Title

Updated guidance regarding the risk of allergic reactions to COVID-19 vaccines and recommended evaluation and management: A GRADE assessment and international consensus approach.

Journal

Journal of Allergy and Clinical Immunology, 152(2)

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Publication Date

2023-08-01

DOI

10.1016/j.jaci.2023.05.019

Peer reviewed

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Journal Pre-proof

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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PII: S0091-6749(23)00746-7

DOI: https://doi.org/10.1016/j.jaci.2023.05.019

Reference: YMAI 15981

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 12 April 2023

Revised Date: 8 May 2023

Accepted Date: 11 May 2023

Please cite this article as: Greenhawt M, Dribin TE, Abrams EM, Shaker M, Chu DK, Golden DB, Akin C, Anagnostou A, ALMuhizi F, Alqurashi W, Arkwright P, Baldwin JL, Banerji A, Bégin P, Ben-Shoshan M, Bernstein J, Bingeman TA, Bindslev-Jensen C, Blumenthal K, Byrne A, Cahil J, Cameron S, Campbell D, Campbell R, Cavender M, Chan ES, Chinthrajah S, Comberiatti P, Eastman JJ, Ellis AK, Fleischer DM, Fox A, Frischmeyer-Guerrerio PA, Gagnon R, Garvey LH, Grayson MH, Clarisse Isabwe GA, Hartog N, Hendron D, Horner CC, O'B Hourihane J, Iglesia E, Kan M, Kaplan B, Katelaris CH, Kim H, Kelso JM, Kahn DA, Lang D, Ledford D, Levin M, Lieberman JA, Loh R, Mack DP, Mazer B, Mody K, Mosnaim G, Munblit D, Mustafa SS, Nanda A, Nathan R, Oppenheimer J, Otani IM, Park M, Pawankar R, Perrett KP, Peter J, Phillips EJ, Picard M, Pitlick M, Ramsey A, Rasmussen TH, Rathkopf MM, Reddy H, Robertson K, Rodriguez del Rio P, Sample S, Sheshradi A, Shiek J, Sindher SB, Spergel JM, Stone CA, Stukus D, Tang ML, Tracy JM, Turner PJ, Vander Leek TK, Wallace DV, Wang J, Wasserman S, Weldon D, Wolfson AR, Worm M, Yacoub M-R, Updated Guidance Regarding The Risk ofAllergic Reactions to COVID-19 Vaccines and Recommended Evaluation and Management: A GRADE Assessment, and International Consensus Approach, *Journal of Allergy and Clinical Immunology* (2023), doi: https://doi.org/10.1016/j.jaci.2023.05.019.

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Key words: SARS-CoV-2; COVID-19; vaccination; adenovirus vector vaccine; mRNA COVID-19 vaccine; anaphylaxis; allergic reactions; repeat allergic reactions; polyethylene glycol; polysorbate 80; skin testing; shared decision-making, GRADE; allergy; allergy specialist

Abbreviations: Coronavirus disease 2019(COVID-19), Vaccine Adverse Event Reaction System (VAERS), vaccine safety datalink (VSD) skin testing (ST), Grading of Recommendations 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), Immunization Stress-Related Response(ISRR), Canadian Society of Allergy and Clinical Immunology (CSACI), Credibility Interval (CrI), Confidence Interval (CI)

Funding: none
Trial Registration: not applicable

Conflicts of Interest

Matthew Greenhawt: has received past research support to his institution from DBV Technologies, and the Agency for Healthcare Research and Quality; receives current research support from Novartis and Silota; is a consultant for Aquestive; is a member of physician/medical advisory boards for DBV Technologies, Nutricia, Novartis, Aquestive, Allergy Therapeutics, AstraZeneca, ALK-Abello, and Prota; is an unpaid member of the scientific advisory council for the National Peanut Board and medical advisory board of the International Food Protein Induced Enterocolitis Syndrome Association; is a member of the Brighton Collaboration Criteria Vaccine Anaphylaxis 2.0 working group; is the senior associate editor for the Annals of Allergy, Asthma, and Immunology, and is member of the Joint Taskforce on Allergy Practice Parameters. He has received honorarium for lectures from ImSci, RMEI Medical Education, MedLearningGroup, and multiple state/local allergy societies.

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David Golden: Speakers bureau honoraria from Genentech, Kaleo; Clinical trial support from Genentech, Thermo Fisher, Novartis, Pfizer, GSK, and Regeneron, all unrelated to vaccine/vaccine development or COVID-19 treatment; Consulting fees from Aquestive, Novartis, ALK; Royalties from UpToDate (section editor).

Cem Akin: consulting fees from Blueprint Medicine, Cogent, and Novartis; research support from Blueprint Medicines and Cogent; and royalties from UpToDate. Ronna L. Campbell: consulting fees from Bryn and royalties from UpToDate.

Aikaterini Anagnostou reports institutional funding from Aimmune Therapeutics and FARE (Food Allergy Research and Education), personal fees from DBV Technologies, ALK, and FARE.

Moshe Ben-Shoshan: Consultant for Novartis

Jonathan A. Berstein: principal investigator, consultant, and speaker for Novartis, Genentech, AZ, Sanofi Regeneron, Takeda/Shire, CSL Behring, Pharming, Biocryst, and Merck; consultant for Kalvista, Ionis, Celldex, Allakos, Amgen, Biomarin, and Blueprint Medicine; principal investigator and speaker for GSK; speaker for Optinose; consultant for Ono, Astria, Incyte, Cycle, and Escient; and royalties from UptoDate, BMJ, Taylor Francis, and Elsevier.

Theresa Bingeman: Consultant- ALK, Speaker-Sanofi, PI- Novartis, Aimmune- advisory board;

Kimberly Blumenthal: receives grant support from the NIH/NIAID (R01AI150295, 2UM1AI109565-08), Phadia Ab (Thermo Fisher Scientific), and the Massachusetts General Hospital; personal fees for legal case review from Weekley Shulte Valdes Murman Tonelli, Piedmont Liability Trust, Vasios Kelly and Strollo PA, and Publix Supermarkets; and royalties from UpToDate, outside the submitted work.

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Cosby Stone: receives research support from the AAAAI Foundation Faculty Development Award
David Stukus: Consultant – ARS Pharmaceuticals, Before Brands, Novartis, Parent MD; Research support – DBV Technologies; Honoraria – American Academy of Pediatrics, American College of Allergy, Asthma and Immunology; Member – Joint Task Force on Practice Parameters for Allergy/Immunology; Board of Regents for the American College of Allergy, Asthma and Immunology
Mimi Tang: declares consultant fees from Pfizer and Abbott Nutrition; was the past employee (ended July 2022) of and share interest/options in Prota Therapeutics; is the member of the Medical Advisory Board of Anaphylaxis & Anaphylaxis Australia; is the member of the Board of Directors of Asia Pacific Association of Allergy Asthma and Clinical Immunology and was the past member of the Board of Directors of the WAO (ended 2019); is the member of expert committees of the American Academy of Allergy, Asthma & Immunology, Asia Pacific Association of Allergy Asthma and Clinical Immunology, Australasian Society of Clinical Immunology and Allergy, and the World Health Organization.

Paul Turner: has received grants from Medical Research Council andcNIHR/Imperial Biomedical Research Centre; personal fees and non-financial support from Allergenis, plus grants from UK Medical Research Council, grants and personal fees from UK Food Standards Agency, personal fees and non-financial support from Aimmune Therapeutics, grants from Jon Moulton Charity Trust, personal fees from Aquestive all outside the submitted work.
Timothy Vander Leek: has served on advisory boards for and received honoraria from Aralez/Miravo, Bausch Health, Covis Pharma, and Pfizer
Julie Wang: receives research support from National Institute of Allergy and Infectious Diseases, Aimmune, DBV Technologies, and Regeneron, and consultancy fees from ALK Abello and Jubilant HollisterStier.
Susan Wasserman: consulting fees from GSK, Novartis, CSL Behring, Pfizer Canada, Sanofi Canada, AZ, Takeda, ALK Abello, Teva, Medexus, MiravoHealth, Mylan, Bausch Lomb, AbbVie, Avir Pharma, and Leo Pharma; research funding from Pfizer Canada, ALK-Abello, Aimmune; and president of Canadian Allergy, Asthma and Immunology Foundation.
Margitta Worm:

No conflicts to declare related to this work: Faisal ALMuhizi, Waleed Alquarshi, Peter Arkwright, James Baldwin, Aleena Banerji, Carsten Bindslev-Jensen, Aideen Byrne, Julia Cahil, Scott Cameron, Michael Cavander, Derek Chu, Pasquale Comberiatti, Jacquelin Eastman, Adam Fox, Pamela Frischmeyer-Gurrerio, Lene Garvey, David Hendron, Catherine Horner, Ghislaine Isabwe, Manstein Kan, Blanca Kaplan, Constance Katelaris, John Kelso, David Khan, Michael Levin, Richard Loh, Ketan Mody, Daniel Munblit, Richard Nathan, Anil Nanda, Miguel Park, Ruby Pawankar, Mitchell Pitlick, Elizabeth Phillips, Hari Reddy, Trine Rassumssen, Kara Robertson, Javed Shiek, Jonathan Spergel, James Tracey, Dana Wallace, David Weldon, Anna Wolfson, Mona-Rita Yacoub

Abstract

This guidance updates 2021 GRADE recomendations regarding immediate allergic reactions following COVID-19 vaccines and addresses re-vaccinating individuals with 1st dose allergic reactions and allergy testing to determine re-vaccination outcomes. Recent meta-analyses assessed the incidence of severe allergic reactions to initial COVID-19 vaccination, risk of mRNA-COVID-19 re-vaccination after an initial reaction, and diagnostic accuracy of COVID-19 vaccine and vaccine excipient testing in predicting reactions. GRADE methods informed rating the certainty of evidence and strength of recommenations. A modified Delphi panel consisting of experts in allergy, anaphylaxis, vaccinology, infectious diseases, emergency medicine, and primary care from Australia, Canada, Europe, Japan, South Africa, the UK, and the US formed the recommendations. We recommend vaccination for persons without COVID-19 vaccine excipient allergy, and re-vaccination after a prior immediate allergic reaction. We suggest against >15-minute post-vaccination observation. We recommend against mRNA vaccine or excipient skin testing to predict outcomes. We suggest re-vaccination of persons with an immediate allergic reaction to the mRNA vaccine or excipients be performed by a person with vaccine allergy expertise, in a properly equipped setting. We suggest against pre-medication, split-dosing, or special precautions because of a comorbid allergic history.

Introduction:

Through March 2023, the novel SARS-CoV-2 coronavirus and subsequent COVID-19 (Coronavirus disease 2019) global pandemic has caused over 676 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 immediate allergic reactions to these vaccines raised initial concern about the potentially allergenic role of vaccine excipients, polyethylene glycol (PEG) in the mRNA vaccines and polysorbate 80 (PS) in the viral vector vaccines, and the need for allergy screening for possible risk factors for allergic reactions.[3-6] In mid-2021, a systematic review and meta-analysis facilitated preliminary GRADE-based guidelines addressing immediate, presumed allergic, reactions following the mRNA COVID-19 vaccines (BNT162b2 or mRNA-1273), noting a rare incidence of immediate severe (e.g. anaphylaxis) 1st dose reactions (e.g., occurring within 4 hours of administration as per the 2007 Brighton Collaboration Criteria [BCC] definition)[7], a low baseline PEG allergy prevalence, and poor test sensitivity for PEG as a skin testing reagent in assessing suspected non-COVID-19 vaccine and medication allergy.[5] There were scant data available to analyze the risk of severe 2nd dose allergic reactions in individuals with 1st dose reactions, or to assess the predictive accuracy of vaccine or vaccine excipient skin testing for vaccine allergic reactions.

Though immediate, severe COVID-19 vaccine allergic reactions occur rarely, many health authorities around the world contraindicate vaccinating persons with a history of allergy to the vaccine or its excipient.[5] However, this may not be necessary in the majority of instances. Additional data have emerged since the 2021 publication, providing evidence to evolve recommendations made earlier in the pandemic. This updated guidance specifically focuses on the approach to assessing a patient with a history of mRNA COVID-19 excipient allergy or an immediate presumed allergic reaction to a dose of a mRNA COVID-19 vaccine, in determining if an initial or additional doses should be given, and how to assess such patients.

Methods:

Following previously published methodology,[5] we convened an ad hoc international panel of 94 clinical experts in allergy, anaphylaxis, vaccinology, infectious diseases, emergency medicine, and primary care from Australia, Canada, Europe, Japan, South Africa, the UK, and the US to evaluate the current evidence regarding mRNA COVID-19 vaccination or revaccination in the context of suspected immediate vaccine or excipient allergy, and the utility of approaches such as vaccine or excipient skin testing in evaluating persons with an immediate, presumed allergic reaction to a mRNA COVID-19 vaccine or excipient from a societal perspective. The choice of questions and topics addressed in this document were intended to update the 2021 review (including the limitations, table of knowledge gaps and feedback received on this document), which was planned as a living systematic review. Final selection of topics addressed was at the purview of the senior authors (MG, MS, EA, DG, DC). Data sources included published systematic reviews and meta-analyses (through the fall of 2022) assessing the risk of initial and recurrent dose reactions, and the accuracy of vaccine and vaccine excipient allergy skin testing (prick and intradermal testing combined) in predicting these risks.[5,8,9] A primary draft was developed by the senior authors using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) format for evidence synthesis from an individual perspective with secondary consideration for the healthcare perspective (Table E1).[10-13] This draft was revised iteratively by the workgroup, and a modified Delphi panel was used to rate

agreement and consensus with the text and recommendations (1=strongly disagree, 2= disagree, 3=neutral, 4=agree, 5=strongly agree, 80% threshold for agreement), as previously described.[5,14]

The guidance statements and recommendations are presented in Table 1. The GRADE strength of recommendations 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). The Evidence to Decision Framework supplement provides a summary reflection of the evidence in the context of the clinical recommendation. The modified Delphi panel results for each recommendation are shown in the Table E3. All questions presume a patient is seeking either initial mRNA-COVID-19 vaccination, re-vaccination after an immediate presumed allergic reaction to a prior dose, or is allergic to a vaccine excipient, in the setting of shared decision-making with a medical professional willing to provide supervised vaccination. A full description of the methods is detailed in the supplemental material.

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 without a history of an immediate allergic reaction to a mRNA COVID-19 vaccine its excipients, we recommend against vaccine or vaccine excipient testing to predict the rare individual who will have a severe allergic reaction to a vaccine dose.
Strong Recommendation; Low Certainty of Evidence

Evidence Summary: A 2021 systematic review and meta-analysis for all estimates of first dose severe allergic reactions following COVID-19 vaccines through March 19, 2021 found an 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) and 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 exists in mRNA COVID-19 vaccines in the form of PEG-2000, a lipid conjugate that stabilizes the lipid nanolayer, and has been suspected (though not definitively proven) as a potential allergen for immediate allergic reactions.[3,4] In the 2021 systematic review, the calculated incidence of PEG allergy was 0.15 cases per million person-years in the US and Canada.[5,15,16] This 2021 systematic review also calculated the pooled sensitivity and specificity for using prick or intradermal PEG skin testing in persons with non-COVID vaccine suspected PEG allergy, which 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 pooled estimate underwent confirmatory PEG challenge, which further limits the precision of such testing.[5] While strong GRADE recommendations with low certainty of evidence are uncommon, the rating down due to risk of bias from studies lacking challenge verification and indirectness of evaluating pre-pandemic PEG-containing medications and other vaccines. Table 3 details the certainty of evidence for this estimate and Table E2 the risk of bias assessment.

A personal history of allergic disease (e.g., asthma, food allergy, drug allergy, non-COVID vaccine or vaccine-excipient allergy) poses no increased risk of a severe, immediate allergic reaction to an initial mRNA COVID-19 vaccine dose.[5,17-22] These patients require no special precautions or investigations to receive their dose, and can be vaccinated in a routine setting.

Discussion: Global adjudicated rates of mRNA COVID-19 vaccine anaphylaxis are slightly higher than other historical vaccine-associated anaphylaxis (1.3-17 events per million doses) rates, but are overall rare.[23-26] To date, no adjudicated, confirmed fatalities related to mRNA-COVID-19 vaccine anaphylaxis have been published in the medical literature, though there have been non-adjudicated passive reports.[27] With COVID-19 vaccination, the 2007 BCC vaccine anaphylaxis definition has led to higher estimates of anaphylaxis than when using the WAO or the NIAID anaphylaxis criteria,[28,29] which led to the BCC being updated in 2022.[30,31] To date, mRNA COVID-19 vaccine reactions have not been proven to be mediated by anti-PEG IgE.[17,32,33] 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 (Table E3).

Question 3*:* Can additional supervised doses of mRNA COVID-19 vaccines be administered to a patient who had an immediate allergic reaction of any severity following their 1st vaccine dose?

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

Evidence Summary: A 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). [32,34-54] 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 immediate allergic reactions from mRNA COVID-19 re-vaccination.[9] Several case series have demonstrated that children allergic to PEGylated medication (specifically PEG-aspargase) tolerate their initial dose of mRNA COVID-19 vaccination.[55-58] More robust experience in administering the initial mRNA COVID-19 vaccine to individuals with known or suspected PEG allergy is needed, though published evidence to date has shown no vaccine reactions in these cases.[58,59] 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: Allergy specialist guidance for non-COVID-19 vaccines recommends against withholding vaccination in vaccine or excipient allergic individuals. This differs from COVID-19 vaccine guidance that recommends withholding vaccination, which may have contributed to limiting the available evidence base for the meta-analysis.[19-22] Severe allergic reactions occur very rarely with either initial or subsequent doses of mRNA COVID-19 vaccination.[5,9] This should not preclude re-vaccinating persons who reacted to their initial dose or vaccinating persons allergic 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 tolerated mRNA COVID-19 vaccine doses, and it has been demonstrated that mRNA COVID-19 vaccine reactions are unlikely to result from IgE mediated reactions to PEG.[55-60]

The very low rate of repeat immediate severe allergic reactions upon re-vaccination may be explainable by two hypotheses. First, there has been speculation that some non-IgE mediated reactions to injectable PEG-containing medications may be mediated through an anti-PEG IgG mechanism [eg. Complement Activation-Related Pseudoallergy (CARPA)]. Second, the phenomenon of Immunization Stress-Related Response (ISRR) – a benign phenomenon mimicking an allergic reaction, which can manifest as anxiety or stress-induced symptoms has

been identified as a common cause of adverse reactions after COVID-19 vaccination (Table E4)[33,61]

In formulating this recommendation, we weighed the potential benefits and harms of vaccination, and an allergic reaction, along with consideration of patient values, preferences, and cost. A shared decision-making approach should align individual contexts and circumstances with clincal action. Some patients may wish to change to a different brand of mRNA vaccine than the one they initially reacted to, which is not felt to represent any additional risk and is a preference-sensitive option to explore. Recommendations 4 and 5 provide 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 (Table E3).

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?**

Recommendation 4: 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

Evidence Summary: A systematic review and meta-analysis detailed 20 studies among 317 individuals with 1st dose immediate allergic reactions to the vaccine. These individuals underwent a total of 578 skin tests to any one or combination of either mRNA COVID-19 vaccine, PEG, and PS for risk stratification assessment prior to being re-vaccinated with the same vaccine provoking the initial reaction.[8,32,34-36,38-42,45,47,48,51,53,54,59,62-65] 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).[8] Combined for using 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 permitting use of graded dosing (n=9 studies), premedication (n=8 studies), or including patients with 1st dose anaphylaxis (n=17 studies) did not alter the main findings, but test sensitivity was increased in one analysis for individual vaccine testing 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 deferring patients underwent full evaluation and were considered as true positive cases (e.g., best-case scenario), which improved sensitivity to 0.22 (any test), 0.32 (PEG), and 0.48 (any vaccine).[8] 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.[38] 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 possible cause of allergic reactions to vaccines.[18,23] Despite suspicion without definitive proof of a role for PEG2000-lipid conjugate as causing IgE-mediated mRNA COVID-19 vaccine reactions,[17,18] the vaccine remains largely contraindicated by health authorities in persons with known or suspected PEG allergy.[19,21,22] PEG skin testing in non-COVID-19 vaccine settings has low sensitivity.[5] Skin testing to both PEG (as well as PS) and the mRNA vaccine was initially proposed to assess vaccine-related immediate allergic reactions.[4] 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.[8] Some groups advocate use of a specific PEG testing algorithm, which includes testing to very high MW PEG, to increase sensivitity.[66] 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, but more likely indicates testing with non-relevant components which also are not irritant.[8] While 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, this approach is independent of incidentally discovering during evaluation of 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.[16,67,68] 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).[69]

Threshold agreement was achieved for the voting on this recommendation on the 1st round of voting (Table E3).

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 suggest 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.

Conditional Recommendation, Moderate Certainty Evidence

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.[8,9] Similarly, studies of PEG or PS allergic individuals who were vaccinated to mRNA COVID-19 vaccines were also performed under allergist guidance.

Discussion: Vaccination or revaccination of patients with a history of an allergic reaction to the vaccine or its excipients most likely lies outside the comfort of most general vaccine clinics, who likely have had limited experience in managing patients with these risks.[5] The panel also recognizes that it may be difficult for both hospital and 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. These patients should ideally be vaccinated under the supervision of a clinician (ideally a physician specialist) with knowledge of ISRR, and who is trained in recognizing and managing anaphylaxis, in a setting equipped to manage such reactions. If the mRNA COVID-19 vaccination being supervised in this context is tolerated, additional doses can be done in standard fashion (e.g., without allergy specialist supervision).[23] Many decisions may still be preference-sensitive, and this guidance relies on the willingness of those within the field to implement the recommendations, and the affected patients to seek care.[5] We caveat 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 (Table E3). The panel, however, further deliberated whether contextual factors such as equitable and rapid access to specialist settings is uniformaly available to all patients, and also considered that patient values and preference for needing to see a specialist before repeat vaccination may vary. Hence, the panel agreed to issue a conditional instead of strong recommendation. This second round also reached threshold consensus with a single vote (Table E3).

Question 6: Should a patient with a history of an immediate allergic reaction to the vaccine or its 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 its excipients 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

Evidence Summary: 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.[8,9] However, none of these included studies were specifically designed or powered to assess these questions. Persons who take daily or frequent antihistamines or glucocorticosteroids for the management of other conditions should not discontinue taking these on the day of receiving their mRNA COVID-19 vaccine. Rather, this

guidance suggests against specific use (or requirement) of pre-medication. A possible exception to this may be in the case of a patient with systemic mastocytosis.[70] 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 or 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 generally safe approaches, neither are required and have not 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.[23] These management options are consistent with recommendations in past vaccine allergy practice parameters, and may still be preferred steps by some patients and administering clinicians.[5] A 2-step graded challenge (and in older guidance, multi-step desensitization) in individuals with previous immediate allergic reactions to a non-COVID vaccine has been a suggested management step, despite no data establishing that this is either necessary or provides a definitive safety benefit (as opposed to an accommodation that makes either the patient or clinician more comfortable).[23] 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.[63,71] 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.[63] 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.[72] Glucocorticoid premedication in the context of anaphylaxis prevention has limited value and potential harm in most, but not all, settings.[73] With mRNA COVID-19 vaccination, there is concern that glucocorticosteroid premedication could potentially inhibit immune response to the vaccine.[5] The panel recognizes there is an important role for shared decision-making in discussing risk and benefits of vaccination, including options for both conservative and aggressive approaches to re-vaccination, given some patients 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 beneficial in helping to assess and manage such patients, especially in determining the likelihood that a prior reaction was allergic and being able to differentiate between anaphylaxis or an immune-mediated reaction and an ISRR.[33,61]

Threshold agreement was achieved for the voting on these recommendations on the 1st round of voting (Table E3).

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.[70]

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. 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.

Please refer to the supplemental material for further discussion of special circumstances.

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 several delayed-onset symptoms that have been reported post-mRNA COVID-19 vaccination, including "Moderna Arm", and unmasking or worsening of chronic urticaria.[74-77] These, as well as non-allergic post-vaccination complications such as myocarditis, dyspnea, Guillian Barre Syndrome, and vaccine-induced thrombocytopenia 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 and skin testing persons with COVID-19 excipient allergy or a 1st dose reaction is limited, and the studies had heterogeneity in the testing methods which could have influenced the low pooled test sensitivity estimates. 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 (some with high risk of bias), performed under allergist supervision at tertiary centers, and we acknowledge an information gap in managing these issues in low to middle income or resource-limited areas.[5,8,9] 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 a clinician with less experience in these issues, resulting in modification to the stated recommendations in 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).*** Some of these outlined approaches 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 recognize anaphylaxis and use epinephrine), 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, and there are remaining questions and unmet needs that could not be answered in this document or at this time, which are summarized in table 4. Lastly, this document follows the Institute of Medicine standards for trustworthy clinical practice guidelines[78] (Table E5) 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, 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 GRADE-based evidence synthesis that underwent further evaluation through a large consensus of international experts. However, these should be considered and adapted within the context of patient care with a role for shared decision-making, which can be very individualized based on particular circumstances, in the setting of an evolving literature. Therefore, there may be individual situations or patients where, under a shared decision-making paradigm, the clinician may choose an alternative practice than outlined in this guidance. Table E6 summarizes the key points of the updated guidance.

Conclusion

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 in the setting of possible immediate allergic complications, 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.

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Table 1: GRADE Recommendations

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?**	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	High
	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	Low
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 or its excipients be performed prior to initial mRNA COVID-19 vaccination?**	2. For patients without a history of an immediate allergic to a mRNA COVID-19 vaccine or its excipients, we recommend against vaccine or vaccine excipient testing to predict the rare individual who will have a severe allergic reaction to a vaccine dose.	Strong	Low
3. **Can additional supervised doses of mRNA COVID-19 vaccines be administered to a patient who had an immediate allergic reaction of any severity following the 1st vaccine dose?**	3. We recommend that individuals who had an immediate allergic reaction of any severity to their 1st mRNA COVID-19 vaccine dose can receive additional doses, and those with a history of an immediate allergic reaction of any severity to its excipients can receive either their initial or additional mRNA COVID-19 vaccine doses.	Strong	Moderate
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?**	4. 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
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?**	5. We suggest 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.	Conditional	Moderate
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?**	6. We suggest against routine H1-antihistamine or systemic corticosteroid pre-medication prior to vaccination to prevent anaphylaxis.	Conditional	Low
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?**	7. We suggest against graded dosing or stepwise desensitization compared to a single dose.	Conditional	Low

Abbreviations: mRNA COVID-19= messenger RNA; mRNA COVID-19= messenger RNA coronavirus disease of 2019 vaccine

Summary of GRADE recommendations regarding the management of primary COVID-19 vaccination and mRNA-COVID-19 re-vaccination in persons with a known or suspected history of allergy to the vaccine excipients (primary, re-vaccination) or to the vaccine (re-vaccination)

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 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

Abbreviations: COVID-19=coronavirus disease of 2019; SARS Co-V 2: severe acute respiratory syndrome novel coronavirus 2; CI=confidence interval; mRNA COVID-19= messenger RNA coronavirus disease of 2019 vaccine

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%.

GRADE summary of the certainty of evidence for questions 1 and 3, which deal with the prevalence of first dose (all COVID-19 vaccine types) and incidence of second dose (mRNA-COVID-19 vaccine only) presumed allergic reactions.

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%						very serious[e]	none	Pre-test probability 0.16%			
True positives (vaccine allergic)	14 studies 14 patients	cohort & case series	not serious	not serious	not serious			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
False negatives (misclassified not allergic)								2 (2 to 2)			

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%	
True negatives (not vaccine allergic)	13 studies 131 patients	cohort & case series						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

Abbreviations: CI=credibility interval; mRNA COVID-19= messenger RNA coronavirus disease of 2019 vaccine; Sn=sensitivity; Sp=specificity; CoE=certainty of evidence

GRADE summary of the certainty of evidence for questions 2 and 4 which pertain to the diagnostic accuracy (sensitivity, specificity) of vaccine excipient testing as a screening measure prior to receiving an initial mRNA COVID-19 vaccine in persons without a history of allergic reaction to the vaccine or its excipients (question 2), or testing to either mRNA COVID-19 vaccine or the vaccine excipients in persons with a history of a reaction to an initial mRNA COVID-19 vaccine (question 4), as a means of predicting an allergic reaction to the vaccine dose.

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

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 [61]
Determination of a known excipient(s) as an allergen	Unlikely to be anti-PEG and/or Polysorbate IgE in most cases [8,17, 32]
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[57-60]
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%.[9]
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%[8]
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[8]
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[8, 10]
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[8,10,62, 63]
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[31]
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 [79]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

Abbreviations: COVID-19=coronavirus disease of 2019; mRNA COVID-19= messenger RNA coronavirus disease of 2019 vaccine; PEG=polyethylene glycol; mRNA=messenger RNA; NIAID=National Institutes of Allergy and Infectious Diseases; WAO=World Allergy Organization; AAAAI=American Academy of Allergy Asthma and Immunology; ACAAI=American College of Allergy Asthma and Immunology; ISRR: Immune Stress Response Reaction

Summary of unmet needs and knowledge gaps regarding the diagnosis, management, and risk of allergic reactions to mRNA COVID-19 vaccines.

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. Published from reference 5 with permission.

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. Adapted and modified from reference 9.

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. Published from reference 8 with permission.

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. Published from reference 8 with permission.

Figure 1:

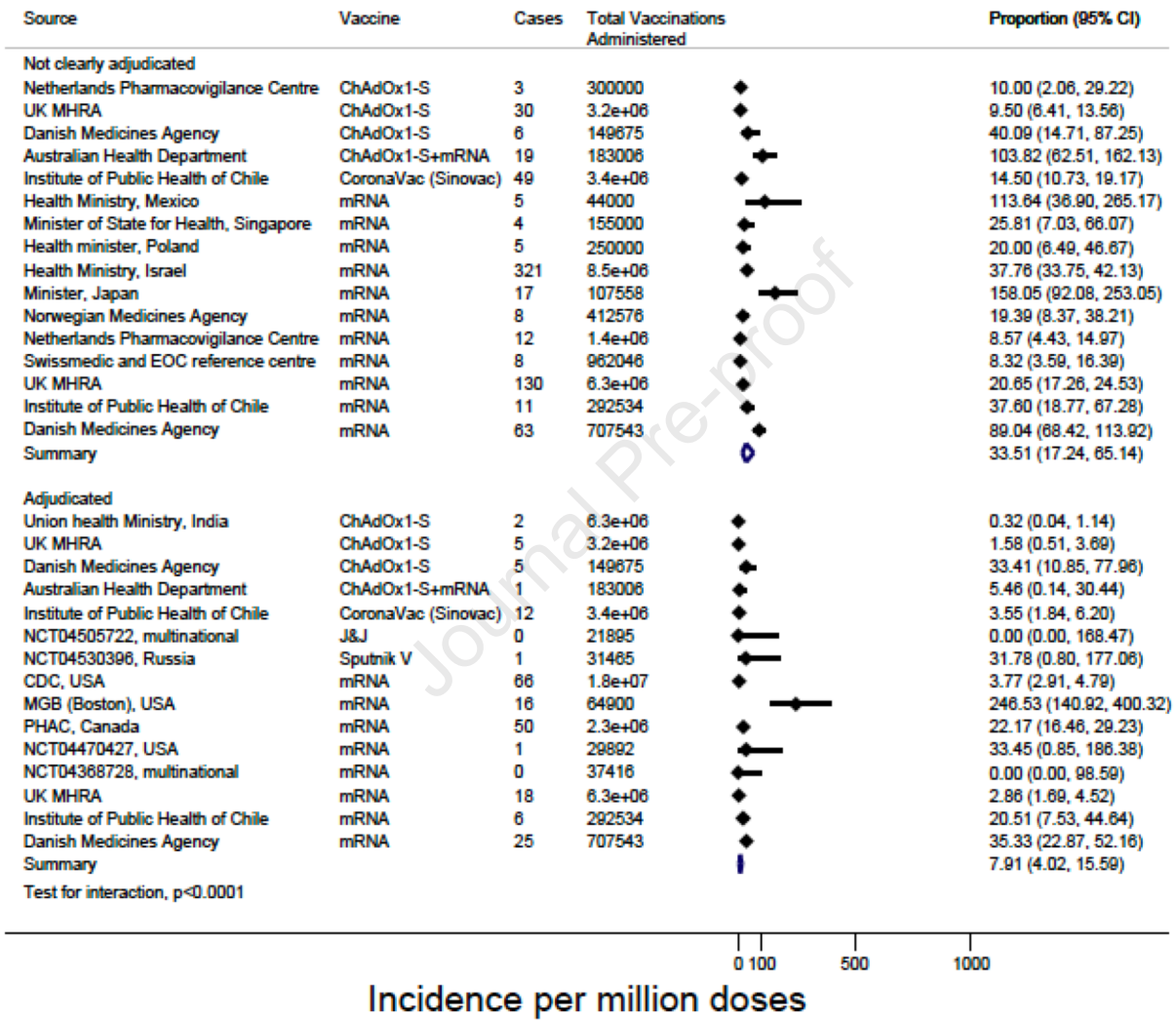

Figure 2

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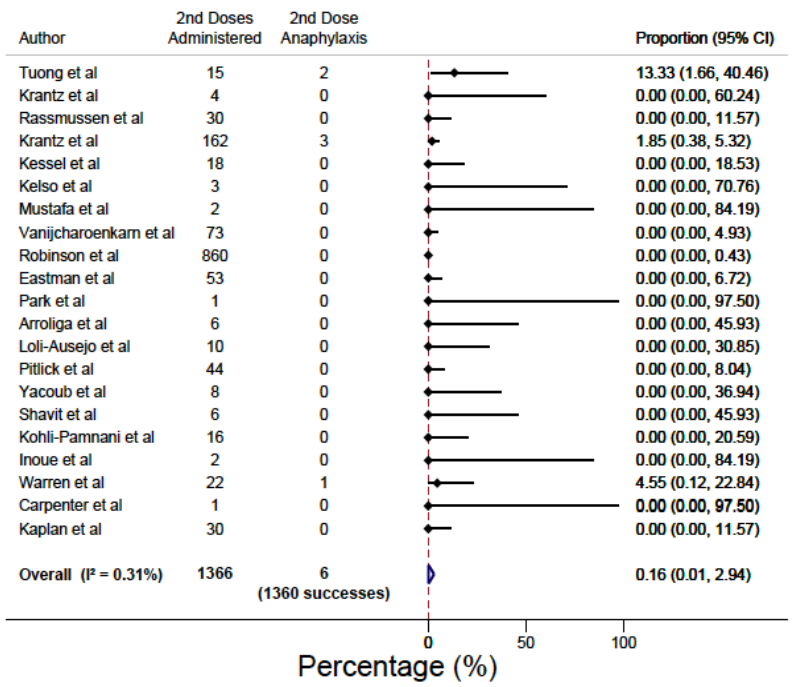

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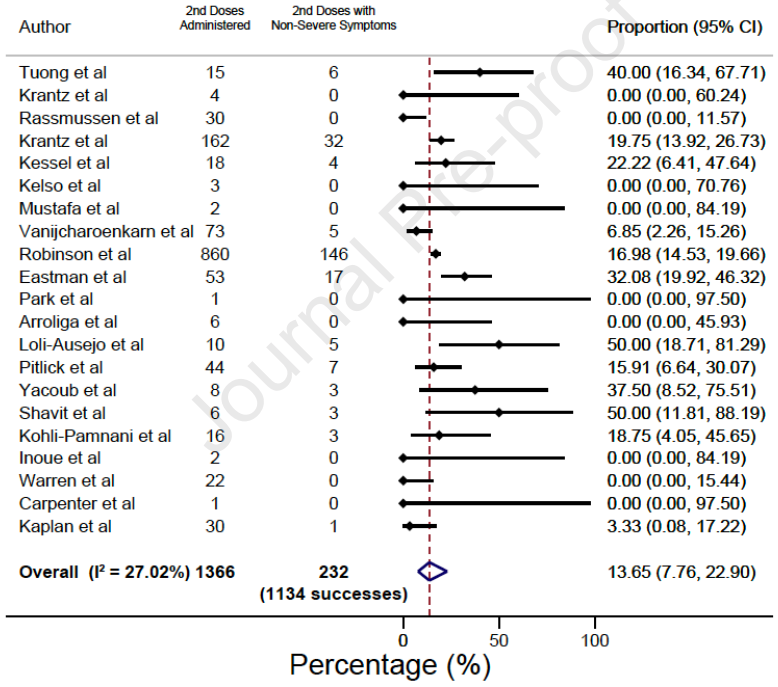

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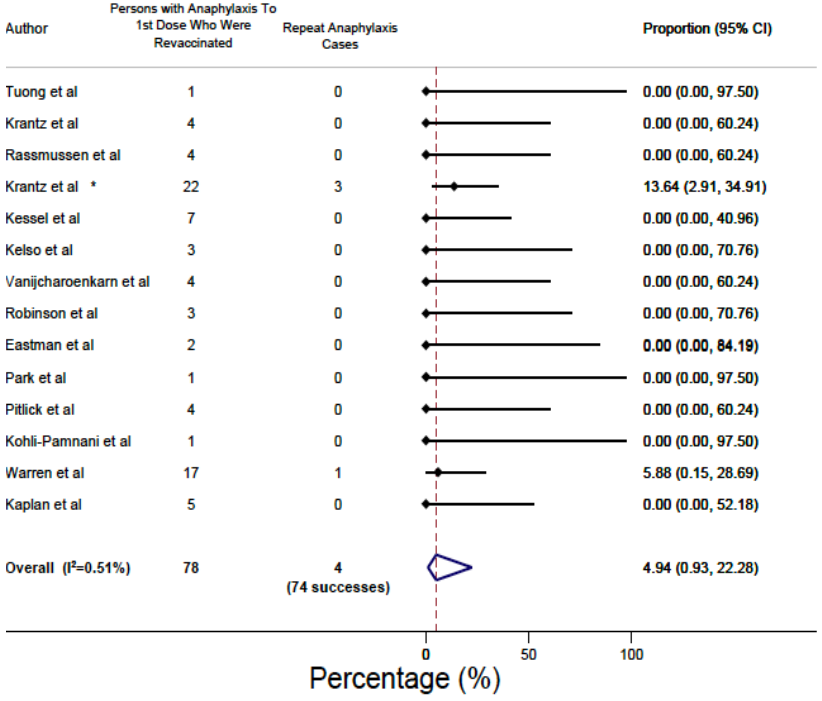

Figure 3

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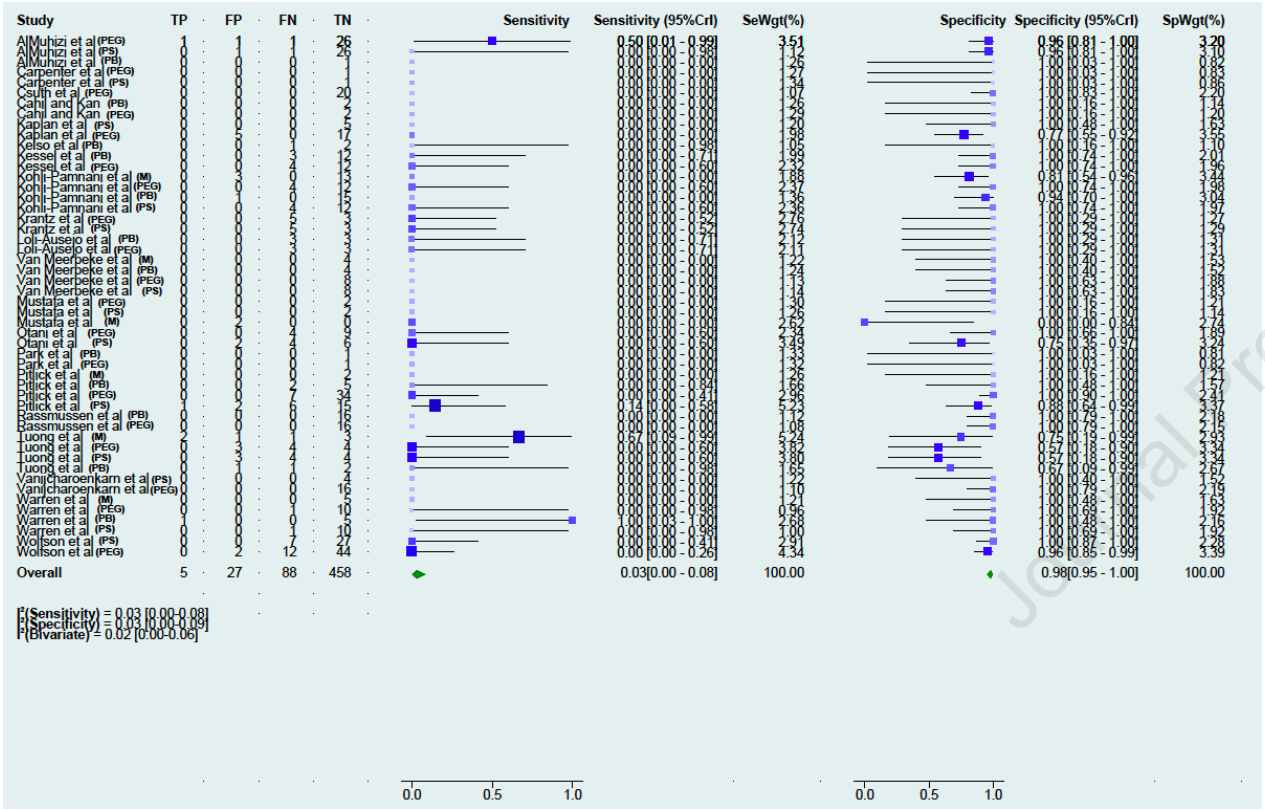

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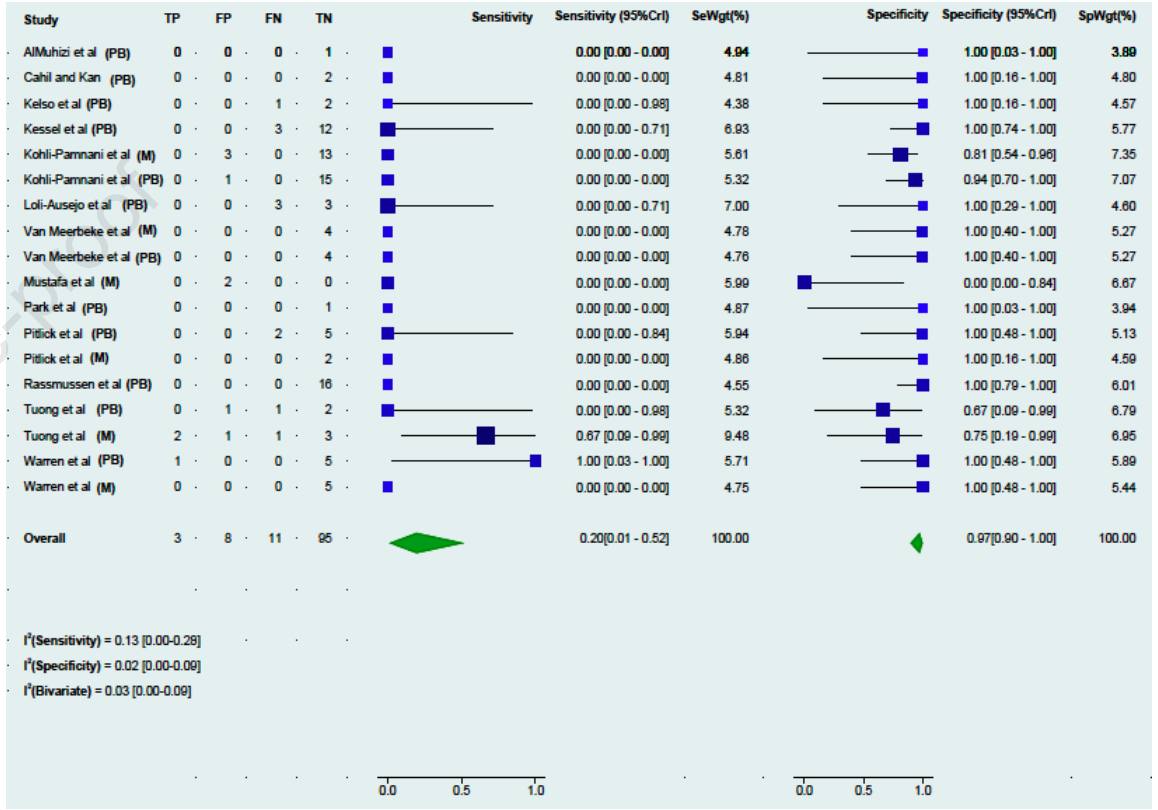

Figure 4

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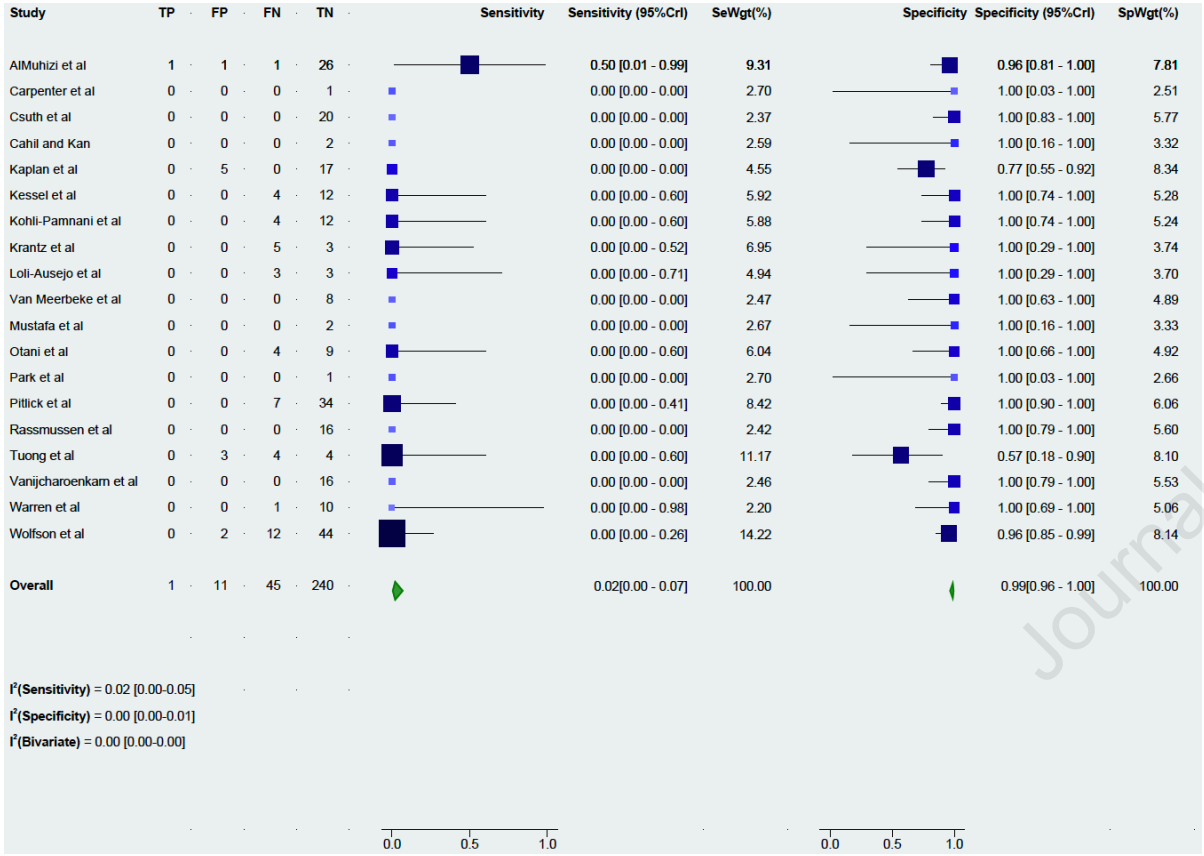

B