Agent	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Setullarnay 2000	PEG	High	High	High	High	High	High	High
Stone 2019	PEG	High	High	High	High	High	High	High
Wenande 2016	PEG	High	High	High	High	High	High	High
Sanchez Moreno 2015	PEG	High	High	High	High	High	High	High
Extremera Ortega 2018	PEG	High	High	High	High	High	High	High
Shah 2013	PEG	High	High	High	High	High	High	High
Pizzimenti 2014	PEG	High	High	High	High	High	High	High
Kim 2018	PEG	High	High	High	High	High	High	High
Sohy 2008	PEG	High	High	High	High	High	High	High
Giangrande 2019	PEG	High	High	High	High	High	High	High
Bommarito 2011	PEG	High	High	High	High	High	High	High
Hryr 2006	PEG	High	High	High	High	High	High	High
JoverCerda 2019	PEG	High	High	High	High	High	High	High
AntonGirones 2008	PEG	High	High	High	High	High	High	High
Badiu 2015	PEG	High	High	High	High	High	High	High
Perez-Perez 2011	PS	High	High	High	High	High	High	High
Wagner 2018	PS	High	High	High	High	High	High	High
Badiu 2012	PS	High	High	High	High	High	High	High
Shelly 1995	PS	High	High	High	High	High	High	High
Coors 2005	PS	High	High	High	High	High	High	High
Limaye 2002	PS	High	High	High	High	High	High	High

PEG= polyethylene glycol
PS= polysorbate

Question 3 (Joanna Briggs Institute Tool)

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[29]
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[e17]	Mustafa et al[e18]	Kelso et al[e19]	Chiang et al[e20]	Warren et al[e21]	Carpenter et al[e22]
Were patient's demographic characteristics clearly described?	Yes	No	No	Yes	Yes	Yes
Was the patient's history clearly described and presented as a timeline?	Yes	Yes	Yes	Yes	Yes	No
Was the current clinical condition of the patient on presentation clearly described?	Yes	Yes	Yes	Yes	No	Yes
Were diagnostic tests or assessment methods and the results clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
Was the intervention(s) or treatment procedure(s) clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
Was the post-intervention clinical condition clearly described?	Yes	Yes	Yes	Yes	No	Yes
Were adverse events (harms) or unanticipated events identified and described?	Yes	Yes	Yes	Yes	Yes	Yes
Does the case report provide takeaway lessons?	Yes	Yes	Yes	Yes	Yes	Yes

Overall Appraisal	**Include**	**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 Question 3

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.

E2. Rasmussen TH, Mortz CG, Georgsen TK, Rasmussen HM, Kjaer HF, Bindslev-Jensen C. Patients with suspected allergic reactions to COVID-19 vaccines can be safely revaccinated after diagnostic work-up. *Clin Transl Allergy*. Jul 2021;11(5):e12044. doi:10.1002/clt2.12044

E3. Krantz MS, Bruusgaard-Mouritsen MA, Koo G, Phillips EJ, Stone CA, Jr., Garvey LH. Anaphylaxis to the first dose of mRNA SARS-CoV-2 vaccines: Don't give up on the second dose! *Allergy*. Sep 2021;76(9):2916-2920. doi:10.1111/all.14958

E4. Krantz MS, Kwah JH, Stone CA, Jr., et al. Safety Evaluation of the Second Dose of Messenger RNA COVID-19 Vaccines in Patients With Immediate Reactions to the First Dose. *JAMA Intern Med*. Jul 26 2021;doi:10.1001/jamainternmed.2021.3779

E5. Wolfson AR, Robinson LB, Li L, et al. First-Dose mRNA COVID-19 Vaccine Allergic Reactions: Limited Role for Excipient Skin Testing. *J Allergy Clin Immunol Pract*. Sep 2021;9(9):3308-3320 e3. doi:10.1016/j.jaip.2021.06.010

E6. Kessel A, Bamberger E, Nachshon L, Rosman Y, Confino-Cohen R, Elizur A. Safe administration of the Pfizer-BioNtTech COVID-19 vaccine following an immediate reaction to the first dose. *Allergy*. Aug 9 2021;doi:10.1111/all.15038

E7. Pitlick MM, Sitek AN, Kinate SA, Joshi AY, Park MA. Polyethylene glycol and polysorbate skin testing in the evaluation of coronavirus disease 2019 vaccine reactions: Early report. *Ann Allergy Asthma Immunol*. Jun 2021;126(6):735-738. doi:10.1016/j.anai.2021.03.012

E8. Vanijcharoenkarn K, Lee FE, Martin L, Shih J, Sexton ME, Kuruvilla ME. Immediate reactions following the first dose of the SARS-CoV2 mRNA vaccines do not preclude second dose administration. *Clin Infect Dis*. May 14 2021;doi:10.1093/cid/ciab448

E9. Robinson LB, Landman AB, Shenoy ES, et al. Allergic symptoms after mRNA COVID-19 vaccination and risk of incomplete vaccination. *J Allergy Clin Immunol Pract*. Aug 2021;9(8):3200-3202 e1. doi:10.1016/j.jaip.2021.05.031

E10. Eastman J, Holsworth A, Kelbel T, Pebbles T, Hartog N. Cohort experience of 2nd mRNA vaccine dose tolerance after an initial dose reaction. Ann Allergy Asthma Immunol 2021; In press.

E11. Arroliga ME, Dhanani K, Arroliga AC, et al. Allergic reactions and adverse events associated with administration of mRNA-based vaccines. A health-care system experience. *Allergy Asthma Proc*. Sep 1 2021;42(5):395-399. doi:10.2500/aap.2021.42.210069

E12. Loli-Ausejo D, Gonzalez de Abreu JM, Fiandor A, et al. Allergic reactions after administration of pfizer-biontech covid-19 vaccine to healthcare workers at a tertiary hospital. *J Investig Allergol Clin Immunol*. Sep 1 2021:0. doi:10.18176/jiaci.0751

E13. Yacoub MR, Cucca V, Asperti C, et al. Efficacy of a rational algorithm to assess allergy risk in patients receiving the BNT162b2 vaccine. *Vaccine*. Sep 28 2021;doi:10.1016/j.vaccine.2021.09.048

E14. Shavit R, Maoz-Segal R, Iancovici-Kidon M, et al. Prevalence of Allergic Reactions After Pfizer-BioNTech COVID-19 Vaccination Among Adults With High Allergy Risk. *JAMA Netw Open*. Aug 2 2021;4(8):e2122255. doi:10.1001/jamanetworkopen.2021.22255

E15. Kohli-Pamnani A, Zapata K, Gibson T, Kwittken PL. Coronavirus disease 2019 vaccine hypersensitivity evaluated with vaccine and excipient allergy skin testing. *Ann Allergy Asthma Immunol*. Sep 3 2021;doi:10.1016/j.anai.2021.08.417

E16. Inoue S, Igarashi A, Morikane K, et al. Adverse reactions to BNT162b2 mRNA COVID-19 vaccine in medical staffs with a history of allergy. *medRxiv*. 2021:2021.09.13.21263473. doi:10.1101/2021.09.13.21263473

E17. Park HJ, Montgomery JR, Boggs NA. Anaphylaxis After the Covid-19 Vaccine in a Patient With Cholinergic Urticaria. *Mil Med*. Apr 14 2021;doi:10.1093/milmed/usab138

E18. Mustafa SS, Ramsey A, Staicu ML. Administration of a Second Dose of the Moderna COVID-19 Vaccine After an Immediate Hypersensitivity Reaction With the First Dose: Two Case Reports. *Ann Intern Med*. Aug 2021;174(8):1177-1178. doi:10.7326/L21-0104

E19. Kelso JM. Misdiagnosis of systemic allergic reactions to mRNA COVID-19 vaccines. *Ann Allergy Asthma Immunol*. Jul 2021;127(1):133-134. doi:10.1016/j.anai.2021.03.024

E20. Chiang V, Mong PPT, Chan EKK, Au EYL, Li PH. Caution against injudicious vaccine allergy skin tests: Adverse reactions after intradermal COVID-19 vaccine testing. *Contact Dermatitis*. Sep 21 2021;doi:10.1111/cod.13977

E21. Warren CM, Snow TT, Lee AS, et al. Assessment of Allergic and Anaphylactic Reactions to mRNA COVID-19 Vaccines With Confirmatory Testing in a US Regional Health System. *JAMA Netw Open*. Sep 1 2021;4(9):e2125524. doi:10.1001/jamanetworkopen.2021.25524

E22. Carpenter T, Konig J, Hochfelder J, Siegel S, Gans M. Polyethylene glycol and polysorbate testing in twelve patients prior to or after COVID-19 vaccine administration. Ann Allergy Asthma Immunol. Oct 11 2021;doi:10.1016/j.anai.2021.10.009

E23: Kaplan B, Farzan S, Coscia G, et al. Allergic reactions to coronavirus disease 2019 vaccines and addressing vaccine hesitancy: Northwell Health experience. *Ann Allergy Asthma Immunol*. Oct 24 2021;doi:10.1016/j.anai.2021.10.019

Question 4 (QADAS-2 Tool)

	Bias				Applicability			
	Patient Selection	**Index Test**	**Reference Standard**	**Flow and Timing**	**Patient Selection**	**Index Test**	**Reference Standard**	**Overall**
Tuong et al [E1]	High	Unclear	Unclear	Low	Low	Low	Low	Unclear
Krantz et al [E2]	Unclear	Unclear	Unclear	Low	Low	Low	Low	Unclear
Rassmussen et al [E3]	Low	Unclear	Unclear	Low	Low	Low	Low	Unclear
Wolfson et al [E4]	Unclear	Unclear	Unclear	Low	Low	Low	Low	Unclear
Kessel et al [E5]	Unclear	Unclear	Unclear	Low	Low	Low	Low	Unclear
Kelso et al [E6]	High	Unclear	Unclear	Low	Low	Low	Low	Unclear
Mustafa et al [E7]	High	Unclear	Unclear	Low	Low	Low	Low	Unclear
Vanijcharoenkarn et al [E8]	High	Unclear	Unclear	Low	Low	Low	Low	Unclear
Park et al [E9]	High	Unclear	Unclear	Low	Low	Low	Low	Unclear
Loli-Ausejo et al [E10]	Unclear	Unclear	Unclear	Low	Low	Low	Low	Unclear
Pitlick et al [E11]	Unclear	Unclear	Unclear	Low	Low	Low	Low	Unclear
Kohli-Pamnani et al [E12]	High	Unclear	Unclear	Low	Low	Low	Low	Unclear
Warren et al [E13]	Unclear	Unclear	Unclear	Low	Low	Low	Low	Unclear
Carpenter et al [E14]	High	Unclear	Unclear	Low	Low	Low	Low	Unclear
Kaplan et al [E15]	High	Unclear	Unclear	Low	Low	Low	Low	Unclear
AlMuhizi et al [E16]	Unclear	Unclear	Unclear	Low	Low	Low	Low	Unclear
Van Meerbeke et al [E17]	High	Unclear	Unclear	Low	Low	Low	Low	Unclear
Otani et al [E18]	Unclear	Unclear	Unclear	Low	Low	Low	Low	Unclear
Csuth et al [E19]	High	Unclear	Unclear	Low	Low	Low	Low	Unclear
Cahil and Kan [E20]	High	Unclear	Unclear	Low	Low	Low	Low	Unclear

Any study not testing to both vaccines and reagent was assigned high bias. All case reports were considered high risk of bias. Overall ranking of low necessitated no more than one category rated high. Overall ranking of high assigned if $\geq$2 category were high, and unclear if $\geq$2 were unclear.

E References Question 4

E1. Tuong LAC, Capucilli P, Staicu M, Ramsey A, Walsth E, Mustafa SS. Graded Administration of Second Dose of Moderna and Pfizer-BioNTech COVID-19
mRNA Vaccine in Patients with Hypersensitivity to First Dose. Open Forum Infectious Diseases 2021; In Press.
E2. Krantz MS, Bruusgaard-Mouritsen MA, Koo G, Phillips EJ, Stone CA, Jr., Garvey LH. Anaphylaxis to the first dose of mRNA SARS-CoV-2 vaccines: Don't give up on the second dose! *Allergy*. Sep 2021;76(9):2916-2920. doi:10.1111/all.14958
E3. Rasmussen TH, Mortz CG, Georgsen TK, Rasmussen HM, Kjaer HF, Bindslev-Jensen C. Patients with suspected allergic reactions to COVID-19 vaccines can be safely revaccinated after diagnostic work-up. *Clin Transl Allergy*. Jul 2021;11(5):e12044. doi:10.1002/clt2.12044
E4. Wolfson AR, Robinson LB, Li L, et al. First-Dose mRNA COVID-19 Vaccine Allergic Reactions: Limited Role for Excipient Skin Testing. *J Allergy Clin Immunol Pract*. Sep 2021;9(9):3308-3320 e3. doi:10.1016/j.jaip.2021.06.010
E5. Kessel A, Bamberger E, Nachshon L, Rosman Y, Confino-Cohen R, Elizur A. Safe administration of the Pfizer-BioNtTech COVID-19 vaccine following an immediate reaction to the first dose. *Allergy*. Aug 9 2021;doi:10.1111/all.15038
E6. Kelso JM. Misdiagnosis of systemic allergic reactions to mRNA COVID-19 vaccines. *Ann Allergy Asthma Immunol*. Jul 2021;127(1):133-134. doi:10.1016/j.anai.2021.03.024
E7. Mustafa SS, Ramsey A, Staicu ML. Administration of a Second Dose of the Moderna COVID-19 Vaccine After an Immediate Hypersensitivity Reaction With the First Dose: Two Case Reports. *Ann Intern Med*. Aug 2021;174(8):1177-1178. doi:10.7326/L21-0104
E8. Vanijcharoenkarn K, Lee FE, Martin L, Shih J, Sexton ME, Kuruvilla ME. Immediate reactions following the first dose of the SARS-CoV2 mRNA vaccines do not preclude second dose administration. *Clin Infect Dis*. May 14 2021;doi:10.1093/cid/ciab448
E9. Park HJ, Montgomery JR, Boggs NA. Anaphylaxis After the Covid-19 Vaccine in a Patient With Cholinergic Urticaria. *Mil Med*. Apr 14 2021;doi:10.1093/milmed/usab138
E10. Loli-Ausejo D, Gonzalez de Abreu JM, Fiandor A, et al. Allergic reactions after administration of pfizer-biontech covid-19 vaccine to healthcare workers at a tertiary hospital. *J Investig Allergol Clin Immunol*. Sep 1 2021:0. doi:10.18176/jiaci.0751
E11. Pitlick MM, Sitek AN, Kinate SA, Joshi AY, Park MA. Polyethylene glycol and polysorbate skin testing in the evaluation of coronavirus disease 2019 vaccine reactions: Early report. *Ann Allergy Asthma Immunol*. Jun 2021;126(6):735-738. doi:10.1016/j.anai.2021.03.012
E12. Kohli-Pamnani A, Zapata K, Gibson T, Kwittken PL. Coronavirus disease 2019 vaccine hypersensitivity evaluated with vaccine and excipient allergy skin testing. *Ann Allergy Asthma Immunol*. Sep 3 2021;doi:10.1016/j.anai.2021.08.417
E13. Warren CM, Snow TT, Lee AS, et al. Assessment of Allergic and Anaphylactic Reactions to mRNA COVID-19 Vaccines With Confirmatory Testing in a US Regional Health System. *JAMA Netw Open*. Sep 1 2021;4(9):e2125524. doi:10.1001/jamanetworkopen.2021.25524

E14 Carpenter T, Konig J, Hochfelder J, Siegel S, Gans M. Polyethylene glycol and polysorbate testing in twelve patients prior to or after COVID-19 vaccine administration. *Ann Allergy Asthma Immunol*. Oct 11 2021;doi:10.1016/j.anai.2021.10.009
E15. Kaplan B, Farzan S, Coscia G, et al. Allergic reactions to coronavirus disease 2019 vaccines and addressing vaccine hesitancy: Northwell Health experience. *Ann Allergy Asthma Immunol*. Feb 2022;128(2):161-168 e1. doi:10.1016/j.anai.2021.10.019
E16 ALMuhizi F, Fein M, Gabrielli S, Gilbert L, Tsoukas C, Ben-Shoshan M, Copaescu, AM, Isabwe GAC. Allergic Reactions to the COVID-19 vaccine (ARCOV) study: the McGill University Health Center (MUHC) experience. Ann Allergy Asthma Immunol 2022. 129; 182-188.e1.
E17 Van Meerbeke SW, Fajt ML, Marini RV, Domsic RT, Petrov AA. Antibody response to graded dosing of coronavirus disease 2019 messenger RNA vaccines after allergic reaction to first dose. Ann Allergy Asthma Immunol. 2022 May 17:S1081-1206(22)00411-2. doi: 10.1016/j.anai.2022.05.004
E18 Otani IM, Tsao LR, Tang M. Coronavirus disease 2019 vaccine administration in patients with reported reactions to polyethylene glycol- and polysorbate-containing therapeutics. Ann Allergy Asthma Immunol. 2022 Jul;129(1):88-94.e1.
E19 Csuth À, Nopp A, Storsaeter J, Nilsson L, Jenmalm MC. COVID-19 vaccines and anaphylaxis-evaluation with skin prick testing, basophil activation test and Immunoglobulin E. Clin Exp Allergy. 2022 Jun;52(6):812-819.
E20 Cahill JA, Kan M. Successful administration of second dose of BNT162b2 COVID-19 vaccine in two patients with potential anaphylaxis to first dose. Allergy. 2022 Jan;77(1):337-338.

Figure E1: Cases Identified by Skin Testing Per 100 Persons Tested