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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

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

Abbreviations: Coronavirus disease 2019(COVID-19), Medicines and Healthcare Products Regulatory Agency(MHRA), emergency use authorization (EUA), U.S. Centers for Disease Control (CDC), Vaccine Adverse Event Reaction System (VAERS), Brighton Collaboration criteria (BCC), Grading of Recommendation, Assessment, Development, and Evaluation (GRADE), Research Electronic Data Capture (REDcap), World Health Organization (WHO), World Allergy Organization (WAO), National Institutes of Allergy and Infectious Diseases (NIAID), polyethylene glycol (PEG), Australasian Society of Clinical Immunology and Allergy (ASCIA), FDA Adverse Event Reporting System (FAERS), Complement Activation-Related Pseudoallergy (CARPA), Toll Like Receptors (TLR), American Academy of Allergy Asthma and Immunology (AAAAI), American College of Allergy Asthma and Immunology (ACAAI), Canadian Society of Allergy and Clinical Immunology (CSACI), European Academy of Allergy and Clinical Immunology (EAACI)

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Abstract: Concerns for anaphylaxis may hamper SARS-CoV-2 immunization efforts. We convened a multi-disciplinary group of international experts in anaphylaxis comprised of allergy, infectious disease, emergency medicine, and front-line clinicians to systematically develop recommendations regarding SARS-CoV-2 vaccine immediate allergic reactions. Medline, EMBASE, Web of Science, the WHO global coronavirus database, and the grey literature (inception-March 19, 2021) were systematically searched. Paired reviewers independently selected studies addressing anaphylaxis after SARS-CoV-2 vaccination, polyethylene glycol (PEG) and polysorbate allergy, and accuracy of allergy testing for SARS-CoV-2 vaccine allergy. Random effects models synthesized the data to inform recommendations based on the GRADE approach, agreed upon using a modified Delphi panel. The incidence of SARS-CoV-2 vaccine anaphylaxis is 7.91 cases/million (n=41,000,000 vaccinations, 95%CI 4.02-15.59; 26 studies, moderate certainty), the prevalence of PEG allergy is 103 cases/million (95%CI 88-120; 2 studies, very low certainty), and the sensitivity for PEG skin testing is poor though specificity is high (15 studies, very low certainty). We recommend vaccination over either no vaccination or performing SARS-CoV-2 vaccine/excipient screening allergy testing for individuals without history of a severe allergic reaction to the SARS-CoV-2 vaccine/excipient, and a shared decision-making paradigm in consultation with an allergy specialist for individuals with a history of a severe allergic reaction to the SARS-CoV-2 vaccine/excipient. We recommend further research to clarify SARS-CoV-2 vaccine/vaccine excipient testing utility in individuals potentially allergic to SARS-CoV2 vaccines or their excipients.

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Background:

Through the middle of April 2021, the novel SARS-CoV-2 coronavirus and subsequent COVID-19 (Coronavirus disease 2019) global pandemic has caused over 140 million infections and 3 million fatalities.[1,2] COVID-19 has caused unprecedented international social and economic disruption, resulting in a global economic cost in 2020 of $11 trillion, with estimates of an additional cost of $10 trillion in 2021.[3]

Vaccines are considered the most effective strategy to end the pandemic. By early 2021, 3 adenovirus vector vaccine agents, 2 mRNA vaccine agents, and 2 inactivated viral vaccine agents completed phase 2/3 trials and were approved for emergency use in multiple countries.[4] Through the middle of April 2021, >878,900,000 doses of these vaccines have been administered globally.[5] These vaccines have an efficacy from 62-95% in reducing symptomatic SARS-CoV-2 infection, and >95% efficacy in reducing severe/critical infections.[6,7] Data have also shown that vaccination can reduce hospitalization. Adverse events were reported in all of the vaccine trials, including hypersensitivity reactions, but no fatalities due to hypersensitivity reactions were reported. During the phase 3 studies for the currently approved vaccines, there was no significant difference in hypersensitivity rates between vaccine and placebo trial arms, with 0-1 cases of anaphylaxis per million doses reported.[7-11]

On December 9, 2020, there were two severe allergic reactions reported after administration of the first 500 Pfizer-BioNTech vaccinations in the UK; both patients responded to treatment with intramuscular epinephrine.[12] In response, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) temporarily recommended a contraindication for the Pfizer-BioNTech vaccine in individuals with a history of a severe allergic reaction to any vaccine, medication or food.[13] This recommendation was modified in early January 2021 to a contraindication only for those with a history of a severe allergic reaction to the SARS-CoV-2 mRNA vaccine or vaccine component/excipient (polyethylene glycol [PEG] in mRNA vaccines, and polysorbate 80, a related excipient contained in the adenovirus vaccines, which is considered potentially cross-reactive with PEG).[8,9,14-18] Similar contraindications have been adopted in multiple other countries by public health regulatory agencies and allergy/immunology societies as detailed in Figure 1.[4,19-21] The evidence base for many of these recommendations remains uncertain, however.

A handful of publications have detailed potentially allergic reactions to SARS-CoV-2 mRNA vaccines, through the early stages of their emergency use authorization (EUA). These reports provide the specific reported symptoms, treatment, co-morbid allergic history and discussion of the confidence that the reaction constituted anaphylaxis as adjudicated by U.S. Centers for Disease Control (CDC) physicians. This was based on adjudication of the data reported to the Vaccine Adverse Event Reaction System (VAERS) using the Brighton Collaboration criteria (BCC) for vaccine anaphylaxis.[22-25] The CDC has continued to periodically update these estimates based on VAERS data.[26,27] Through the first month after the U.S. EUA for both mRNA vaccines, the CDC described 66 anaphylaxis events in 17,524,676 vaccinations, or approximately 3.7 events per million.[26,27] One large US academic medical center reported 16 cases of anaphylaxis among 64,900 vaccinations (250 cases per million vaccinations) over a 2 month period, based on electronic health record review (by allergy investigators) of reported

symptoms within 3 days of vaccination.[28] These reports all indicate that anaphylactic reactions to the SARS-CoV-2 mRNA vaccines may occur but are rare.

Reports of severe allergic reactions, including anaphylaxis, have prompted concern that the new mRNA vaccine platform has the potential to cause allergic reactions (including anaphylaxis) at a greater rate than other vaccines. A lesser degree of concern is shared for adenovirus vector vaccines as there is more experience with this platform. These concerns likely contribute to vaccine hesitancy and must be weighed against the life-saving and disease-mitigating benefits of SARS-CoV-2 vaccination. Given the lack of an established international evidence-based approach to reactions attributable to these vaccines, this group of international experts in the diagnosis and management of anaphylaxis has organized an evidence-based, consensus guidance for the diagnosis and management of severe allergic reactions, including anaphylaxis, to SARS-CoV-2 vaccines.

Methods:

An ad hoc panel of clinical experts from the US, Canada, UK, Europe (Ireland, Germany, Italy), South Africa, and Australia came together to synthesize the current evidence regarding severe allergic reactions to the SARS-CoV-2 vaccines, and provide consensus recommendations regarding the epidemiology, risk factors, assessment, and management of patients at possible risk for a severe allergic reaction to a SARS-CoV-2 vaccine from a societal perspective. The panel was chosen based on expertise in anaphylaxis diagnosis, management, and policy. The group included representation of Infectious Disease clinicians, clinicians serving as front-line vaccinators, and allergy specialists with prior expertise in policy related to adverse reactions to vaccines for infectious diseases. Direct financial and industry-related conflicts of interest (e.g., direct or indirect involvement with the development or clinical trials related to SARS-CoV-2 vaccines) were not permitted and were considered disqualifying. Work unrelated to vaccine development with companies (e.g., asthma, allergic rhinitis, atopic dermatitis, etc.) was not considered either a direct or indirect conflict, but such involvement was disclosed. 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.

A primary draft, inclusive of four focused questions, was iteratively developed by the senior authors (MG, MS, EA, DG, DC, DK) 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. This draft was circulated and revised/edited iteratively over multiple draft versions by the workgroup. A modified Delphi panel among the members was used to rate agreement and consensus with the final recommendations.[29] GRADE methodology is explained in detail elsewhere,[30-32] and the full details of the methods for this analysis are detailed in the EMethods. An electronic REDCap survey (Research Electronic Data Capture, Nashville, TN) was sent to 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).[33] Additionally, panel members were encouraged to submit free text comments for statements, and could choose "not applicable" if they did not feel they had the expertise to answer a question. *A priori* consensus was defined as agreement of >75% for recommendations; "strongly disagree" and "disagree" were grouped together and

"strongly agree" and "agree" were grouped together. For recommendations in which consensus was not achieved after the initial survey, an iterative discussion was undertaken with the intent to resolve the key points and adjust language. Subsequent surveys were then sent to panel members incorporating the de-identified responses from the prior survey with the goal of reaching consensus. This process was repeated until consensus was reached or, if no consensus was achieved by the 3rd round, the statement was categorized as "no consensus reached." An authorship statement detailing author roles can be found in the EMethods.

Outcomes prioritized in this systematic review and meta-analysis were anaphylaxis to the vaccine and vaccine excipients, as well as the diagnostic accuracy of allergy testing to the vaccine and vaccine excipients. The literature searched included (1) Global coronavirus databases for country by country vaccine allergy or anaphylaxis reporting (2) national passive vaccine safety reporting systems, and (3) Pub Med/Medline and clinical trials registries related to SARS-CoV-2 vaccine clinical trials and published case series related to SARS-CoV-2 vaccine adverse events. Systematic reviews and literature searches (supplement) were conducted by 5 authors (MG, MS, DC, AWB, AB) using Covidence (Cochrane Group, Brighton, UK). Searches and manuscript selections are detailed in the PRISMA diagrams in Figure E1. Specific inclusion and exclusion criteria for each search are detailed in the EMethods. We considered but did not rely on indirect evidence from similar event reporting from other vaccines given differences in the context and technology of the vaccines. However, we considered indirect evidence for management strategies of those with vaccine allergy as this comprises the extant literature regarding vaccine allergy, and the acute management of severe allergic reactions, including anaphylaxis, to vaccines is sufficiently similar to the experience with diagnosis and management of anaphylaxis to foods, drugs and insect stings. 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.[34] While not systematically reviewed, we examined vaccine efficacy as an outcome as this was identified as being of major importance to patients.

We use the wording "we recommend" for strong recommendations and "we suggest" for conditional recommendations. The implications of the recommendation strength are presented in Table E1, the certainty of evidence in Table E2, and the risk of bias assessment in Figures E2-4. The final list of recommendations was developed by panel discussion and consensus. We present the guideline statements and recommendations in Table 1. 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.

Results:

Part 1: Recommendations for individuals before their initial SARS-CoV-2 vaccination who do not have a history of a severe allergic reaction, including anaphylaxis, to SARS-CoV-2 vaccine or its excipients

Question 1: What is the risk of a severe allergic reaction, including anaphylaxis, to a SARS-CoV-2 vaccine in a patient with no history of a severe allergic reaction to a SARS-CoV-2 vaccine or its excipients?

Recommendation 1:
For patients with no history of a previous severe allergic reaction to a SARS-CoV-2 vaccine or its excipients, the risk of SARS-CoV-2 vaccine-induced anaphylaxis is very rare and we recommend vaccination over no vaccination based on this risk.
Strong Recommendation; High Certainty of Evidence

Recommendation 2:
For patients with a history of a severe allergic reaction, including anaphylaxis, unrelated to a SARS-CoV-2 vaccine or excipient, the requirement for additional observation beyond standard wait time (e.g. recommended by local health authorities for the general population) provides a minimal absolute risk reduction in severe allergic reaction outcomes and may also contribute to vaccine hesitancy. Therefore, we suggest against prolonged observation in those with a history of severe allergic reactions unrelated to a SARS-CoV-2 vaccine or excipient.
Conditional Recommendation; Low Certainty of Evidence

Rationale

Systematic review and meta-analysis:

We 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 SARS-CoV-2 vaccines up to March 19, 2021, identifying 46 total reports meeting inclusion criteria (see EMethods).[10,27,35-74] We performed a random effects meta-analysis of proportions using hierarchical logistic regression and Clopper-Pearson CIs. Among 26 reports involving reported cases adjudicated to meet BCC for anaphylaxis with a sample size of at least 20,000 doses, the meta-analyzed incidence of anaphylaxis was 7.91 (95%CI 4.02-15.59) per million, and no anaphylaxis-related fatalities were reported. In multivariable meta-regression, we found that reports of anaphylaxis without adjudication were associated with a higher reported rate of anaphylaxis (OR 5.53, 95%CI 4.01-7.61) and compared to mRNA-based vaccines, lower rates of anaphylaxis were associated with vaccines using adenoviral-vectors (OR 0.47, 95%CI 0.33-0.68) and inactivated virus (OR 0.31,95%CI 0.18-0.53). Findings were similar when analyzing all 46 reports (e.g., regardless of sample size). (Figure 2). Table E2 details the certainty of evidence for this estimate, and Figure E2 the risk of bias assessment.

Discussion: Vaccine-related fatalities from severe allergic reactions, including anaphylaxis, are very rare. Anaphylactic reactions to vaccines are historically cited at about 1.3 events per million doses.[75,76] A 2019 study by Su et al using the VAERS noted a cumulative incidence rate of 17 cases of anaphylaxis per million vaccinations from 1990-2016.[77] By comparison, the published rate for anaphylaxis to penicillin is 5-10 cases per million persons,[78] and in the general population, drug allergy fatalities occur on the order of 0.1 to 1 event per million persons.[79] Moreover, the estimated fatality rate from SARS-CoV-2 viral infection as of early March 2021 ranges from 36.4 to 1852.7 per 1,000,000 persons in countries represented by authors on this consensus document.[2] Data from a physician-reported national Canadian vaccine registry showed a rate of allergic reactions of any severity to vaccines of approximately 370 reactions per million doses, with most being attributable to influenza vaccines.[80] Slightly older data have noted the estimated rate of allergic reactions of any severity (including anaphylaxis) ranges between 1-20 per million persons.[75] Since SARS-CoV-2 mRNA vaccines are novel, historical

estimates of severe reactions to these agents are not available. While fatality attributed to SARS-CoV-2 vaccines has occurred, none has been the result of a severe allergic reaction.[81]

Comparing reported rates of anaphylaxis following vaccination is hampered by variation in anaphylaxis definitions across regions and between organizations, as shown in Table E4. This causes reactions considered to be anaphylaxis by some definitions to not be considered anaphylaxis by other definitions. For example, while the BCC are the accepted standard for anaphylaxis from vaccines and are used by VAERS,[25] some of the cases in the MMWR reports would not meet other international diagnostic criteria, such as either the National Institutes of Allergy and Infectious Diseases (NIAID) criteria or those from the World Allergy Organization (WAO).[82-85] Table 2 demonstrates how the cases published in the medical literature by the CDC could be rated differently based on what classification system for anaphylaxis was used.[86] One study has compared the NIAID criteria and BCC, noting agreement of the criteria on 92/128 (72%) of cases, which based on a kappa statistic of 0.414, is at the lower limit of what is considered statistical "moderate" agreement.[87]

Importantly, VAERS is a passive case reporting system which allows the public, manufacturers, and healthcare workers to report signs and symptoms considered to be adverse events occurring around vaccine administration. VAERS and other similar reporting systems in other countries (e.g., Yellow Card Reporting in the UK), are not designed to determine causality or validity of the event in question. Such reporting makes it difficult to definitively discern objective vs. subjective symptoms, making it impossible to exclude other common causes that can mimic symptoms of an acute allergic reaction. Thus, based on evidence to date, while severe allergic reactions, including anaphylaxis, may occur with SARS-CoV-2 vaccination, this is a rare event and represents a very low (but not completely absent) risk according to pooled adjudicated data.[26] In formulating recommendations 1 and 2, we weighed the potential benefits and harms of vaccination against each other, along with consideration of patient values, preferences, and cost. While we acknowledge that well-informed individuals may have values and preferences that could lead to vaccine refusal in spite of very high-certainty of evidence regarding the rarity of severe allergic reactions to these vaccines, it was felt that most informed individuals would be highly likely to choose vaccination over vaccine refusal based on the very rare risk of a severe allergic reaction and the benefit of vaccination in this situation.

Risk-Stratification Based on Allergic History

In the phase 2 and 3 clinical trials for the currently approved vaccines, participants were excluded from participation if they had a known or suspected allergy or history of anaphylaxis, urticaria, or other significant adverse reaction to the vaccine or its excipients, including polyethylene glycol (PEG) and polysorbate 80, but not for any other baseline allergic or atopic condition.[4,8-11,50,71,73,88] Of note, a high percentage of individuals reporting severe allergic reactions to the SARS-CoV-2 mRNA vaccines in the CDC reports also had a self-reported history of an underlying allergic condition including past medication and unrelated vaccine allergy, and were female; however, the significance and validity of these allergy diagnoses or male/female differences are difficult to assess if these signify a risk signal or not.[22,24,89] Allergic conditions are very common in the general population and self-reported allergy is typically much higher than confirmed allergy. As well, the rate of individuals with similar allergic comorbidity who successfully tolerated their vaccine has not been calculated, and this is needed to properly

quantify a risk ratio related to a general or specific type of allergic history (or sex). Mechanistically, it is unclear why allergies to food, venom, or other non-PEG/mRNA containing vaccines/medications would pose any hazard requiring additional post-vaccination observation or contraindication to vaccine administration. Therefore, pending emergence of additional data showing there is a clearly increased risk relative to a control population, allergic or atopic comorbidity should not be considered a risk greater than the general population for a vaccine-associated allergic reaction, and inclusion of these precautions risks harm in promoting vaccine hesitancy.[14,18,90] There is an ongoing study that is exploring risks of SARS-CoV-2 vaccination related to allergic co-morbidity (www.clinicaltrials.gov, NCT04761822).

Shaker et al modeled the cost-effectiveness of applying broad restrictions based on underlying allergic history in the US, and the impact of extended wait time as a precaution.[91] 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 (comparing a standard of 15 minutes recommended by the CDC for the general population vs. 30 minutes for persons considered potentially at risk for a vaccine-associated allergic reaction) by anaphylaxis history was not cost-effective without >1% anaphylaxis case-fatality and >6% risk of vaccination-associated anaphylaxis. Furthermore, withholding of a second mRNA 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.[92,93] (Figure E5, Table E5) Emerging data from a real-world US study of both mRNA vaccines in 3950 recipients noted an 80% relative risk reduction in SARS-CoV-2 infection risk 14 days after a single dose of either vaccine may help to enhance this model.[94]

As shown in Figure 1, multiple international public health agencies and allergy organizations around the world have issued guidance related to concerns for severe allergic reactions specifically to the mRNA vaccines that generally echo the CDC recommendations. Many also emphasize shared decision making and all suggest consideration of allergy-immunology consultation. Most lack explicit language formally recommending testing to excipients (including PEG) or the vaccine itself as part of the evaluation (due to the absence of evidence and predictive values for the testing).[90,95] Only the Australasian Society of Clinical Immunology and Allergy (ASCIA) and World Allergy Organization (WAO) suggest consideration for skin testing to the vaccine or its components (e.g., PEG, polysorbate) in some cases.[8, 25] A recommendation for such patients to undergo evaluation by an allergist may or may not imply consideration for testing as part of this evaluation, though the nature of what should be part of such evaluation is not specified. Threshold agreement was achieved for the voting on these recommendations on the first round of voting (Table E3)

Question 2: In patients without a history of a severe allergic reaction, including anaphylaxis, to a SARS-CoV-2 vaccine or its excipients, should allergy skin testing to SARS-CoV-2 vaccines or its excipients be performed?

<u>Recommendation 3:</u>

In patients with no history of a severe allergic reaction, including anaphylaxis, to SARS-CoV-2 vaccines or its excipients, we recommend against vaccine or vaccine excipient testing prior to vaccination in an attempt to predict the rare individual who will have a severe allergic reaction to vaccination.
Strong recommendation; Low Certainty of Evidence.

Rationale

Systematic review and meta-analysis:

Systematic review regarding the incidence and/or prevalence of PEG or polysorbate allergy identified 1 study among 608 citations, with an additional study under review also identified.[16] In a review of a Canadian national physician-reported drug allergy database entries from 2015-2018, Abrams et al. found allergy to PEG or medications containing PEG/polysorbate in 135 cases out of 1,055,667 entries of allergic drug reactions, for an incidence of 42.6 cases per million person-years. This report described no cases where PEG allergic individuals had reported cross-reactivity to any polysorbate containing medicine (and the individuals with polysorbate allergy only reacted to a single agent).[80] In the other report, Stone et al compiled a review of the FDA Adverse Event Reporting System (FAERS) database from 1989 through 2017, finding 53 probable cases of anaphylaxis to PEG among 25,905 reports, for an estimated incidence of 4 cases of PEG allergy per year (0.012 cases per million person-years).[16] To allow for pooling, we presumed all cases in the Abrams et al report were anaphylaxis, and the combined incidence rate between these studies is 0.15 cases per million person-years (Figure 3). No studies describing a polysorbate allergy rate were identified. Table E2 details the certainty of evidence for this estimate and Figure E3 the risk of bias assessment.

Discussion: Historically, vaccines have contained inert excipients such as food proteins (e.g., egg, gelatin, yeast) or other substances (e.g., thimerosal, formaldehyde, latex, neomycin, adjuvants), as well as viral proteins and bacterial toxoids, to which reported adverse reactions, including allergic reactions of varying severity have been attributed. [96] mRNA vaccines utilize newer technology that differs from existing vaccines in that they do not contain historically commonly used excipients. Because these vaccines involve nanotechnology to deliver mRNA to recipient cells, they use other excipients, most notably PEG 2000 but also additional lipids and cholesterol.[8,9] The AstraZeneca, Sputnik, and Johnson and Johnson vaccines each contain recombinant adenovirus and polysorbate 80.[10,11,88] Adenovector virus vaccines are not novel technologies. Table 3 details the excipients in the SARS-CoV-2 vaccines.

From a societal standpoint, the population prevalence of PEG and polysorbate allergies are very rare. In addition, data regarding population-based skin test screening using SARS-CoV-2 vaccine are sparse--only one published study detailing SARS-CoV-2 prick testing prior to initial vaccination for persons (who had not yet received SARS-CoV-2 vaccine) with a general history of anaphylaxis, which noted no positive skin tests.[97] The very rare rate of adjudicated cases of SARS-CoV-2 vaccine anaphylaxis and a lack of evidence that COVID-19 vaccine reactions are attributable to PEG or polysorbate, strongly suggests against any population based approach that would involve screening for pre-existing specific-IgE against PEG or polysorbate as a means to predict risk of a severe allergic reaction to a SARS-CoV 2 vaccine.[14,18] Threshold agreement was achieved for the voting on this recommendation on the first round of voting (Table E3)

Part 2: Recommendations for individuals before their initial or additional SARS-CoV-2 vaccination who have a history of an allergic reaction to SARS-CoV-2 vaccine or its excipients

Question 3: In patients with a history of a severe allergic reaction, including anaphylaxis, to a SARS-CoV-2 vaccine or its excipients, should allergy skin testing to SARS-CoV-2 vaccines or its excipients be performed to determine if vaccine withholding is needed?

Recommendation 4: We suggest against the clinician routinely performing skin or in vitro testing using SARS-CoV-2 vaccines or excipients outside of the research setting for the purpose of vaccine withholding, given such testing has unknown sensitivity/specificity in predicting severe allergic reactions, including anaphylaxis, to SARS-CoV-2 vaccines.

Conditional recommendation; Low Certainty of Evidence

Rationale:

Systematic Review and Meta-analysis:

The utility of PEG testing to inform SARS-CoV-2 vaccine risk of allergic reaction is uncertain. However, data are available to understand how well such testing performs in evaluating persons with a known or suspected allergic reaction to PEG or polysorbate in other contexts. A systematic review identified 21 studies (all case reports/series) out of 548 citations (excluding duplicates) that described skin testing (skin prick or intradermal) to PEG of any MW and/or polysorbate 80, where control subjects were also tested.[15,16,98-116] A positive case was defined as any method of skin testing performed with PEG or Polysorbate concentration where the authors deemed the test positive for identification of a wheal and/or flare, without any specific or uniform threshold reported. For PEG, there were 15 reports detailing skin testing to varying agents and concentrations.[15,16,98-110] Following removal of 7 positive skin tests that were duplicated from 5 other studies in one large case series of 37 cases since 1977, we calculated a pooled sensitivity of 58.8% (30 true positive, 21 false negative) and specificity of 99.5% (247 true negative, 1 false positive). However, the specificity may be falsely high due to the case series/report study designs. As well, among the reports, not all patients were challenged to confirm the history of PEG reaction, the diagnostic gold standard, which lowers the certainty of evidence due to indirectness of the testing. There were 6 reports detailing 7 total patients with suspected allergy to polysorbate that had skin testing (no false positives, and 57 controls tested that were non-reactive).[111-116] Polysorbate testing sensitivity/specificity were not calculated given the low number of patients tested. Table E2 details the certainty of evidence for this estimate and Figure E4 the risk of bias assessment.

The same systematic review identified no studies that investigated vaccine or excipient testing compared to negative controls in individuals with a known or suspected allergic reaction of any severity to a SARS-CoV-2 vaccine. However, 4 case reports (without controls) were identified describing testing with SARS-CoV-2 mRNA vaccine or PEG/polysorbate in persons with reported severe allergic reactions to the vaccine, and vaccine testing in negative controls to establish a non-irritating testing concentration.[117,118 119] The first report details negative vaccine skin testing among 4 persons with reported allergic reactions to their initial vaccination, 3 of whom elected to receive a second dose and did so without reaction.[118] The second report details

negative PEG 3350 testing in 8 persons with reported allergic reactions their initial vaccine, 7 of whom elected to receive a second dose and did so without reaction; as well as negative polysorbate 80 testing in 6/7 persons tested prior to their initial vaccination, with all 6 receiving their initial dose without reacting.[117] The third report details no irritant response detected among 55 negative controls tested to SARS-CoV mRNA vaccine.[119] The fourth detailed 2 adult patients with severe allergic reactions to their initial mRNA (Moderna) vaccine, who underwent skin testing to PEG, polysorbate, and the mRNA vaccine itself. In both patients, excipient skin testing was negative but intradermal skin tests to the Moderna vaccine were positive. However, both tolerated graded dosing administration of the vaccine without issue.[120] Lastly, one case report of PEG testing was identified in a female patient with a past history of skin and oropharyngeal reactions to PEG containing products, who sought evaluation after experiencing a reported systemic reaction to her initial dose of the Pfizer-BioNTech vaccine that was treated with epinephrine but was not associated with tryptase elevation. While undergoing testing, approximately 12 minutes after PEG 4000 prick skin test was applied, she developed a multi-system systemic reaction treated with epinephrine treatment, which also was not associated with tryptase elevation. Skin testing to the Pfizer-BioNTech vaccine and to PEG MW less than 4000 were all negative, and neither vaccine re-challenge nor challenge to PEG 4000 or any other molecular weight PEG were attempted.[121] One additional case report was noted regarding an atopic female with a past episode of urticaria attributable to a topical product possibly containing PEG, who developed an erythematous rash, then slurred mouth and hoarseness over the course of 5 hours post her initial Pfizer-BioNTech vaccine (though had no symptoms at 30 minutes). Her serum tryptase level was normal, and this reaction occurred despite steroid premedication starting 14 hours before vaccination and antihistamine an hour before vaccination. During evaluation by an allergy specialist 2 weeks after the event, while no PEG or vaccine skin testing was reported, she was noted to have an elevated basophil activation test (14.79 $CD203c^{high}$%) to PEG 4000 at 0.2mg/mL (and no activation seen in 5 negative control patients).[122]

Discussion: PEG-2000 is speculated to be a potential culprit in allergic reactions to SARS-CoV-2 mRNA vaccines.[14,123] PEG and polysorbate are ubiquitous compounds, found in many health and beauty products and in foods and beverages, and are routinely used and tolerated in daily life.[14] There are limited case reports in the medical literature of allergic reactions attributable to PEG contained in therapeutic agents and radiocontrast media.[15,16,98,124-126] PEG is available in different molecular weights and structural formats. Allergic reactions may be more likely with higher molecular weight (MW) PEG agents, higher concentrations, or parenteral administration. It is uncertain if the concentration and MW of PEG in SARS-CoV-2 mRNA vaccines would be sufficient to cause reactions [15,16] There is theoretical concern, but limited evidence, that PEG may cross-react with certain polysorbates.[16] Polysorbate-80 in adenovirus-vector vaccines was not implicated as causing allergic reactions in their trials, and there is limited reporting of allergic reactions of any severity with these vaccines.

Evaluation for suspected PEG allergy is largely based on history. Use of high MW PEG solutions as skin testing agents has not consistently demonstrated the ability to elicit wheal and flare responses, and it remains unclear if this approach would reliably indicate the presence (or absence) of specific IgE.[125] In this meta-analysis, the pooled sensitivity of PEG skin testing is only 58.8%, but the pooled specificity is 99.5%, which implies that the test will miss identifying the presence of PEG-specific IgE in a significant number of PEG allergic patients, but non-PEG allergic individuals do not appear to have falsely positive tests. There have been few cases of

anaphylaxis reported to intradermal skin testing, mainly using PEG with MW>3000. Other non-validated methods of detection for PEG-induced allergic response have been described, as has PEG oral provocation challenge.[15,16,98] In individual with a high pre-test probability of PEG allergy, testing to PEG, from these data in the meta-analysis show a very uncertain (very serious risk of bias) high positive likelihood ratio to confirm the diagnosis. However, this is distinct from the suggestion that PEG testing can inform the likelihood of a SARS-CoV-2 vaccine reaction (very serious indirectness). This was noted in case series to date where 10 persons who reacted to their mRNA vaccine in fact had negative PEG skin testing, and where 2 patients additionally were skin tested to PEG as well as to both polysorbate (negative) and the Moderna vaccine (positive intradermal test) and tolerated re-administration.[117,120] In the case of a person with a mRNA vaccine reaction where PEG sensitization was detected, this was only to PEG 4000, and not the vaccine or the concentration of PEG in the vaccine. There is not yet any convincing evidence to confirm PEG as a causative agent in the reported SARS-CoV-2 mRNA vaccine reactions and the diagnostic utility of PEG and polysorbate allergy testing is highly uncertain.[14,18,90,123] Of note, skin testing to the vaccines is not approved under any of the EUAs. Further research regarding excipient and vaccine skin testing in this context is needed.

Other mechanisms might potentially cause allergic symptoms following administration of SARS-CoV-2 mRNA vaccines. Complement Activation-Related Pseudoallergy (CARPA) has been theorized as a possible mechanism, in particular with lipids used in drug delivery.[127] [128] mRNA particles themselves may also potentially be a causative agent, acting as a direct mast cell degranulation agent. There is one report that trometamol, a buffer specific to the Moderna vaccine, was associated with anaphylaxis to gadolinium-based contrast agents, also by a direct degranulation mechanism.[129] Toll Like Receptors (TLR) 3,7, and 8 can be directly activated by double-stranded and single-stranded RNA particles from viruses, and can cause mast cell degranulation.[130,131] Although the likelihood of such events from a SARS-CoV-2 mRNA vaccine is unclear, these pathways should be considered among the potential mechanisms for allergic reactions to these vaccines.[132]

Caution should be exercised in considering excipients as a provoking cause of vaccine reactions. While excipients have occasionally caused allergic reactions with other vaccines, historically many excipients have also been wrongly implicated based on theoretical rather than actual risk, most prominently egg (ovalbumin) in modern influenza vaccines.[75,96,133] This may be due to excipient concentrations being well below a threshold necessary to provoke a reaction.[134,135] This may also prove to be the case for excipients that are suspected triggers for the SARS-CoV-2 vaccine reactions.

There is one published approach for SARS-CoV-2 mRNA vaccination with guidance based on skin testing to excipients. [14,18] Notably, if methylprednisolone acetate is used for testing, the clinician should be aware this may contain both PEG and Polysorbate 80, and should test only with brands of methylprednisolone that do not also contain Polysorbate 80.[14] The clinician should also be aware that the quantity of PEG administered by intradermal testing using this agent could exceed the quantity of PEG in the Pfizer-BioNTech mRNA vaccine, which only contains 0.05mg PEG-2000 per dose (Table E6). Therefore, even in persons with known PEG allergy who have positive PEG skin testing, it is likely that graded or full dose SARS-CoV-2 mRNA vaccine would be well tolerated if no systemic allergic reaction occurred during skin

testing. The positive PEG test is less problematic to interpret, given this specificity, but no data exists to specify that positive PEG sensitization definitively infers a significant risk that such patients will not tolerate PEG-containing vaccines. As such, there is no clear role for the use of skin testing to PEG to inform a decision to withhold the vaccine or not, which is consistent with the last published vaccine allergy practice parameter which suggests excipient or vaccine sensitized individuals should be offered a graded dose challenge or multi-step desensitization instead of withholding the vaccine.[14,96] Data regarding skin testing to SARS-CoV-2 vaccine itself are scant. There are a small number of patients with suspected SARS-CoV-2 vaccine reactions who have undergone vaccine testing, most with negative results, but all who were willing to receive a second dose tolerated it without reaction irrespective of positive vaccine skin testing.[117,118,120] The 3 individuals with a history of mRNA reaction with sensitization to either the vaccine or PEG either declined or were not offered the opportunity to receive a second dose. If vaccine testing is to be performed in persons hesitant to proceed with vaccination, the vaccine should be prepared per manufacturer instructions with regard to storage, thawing, and diluting for reconstitution. Consistent with the last published vaccine practice parameter, patients with positive skin testing to a SARS-CoV-2 vaccine may receive vaccination through graded or full dosing (see below).[120] Limited safety data are available for testing to the vaccine or the vaccine excipients in this context. Further details regarding international variation about recommendations for vaccine/excipient testing are detailed in Figure 1.

While testing may be considered as a preference-sensitive option in shared decision-making, options for cautious administration of vaccine (Figure 4) or the use of an alternative vaccine with a different platform and excipient may be additional considerations. Testing for PEG has not been shown to be necessary or of value in individuals with a history of severe allergic reactions, including anaphylaxis, to mRNA SARS-CoV-2 vaccines, nor has PEG yet been demonstrated as the causative agent of mRNA SARS-CoV-2 vaccine allergic reactions. Moreover, it has poor sensitivity in evaluating those with known severe allergic reactions to PEG. However, PEG testing may be considered in the very narrow context of shared decision-making in individuals who would otherwise be unwilling to be vaccinated and would decline vaccination if not offered testing. Testing-specific guidance could change if and when convincing evidence emerges for a role for PEG as a culprit agent. PEG-2000, the actual excipient, would likely be preferable to higher MW PEG as a testing agent, if available. Given the low mortality of anaphylaxis (<0.5%) in general,[136] and the higher mortality/morbidity of COVID-19, the risk of withholding SARS-CoV-2 vaccination is highly likely to exceed the risk of a severe allergic reaction, including anaphylaxis, after administration of the vaccine for many patients. However this consideration regarding withholding additional vaccine doses could change if additional estimates emerge of potentially high efficacy of a single dose of an mRNA vaccine, which could allow more time for decision-making regarding the risk/reward of additional dosing.[94] Threshold agreement was achieved for the voting on this recommendation on the first round of voting (Table E3).

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

Recommendation 5: We recommend a shared decision-making paradigm of care favoring vaccination through full or graded dosing (with or without additional observation time post-vaccination) or changing vaccine platforms to another agent over no vaccination because there is no single best approach to assessment and management of the patient with a suspected SARS-CoV-2 mRNA or adenovirus vector vaccine reaction, or the patient with an allergy to an excipient in either of these vaccines who has not yet been vaccinated.
Strong Recommendation; Moderate Certainty of Evidence

Recommendation 6: In patients with suspected immediate allergic reaction to SARS-CoV-2 vaccine whose standard schedule requires more than one dose, we recommend referral to an allergist for assessment of additional vaccination over no vaccination/vaccination being withheld. In resource limited settings where specialist referral is not readily available, alternatives may be presented in a shared decision-making context to provide assessment and opportunity for vaccination by remote consultation, use of alternative vaccine products, or delay in vaccination until a solution can be determined.
Strong Recommendation; Moderate Certainty of Evidence

Recommendation 7: In patients with a suspected or confirmed but remote past medical history of reaction to a SARS-CoV-2 vaccine excipient, we recommend referral to an allergist for assessment of additional vaccination over no vaccination/vaccination being withheld. In resource limited settings where specialist referral is not readily available, alternatives may be presented in a shared decision-making context to provide assessment and opportunity for vaccination by remote consultation, use of alternative vaccine products, or delay in vaccination until a solution can be determined.
Strong Recommendation; Moderate Certainty of Evidence

Recommendation 8: In patients with a definite/confirmed recent allergic reaction to SARS-CoV-2 vaccine and/or excipient, we recommend referral to an allergist for assessment of additional vaccination over no vaccination/vaccination being withheld. In resource limited settings where specialist referral is not readily available, alternatives may be presented in a shared decision-making context to provide assessment and opportunity for vaccination by remote consultation, use of alternative vaccine products, or delay in vaccination until a solution can be determined.
Strong Recommendation; Low Certainty of Evidence

Recommendation 9: While all vaccines should be administered in facilities capable of treating anaphylaxis, particularly for individuals with a prior immediate systemic allergic reaction to a SARS-CoV-2 vaccine or vaccine excipient, we recommend the clinician should administer SARS-CoV-2 mRNA or adenovirus vector vaccine in a setting equipped to manage anaphylaxis (e.g. hospital, mass immunization clinic, specialist office), under the supervision of personnel trained in the recognition and management of anaphylaxis. In resource limited settings where specialist referral is not readily available, alternatives may be presented in a shared decision-making context to provide assessment and opportunity for vaccination by remote consultation, use of alternative vaccine products, or delay in vaccination until a solution can be determined.
Strong Recommendation; Moderate Certainty of Evidence

Recommendation 10: We suggest against routine H1-antihistamine or systemic corticosteroid pre-medication prior to vaccination as it has low certainty evidence in preventing anaphylaxis, and theoretically corticosteroid pre-medication could diminish the immune response. Conditional Recommendation; Low Certainty of Evidence

Recommendation 11: We recommend in favor of globally coordinated research studies being conducted to address i) vaccine and vaccine excipient testing diagnostic accuracy for allergy to SARS-CoV-2 vaccines; ii) administration of the vaccine to individuals with prior anaphylaxis to the vaccine or vaccine excipient; iii) the necessity and efficacy of graded vaccine administration in the context of a patient with possible SARS-CoV-2 vaccine allergy; iv) the safety, efficacy, and necessity of mixing SARS-CoV-2 vaccine platforms; and v) the incremental benefit of additional doses of an mRNA or certain adenovirus-vector vaccines following an initial dose. Research Recommendation

Rationale/Discussion: Almost all allergy organizations recommend that the routine administration of SARS-CoV-2 vaccines are contraindicated in individuals with a suspected immediate allergic reaction to the SARS-CoV-2 vaccines or their components (i.e., PEG or polysorbate 80), although all allow consideration of referral to an allergist-immunologist to determine the likelihood the initial reported reaction was consistent with an allergic reaction of any severity, and if so, if a SARS-CoV-2 vaccine can be safely administered. (Figure 1) There is similar consistency in the precaution for patients with non-anaphylactic reactions to the initial vaccine dose (and for the CDC, a history of immediate allergic reactions to other vaccines or injectable medications) to be considered for vaccination under observation.[137,88] The Sputnik vaccine is contraindicated in people with a hypersensitivity to any of the vaccine components or any vaccine containing similar components, as well as contraindicated in people with a history of severe allergic reaction to the vaccine or its excipients. Additionally, the second dose of the Sputnik vaccine is contraindicated where severe complications, such as anaphylactic shock, severe generalized allergic reaction, seizures, fever over 40°C were noted after the first dose.[138] The CDC has issued a precaution to receiving the Johnson & Johnson vaccine in persons in whom the SARS-CoV-2 mRNA vaccine is contraindicated and suggested an option for administration of the Johnson & Johnson vaccine at least 28 days after the initial SARS-CoV-2 mRNA vaccine dose, although the incremental safety and effectiveness of such a substitution is unknown.[139] The Johnson & Johnson vaccine carries with it a risk of thrombotic events (as does the AstraZeneca vaccine), which should be a consideration in this decision.[140,141]

Preference-sensitive care is defined by scenarios where there are multiple treatment options having significant tradeoffs and varying potential outcomes, where treatment decisions reflect the patient's personal values and preferences.[142] Despite general international agreement that evaluation by an allergist-immunologist be considered for patients with suspected risk of allergic reaction to the vaccine, there is no elaboration on how the allergy specialist should evaluate these patients to determine whether vaccination is advisable and how to proceed. The allergist can be of central importance in this evaluation process by taking a detailed history that thoroughly investigates the nature and timing of the reported reaction, and carefully considers the nature of the reported symptoms and whether they are the result of an immune mediated process and not the result of any mimicking condition that could be the result of a non-allergic process. This step alone is of critical importance and may represent the greatest value that the allergist can offer as

an expert in such evaluation. Also critical to involvement of the allergist in this process is for the persons providing vaccination to be trained to ask questions regarding risk of reaction and help facilitate referral to the allergist if there is a contraindication to receiving a dose, or in the case of a suspected allergic reaction occurring at their site. If possible, patients with a history of a possible allergy to PEG, polysorbate, other vaccines, or even their initial SARS-CoV-2 vaccine should be encouraged to be proactive in discussing this with their primary care provider before seeking initial or additional SARS-CoV-2 vaccine doses.

The 2012 Adverse Reactions to Vaccine Practice Parameter (from the American Academy of Allergy Asthma and Immunology [AAAAI] and American College of Allergy Asthma and Immunology [ACAAI] Joint Task Force on Practice Parameters) outlines a general approach for a patient with a known or suspected history of a vaccine/vaccine excipient reaction.[96] This includes possible vaccine and excipient testing, and several contextualized ways for vaccines to be administered. This approach recognizes that while administration of a vaccine in ***routine medical settings (e.g., non-allergy specialist)*** is contraindicated, with allergy specialist evaluation and supervision, the vaccine can still potentially be given. The ACAAI COVID-19 task force outlines, but does not endorse, an approach of graded vaccine challenge that could be considered for certain individuals. At least one case report has demonstrated this is both safe and feasible, though it is unclear if this is necessary.[120] The Australasian Society of Clinical Immunology and Allergy (ASCIA), Canadian Society of Allergy and Clinical Immunology (CSACI) and European Academy of Allergy and Clinical Immunology (EAACI) provide guidance for graded challenges in these patients and are consistent with the 2012 Practice Parameter.[21,143,144] However, none of these recommendations have data denoting safety.

COVID-19 and ramifications of SARS-CoV-2 infection represent a highly unique situation relative to other infectious diseases in terms of the global burden of this disease, and an imperative international public health need to attain herd immunity through vaccination. Any potential for vaccine refusal or the vaccine being withheld in a pandemic must be approached from an ethical perspective which considers whether SARS-CoV-2 infection and viral propagation are riskier outcomes than vaccination in a setting where severe allergic reactions can be managed.[145] While no single best choice in these contexts exists, it can be addressed through an individualized, shared decision-making approach reviewing treatment options and the risk-to-benefit trade-offs related to vaccine reactions vs. SARS-CoV-2 infection risk. Regardless of how the vaccine is administered, we recommend against routine pre-medication prior to vaccination (particularly with glucocorticosteroids) as it has low certainty evidence in preventing anaphylaxis, and glucocorticosteroid pre-medication (or glucocorticosteroid treatment of any suspected allergic reactions to SARS-CoV-2 vaccines including anaphylaxis) could diminish the immune response.[146,147]

Figure 4 outlines preference-sensitive approaches to the individual who had an allergic reaction to the initial dose of the vaccine. The allergist role here is central as well in helping a patient clarify their values as to their choices and the outcomes of those choices in proceeding with or declining vaccination. This process is highly distinct from evaluating someone with a history of allergy to a vaccine excipient, who has not yet received the initial vaccine. These approaches are only recommended for trained experts in the diagnosis of medication allergy (including allergic reactions to vaccines and medication provocation challenge), in facilities staffed with personnel

skilled and trained to be able to assess and treat an allergic reaction resulting from testing or vaccine administration. Resources must be available to provide direct observation of patients for a minimum of 30 minutes after the vaccine is administered. The outlined approaches all involve some degree of trade-off, and the ultimate choice must be informed by the values, goals, and preferences of patients. These issues must be balanced against increased infection risk, with increased morbidity and mortality, which becomes a risk from vaccine refusal or withholding vaccination. Graded vaccine challenge does offer some practical reassurance to the patient and clinician reluctant to proceed with single-dose vaccination, though full dose vaccination may be just as safe as a graded approach in many circumstances. In resource limited settings or if consultation with an allergy specialist is not readily available, such as in rural settings or in low- and middle-income countries, such shared decision-making does not need to be exclusively provided by a specialist. While specialist referral would be preferred any clinician may engage the patient in shared decision-making based on the options in Figure 4, allowing for local context in decision making, with input to the patient from the practitioners who are trusted by the local population. In particular, if first dose protection of any SARS-CoV-2 vaccine is high, or there is availability of an alternative vaccine platform, particular preference may be given for vaccine refusal/withholding the vaccine or administering this alternative agent in certain local and regional settings.

Experience with graded challenge with SARS-CoV-2 mRNA vaccines is limited at present to one very small case series. The efficacy of graded vaccination is unknown, though one report has shown this can be successful.[120] It is unknown if splitting doses and/or diluting the vaccine outside of the initial manufacturer recommendation would disrupt the vaccine integrity or impair immune response. However, these variables may potentially contribute to unforeseen issues in trying to adapt previously recommended approaches for vaccine administration where there is concern of possible allergy, rendering this option for graded-dose administration less preferable than single-dose administration.[96] Switching from one vaccine platform to another is an additional alternative to consider in this decisional matrix that may reduce reliance on graded-dosing and may be a more feasible office-based choice, which is endorsed by a number of international regulatory health agencies where multiple vaccine options are approved (Figure 1).[139]

The evaluation of individuals with a known or suspected PEG allergy (including anaphylaxis) but who have not yet received a vaccine is distinct. An algorithm for excipient testing has been published, but without evidence that the vaccine excipients are the cause of any vaccine reactions, or that excipient allergic/sensitized individuals cannot tolerate the vaccine. Our meta-analysis suggests skin testing to excipients as a screening measure prior to vaccination has low sensitivity and is unlikely to reliably identify persons at risk. A choice to test and then recommend a sensitized person not receive an mRNA vaccine could unnecessarily withhold an intervention based on speculation of risk, or force choice of an alternative vaccine platform (if available) that may have different non-immunologic risks. However, this could be a preference-sensitive option that concerned patients elect, and a negative skin test could be viewed as reassuring to proceed with use of an mRNA vaccination, despite the test having poor sensitivity. Similarly, it is reasonable to administer an mRNA vaccine following a shared decision-making process with an allergy specialist, either as a single or graded dose, or to provide an adenovirus vector vaccine (with precaution given polysorbate content) without testing. For individuals with

a polysorbate allergy, it is reasonable to administer an adenovirus vector vaccine following a shared decision-making process with an allergy specialist, either as a single or graded dose, or to provide an mRNA vaccine (with precaution given PEG content) without testing. Either vaccine should be given in a setting where the patient can be monitored for up to 30 minutes after vaccination and that is staffed and equipped to treat potential vaccine-associated anaphylaxis.

Withholding or refusing a second dose of an mRNA vaccine (either Moderna or Pfizer-BioNTech) has been considered by some, in the belief that the initial dose will provide adequate protection. Although we lack precise estimates of what constitutes durable protective adaptive immunity post-vaccination, data from the EUA suggest there is $\geq$50% protection at $\geq$2 weeks after the first dose (prior to administration of the second dose). Israeli reports suggest 33% to 60% protection more than 2 weeks after the first dose up to the time of the second dose.[148] Additional studies have suggested first-dose protection of up to 93% but with wide ranges of protection reported.[9,60,92,94,149-151] However, the duration of this partial protection is unknown, but likely shorter-lived than the immunity achieved after 2 doses or achieved naturally from SARS-CoV-2 infection. Optimal longer-term protection would be ensured by complete vaccination. Partial immunity at a community level is of concern because it might theoretically enable the spread of more virulent variants of the virus. Even within a shared decision-making paradigm, vaccine refusal or withholding a vaccine should remain an option of last resort, and all steps taken to avoid this outcome. Withholding/refusal, if chosen, should be clearly documented in the medical record, and the decision to do so made collaboratively by the patient after having been provided data regarding the nature of the risks.[92]

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

This document has several limitations. First, SARS-CoV-2 vaccination is a new and evolving topic, and data to date regarding allergic reactions, potential provoking causes of these reactions, and best management practices are limited. As such, there is intent to continue to re-evaluate and update these recommendations as more data are published regarding reactions and their management. Second, GRADE is one evidence rating approach, and has well-described limitations. Third, in this context, several recommendations are conditional, and have low certainty of evidence, which underscores the first limitation. This in particular may impact recommendations regarding excipient and/or direct vaccine testing, as well as considerations about withholding/refusing vaccination (initial or subsequent doses) or the best initial choice of a vaccine given a patient's history. Fourth, to perform the meta-analysis and data pooling for questions 2 and 3, we made two major assumptions: i) we considered all reactions coded in a Canadian drug allergy database as allergy to PEG or PEG containing medications as anaphylaxis; and ii) we considered any positive PEG skin test, by any method (prick or intradermal), to any listed concentration, as the same for the purposes of denoting a positive result to assess testing sensitivity and specificity. Both these assumptions allow for a liberal consideration of what defines a case, and increases the potential sensitivity of the analysis, at the risk of inflating both estimates. However, given limited data, we feel these are justified. Fifth, while our approach and recommendations were developed through systematic evidence synthesis, in some instances these recommendations contradict more empiric approaches from allergy professional societies and governmental health authorities. It is of note that no approach

or recommendation—ones made in this document or made previously by any society or governmental health authority—have been proven safe by high certainty of evidence in the context of evaluating suspected allergic reactions to these vaccines. Lastly, our recommendations may be limited to the populations that have been studied. Our approaches and considerations may be more or less relevant in particular countries or regions, depending on government policy, access to vaccination, access to allergy specialists for evaluation of potential reactions, and availability of resources for some of the options in our shared decision-making paradigm. In this analysis, there were no studies identified that addressed this issue in the context of low to middle income areas or resource-limited areas, and most of the studies on vaccine anaphylaxis are from tertiary care centers, which by definition are areas with access to specialty care, including allergists. In areas without access to an allergist, remote healthcare options or involvement of a healthcare provider who can assess and manage vaccine reactions could be considered, though this does not address individuals without access to care or locations lacking in some of the resources described. It is possible that recommendations made by an allergy specialist who is not actually administering the vaccine, to another care provider who is doing so, may not necessarily be accepted by others who may have less experience in treating anaphylaxis, or with administering a vaccine to someone who has been evaluated for a vaccine-associated allergic reaction. These factors may modify the recommendations stated. 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.

Conclusion

SARS-CoV-2 is a devastating global pandemic with limited treatment options, which has caused >3,000,000 global fatalities and >$10 trillion in global economic costs.[3] To achieve an optimal population herd immunity and mitigate the devastating impact of this infection, vaccination represents the optimal global strategy. Multiple vaccines have proven to be safe and effective in clinical trials and are now in use. Potential allergic reactions, including anaphylaxis, have been reported, but these have occurred very rarely. No uniform recommendations exist on an approach to the assessment and management of individuals with a known or suspected allergy to the excipients or the vaccine itself. This document provides evidence-based (where available) expert consensus that incorporates guidance from clinical specialists in Australia, Canada, Europe, South Africa, the United States, and the United Kingdom stressing a patient-centered approach involving consideration of the risks and benefits of receiving COVID-19 vaccination, the value and cost-effectiveness of testing and precautionary measures, and shared decision-making in recognition of multiple preference-sensitive approaches to this issue from an international perspective. There is no clear evidence that any pre-existing factor, or testing with the vaccine or excipients, can predict risk of reaction to the vaccine. As this is the first experience with these vaccines, this is intended 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. There are continued knowledge gaps and unmet needs outlined in Table 4 that must be addressed as the vaccine rollout continues. Given an imperative global need to vaccinate as many people in as many countries as possible, the clinician should be familiar with the risk of potential reactions to these vaccines, and the approach to their evaluation and management.

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Figure Titles/Legends:

Figure 1: Comparison of Contraindications and Warnings Regarding Allergic Reactions in Receiving SARS-CoV-2 Vaccination
Legend: Recommendations regarding precautions and contraindications regarding SARS-CoV-2 vaccinaion

Figure 2: Incidence of Anaphylaxis Reported in Association with SARS-CoV-2 Vaccination
Legend: Adjudicated and non-adjudicaed internationally reported rates of anaphylaxis to SARS-CoV-2 vaccines

Figure 3: Incidence of Polyethylene Glycol Allergy
Legend: Pooled incidence of reported polyethlene glycol allergy, in cases per million person years

Figure 4: Decisional Matrix for the Approach to Vaccinating the Patient with a Known or Suspected Potential Allergic Reaction to SARS-CoV-2 Vaccination
Legend: Considerations for Options in the Approach SARS-CoV-2 Vaccination in Patients with Known or Suspected Reaction to the Vaccine or Vaccine Excipient

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Table 1: Summary Recommendations

Question	Recommendation	Recommendation Strength	Evidence Certainty
What is the risk of SARS-CoV-2 vaccine anaphylaxis in a patient with no history of anaphylaxis to a SARS-CoV-2 vaccine or its excipients?	For patients with no history of a previous severe allergic reaction to a SARS-CoV-2 vaccine or its excipients, the risk of SARS-CoV-2 vaccine-induced anaphylaxis is very rare and we recommend vaccination over no vaccination based on this risk.	Strong	High
	For patients with a history of a severe allergic reaction, including anaphylaxis, unrelated to a SARS-CoV-2 vaccine or excipient but no history of a previous severe allergic reaction to a SARS-CoV-2 vaccine or its excipients, the requirement for additional observation beyond standard wait time (e.g., recommended by local health authorities for the general population) provides a minimal absolute risk reduction in severe allergic reaction outcomes and may also contribute to vaccine hesitancy. Therefore, we suggest against prolonged observation in those with a history of severe allergic reactions unrelated to a SARS-CoV-2 vaccine or excipient.	Conditional	Low
In patients without a history of anaphylaxis to a SARS-CoV-2 vaccine or its excipients, should allergy skin testing to SARS-CoV-2 vaccines or its excipients be performed?	In patients with no history of a severe allergic reaction, including anaphylaxis, to SARS-CoV-2 vaccines or its excipients, we recommend against vaccine or vaccine excipient testing prior to vaccination in an attempt to predict the rare individual who will have a severe allergic reaction to vaccination.	Strong	Low
In patients with a history of anaphylaxis to a SARS-CoV-2 vaccine or its excipients, should allergy skin testing to SARS-CoV-2 vaccines or its excipients be performed to determine if vaccine withholding is needed?	We suggest against the clinician routinely performing skin or in vitro testing using SARS-CoV-2 vaccines or excipients outside of the research setting for the purpose of vaccine withholding, given such testing has unknown sensitivity/specificity in predicting severe allergic reactions, including anaphylaxis, to SARS-CoV-2 vaccines.	Conditional	Low
Should SARS-CoV-2 mRNA or adenovirus vector vaccines be administered to an individual who had an immediate allergic reaction to the first dose of the vaccine (defined as a generalized, systemic allergic reaction with acute onset occurring within 4 hours of vaccine administration), or given as a first dose to an individual who is suspected to have reacted previously to an excipient ingredient that is also present in the SARS-CoV-2 mRNA or adenovirus vector vaccines?	We recommend a shared decision-making paradigm of care favoring vaccination through full or graded dosing (with or without additional observation time post-vaccination) or changing vaccine platforms to another agent over no vaccination because there is no single best approach to assessment and management of the patient with a suspected SARS-CoV-2 mRNA or adenovirus vector vaccine reaction, or the patient with an allergy to an excipient in either of these vaccines who has not yet been vaccinated.	Strong	Moderate
	In patients with suspected immediate allergic reaction to SARS-CoV-2 vaccine whose standard schedule requires more than one dose, we recommend referral to an allergist for assessment of additional vaccination over no vaccination/vaccination being withheld. In resource limited settings where specialist referral is not readily available, alternatives may be presented in a shared decision-making context to provide assessment and opportunity for vaccination by remote consultation, use of alternative vaccine products, or delay in vaccination until a solution can be determined.	Strong	Moderate
	In patients with a suspected or confirmed but remote past medical history of reaction to a vaccine excipient, we recommend referral to an allergist for assessment of additional vaccination over no vaccination/vaccination being withheld. In resource limited settings where specialist referral is not readily available, alternatives may be presented in a shared decision-making context to provide assessment and opportunity for vaccination by remote consultation, use of alternative vaccine products, or delay in vaccination until a solution can be determined.	Strong	Moderate
	In patients with a definite/confirmed recent allergic reaction to COVID vaccine and/or excipient, we recommend referral to an allergist for assessment of additional vaccination over no vaccination/vaccination being withheld. In resource limited settings where specialist referral is not readily available, alternatives may be presented in a shared decision-making context to provide assessment and opportunity for vaccination by remote consultation, use of alternative vaccine products, or delay in vaccination until a solution can be determined.	Strong	Low
	While all vaccines should be administered in facilities capable of treating anaphylaxis, particularly for individuals with a prior immediate systemic allergic reaction to a SARS-CoV-2 vaccine or vaccine excipient, we recommend the clinician should administer SARS-CoV-2 mRNA or adenovirus vector vaccine in a setting equipped to manage anaphylaxis (e.g. hospital, mass immunization clinic, specialist office), under the supervision of personnel trained in the recognition and management of anaphylaxis. In resource limited	Strong	Moderate

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	settings where specialist referral is not readily available, alternatives may be presented in a shared decision-making context to provide assessment and opportunity for vaccination by remote consultation, use of alternative vaccine products, or delay in vaccination until a solution can be determined.		
	We suggest against routine H1-antihistamine or systemic corticosteroid pre-medication prior to vaccination as it has low certainty evidence in preventing anaphylaxis, and theoretically corticosteroid pre-medication could diminish the immune response.	Conditional	Low
	We recommend in favor of globally coordinated research studies being conducted to address i) vaccine and vaccine excipient testing diagnostic accuracy for allergy to SARS-CoV-2 vaccines; ii) administration of the vaccine to individuals with prior anaphylaxis to the vaccine or vaccine excipient; iii) the necessity and efficacy of graded vaccine administration in the context of a patient with possible SARS-CoV-2 vaccine allergy; iv) the safety, efficacy, and necessity of mixing SARS-CoV-2 vaccine platforms; and v) the incremental benefit of additional doses of an mRNA or certain adenovirus-vector vaccines following an initial dose.	Research Recommendation	

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Table 2: Comparison of Reported US Cases of mRNA Vaccine Anaphylaxis Using Different Anaphylaxis Rating Criteria

Anaphylaxis definition	Certainty	Pfizer-BioNTech 14–23 Dec 2020	Moderna 21 Dec 2020–10 Jan 2021	Non-COVID vaccines 2009-2011, USA
Brighton criteria (as reported)	Level 1-3	21 cases in 1, 893 360 doses 11.1/million (95%CI 6.9-17.0)	10 cases in 4,041,396 doses 2.5/million (95%CI 1.2-4.6)	33 cases in 25,173,965 doses 1.3/million (95%CI 0.9-1.8)
Brighton criteria (reassessed)	Level 1-3	15 cases 7.9/million (95%CI 4.4-13.1)	5 cases 1.2/ million (95%CI 0.4-2.9)	31 cases 1.2/million (95%CI 0.8-1.8)
National Institute of Allergy and Infectious Disease (NIAID)	Probable	4 cases 2.1 /million (95%CI 0.6-5.4)	3 cases 1.5/million (95%CI 0.2-2.2)	18 cases 0.7/million (95%CI 0.4-1.1)
	Possible	Up to 8 cases 4.2 /million (95%CI 1.8-8.3)	Up to 6 cases 1.5/million (95%CI 0.5-3.2)	Up to 31 cases 1.2/million (95%CI 0.8-1.8)
World Allergy Organization (WAO)	Probable	10 cases 5.3/million (95%CI 2.5-9.7)	4 cases 1.0/million (95%CI 0.3-2.5)	25 cases 1.0 /million (95%CI 0.6-1.5)
	Possible	Up to 12 cases 6.3 /million (95%CI 3.2-11.1)	Up to 7 cases 1.7 /million (95%CI 0.7-3.6)	Up to 31 cases 1.2/million (95%CI 0.8-1.8)

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Table 3: Comparison of SARS-CoV-2 Vaccines and Excipients

Vaccine	Availability	Vaccine type	Excipients
CoronaVac (Sinovac, China)	Brasil, China (essential workers and high-risk groups), Indonesia, Turkey.	Inactivated vaccine (formalin with alum adjuvant)	Aluminum hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride
Convidicea Ad5-nCoV (CanSino Biologics, Beijing Inst. Biotech., NPO Petrovax)	China (limited to military use only), Mexico, Pakistan	Recombinant adenovirus type 5 vector against spike RBD protein	N/A
BBIBP-CorV (Sinopharm, Beijing Institute & Wuhan Inst. of Biological Products)	China, Bahrain, Egypt, UAE.	Inactivated SARS-CoV-2 (vero cells) + aluminum hydroxide adjuvant	Aluminum hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, sodium hydroxide, sodium bicarbonate, M199
Pfizer-BioNTech BNT162b2	Argentina, Australia, Bahrain, Canada, Chile, Costa Rica, Ecuador, EU, Israel, Japan, Jordan, Kuwait, Mexico, Oman, Panama, Saudi Arabia, Singapore, Switzerland, UK, USA, WHO.	mRNA-based vaccine (encoding the viral spike (S) glycoprotein)	(4-hydroxybutyl) azanediyl)bis (hexane-6,1-diyl)bis(2-hexyldecanoate)] (ALC-0315), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159),1,2-Distearoyl-sn-glycero-3-phosphocholine cholesterol, potassium chloride, potassium dihydrogen phosphate, sodium chloride, disodium hydrogen phosphate dihydrate, sucrose, water for injection
Moderna mRNA-1273	Canada, EU, Israel, Switzerland, UK, USA	mRNA-based vaccine (encoding the pre-fusion stabilized spike (S) glycoprotein)	Lipids (SM-102, 1,2-dimyristoyl-rac-glycero3-methoxypolyethylene glycol-2000 [PEG2000-DMG], cholesterol, and 1,2-distearoyl-snglycero-3-phosphocholine [DSPC]), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose.
ChAdOx1 (Oxford/AstraZeneca; Covishield in India)	Argentina, Australia, Canada, Dominican Republic, El Salvador, EU, India, Mexico, Morocco, UK.	Replication-deficient viral vector vaccine (adenovirus from chimpanzees)	L-Histidine, L-Histidine hydrochloride monohydrate, Magnesium chloride hexahydrate, polysorbate 80, Ethanol, Sucrose, Sodium chloride, Disodium edetate dihydrate, Water for injection
Covaxin (BBV152) (Bharat Biotech, India)	India	Inactivated vaccine	N/A
Sputnik V (Gamaleya Research Inst)	Russia, Palestine	Non-replicating, two-component vector (adenovirus) against spike (S) glycoprotein	Tris (hydroxymethyl) aminomethane, sodium chloride, sucrose, magnesium chloride hexahydrate, Sodium EDTA, polysorbate 80, ethanol, water for injection
EpiVacCorona (Federal Budgetary Research Institution State Research Ctr, Russia)	Russia	Peptide vaccine with alum adjuvant	Aluminum hydroxide, potassium dihydrogen phosphate, potassium chloride, sodium hydrogen phosphate dodecahydrate, sodium chloride, water for injection

Adapted and modified from Turner PJ, Ansotegui IJ, Campbell DE, Cardona V, Ebisawa M, El-Gamal Y, et al. COVID-19 vaccine-associated anaphylaxis: A statement of the World Allergy Organization Anaphylaxis Committee. World Allergy Organ J 2021;14:100517. (Open Access)

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Table 4: Knowledge Gaps and Unmet Needs Regarding SARS-CoV-2 Vaccination and Risk of Allergic Reactions

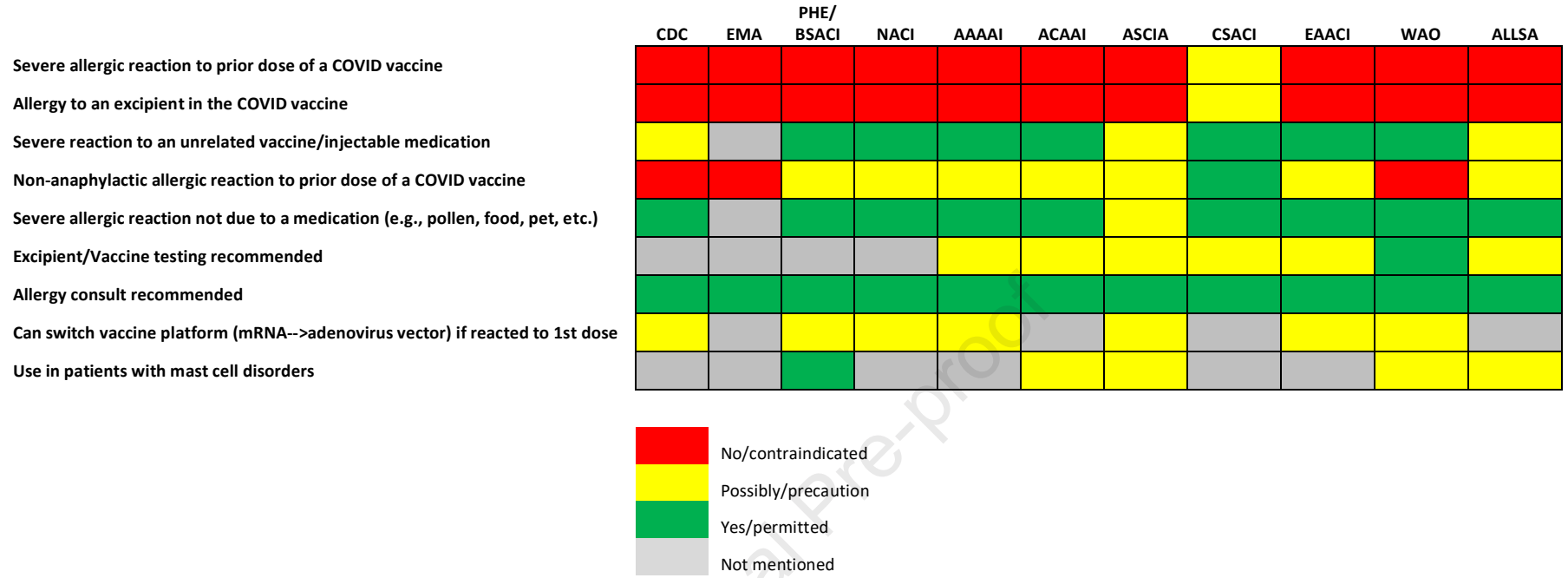
Knowledge Gaps and Unmet Needs
Knowledge Gaps
Definitive identification of an immunologic mechanism for reactions
Determination of a known excipient(s) as an allergen
Determination of risk for receiving SARS-CoV-2 vaccines containing an excipient to which a recipient is allergic
Determination of risk in receiving a second dose of a SARS-CoV-2 vaccine after an allergic reaction to the first dose
Establish test sensitivity, specificity, and reliability for use of the vaccine and/or vaccine excipients as a testing reagent
Accurate determination of the incidence of allergic reactions, including anaphylaxis
Identification of potential risk factors associated with allergic reactions
Necessity of testing or how test results may influence patient hesitancy to receive vaccination
Necessity of single vs. graded/split dosing for risk-assessment
Necessity of additional post-vaccination observation time for risk-assessment
Efficacy of mixed vaccine platform schedule
Stability of graded /split dosing for mRNA vaccines
Determination of durable immunity conferred by 1st dose of a vaccine to assist in determining risk/reward of additional doses
Unmet Needs
Consensus on reporting standards for anaphylaxis related to vaccines (Brighton Collaboration Criteria vs. NIAID or WAO criteria
Development of an active surveillance system for vaccine reactions
Preparedness and training of personnel at vaccination clinics to properly identify and treat potential anaphylaxis.
Consideration for use of placebo dosing, under a shared decision-making paradigm, for determining validity of a reaction in patients with underlying anxiety
Evidence-based algorithmic approach to individuals with reactions to the first dose of a SARS-CoV-2 vaccine or who have a history of SARS-CoV-2 vaccine excipient allergy
Handling of assessment of patients with a vaccine reaction or an excipient allergy in settings where there is reduced access to specialist care or persons with experience in managing anaphylaxis (e.g., rural, low/middle income countries)

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Figure 1:



Links:

CDC	https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html#Appendix-B
EMA	https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised
PHE/BSACI	https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/961287/Greenbook_chapter_14a_v7_12Feb2021.pdf
NACI	https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-use-covid-19-vaccines.html#b9
AAAAI	https://education.aaaai.org/resources-for-a-i-clinicians/reactionguidance_COVID-19
ACAAI	https://college.acaai.org/acaai-guidance-on-risk-of-allergic-reactions-to-mrna-covid-19-vaccines-2/
ASCIA	https://www.allergy.org.au/hp/papers/guide-allergy-and-covid-19-vaccination
CSACI	https://csaci.ca/wp-content/uploads/2021/01/COVID-19-VaccineTesting-AdministrationGuidance-JAN5.pdf
EAACI	https://onlinelibrary.wiley.com/doi/epdf/10.1111/all.14739
WAO	https://reader.elsevier.com/reader/sd/pii/S1939455121000119?token=2F0FBD2611406DCF769C5E18985FED1C4436016F11D60C405BEE091ACDDE98F9C76DF5DDA146DFE68E17095B7BFD9E5B
ALLSA	https://sacoronavirus.co.za/vaccine-updates/

Centers for Disease Control and Prevention (CDC, US); European Medicines Agency (EMA, EU), Public Health England/British Society for Allergy and Clinical Immunology (PHE/BSACI), National Advisory Committee on Immunizations (NACI, Canada), American Academy of Allergy, Asthma and Immunology (AAAAI, US); American College of Allergy, Asthma and Immunology (ACAAI, US); Australasian Society of Clinical Immunology and Allergy (ASCIA, Australia and New Zealand); Canadian Society of Allergy and Clinical Immunology (CSACI, Canada); European Academy of Allergy and Clinical Immunology, (EAACI, EU); World Allergy Organization (WAO, global), ALLSA (Allergy Society of South Africa)

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Figure 2:

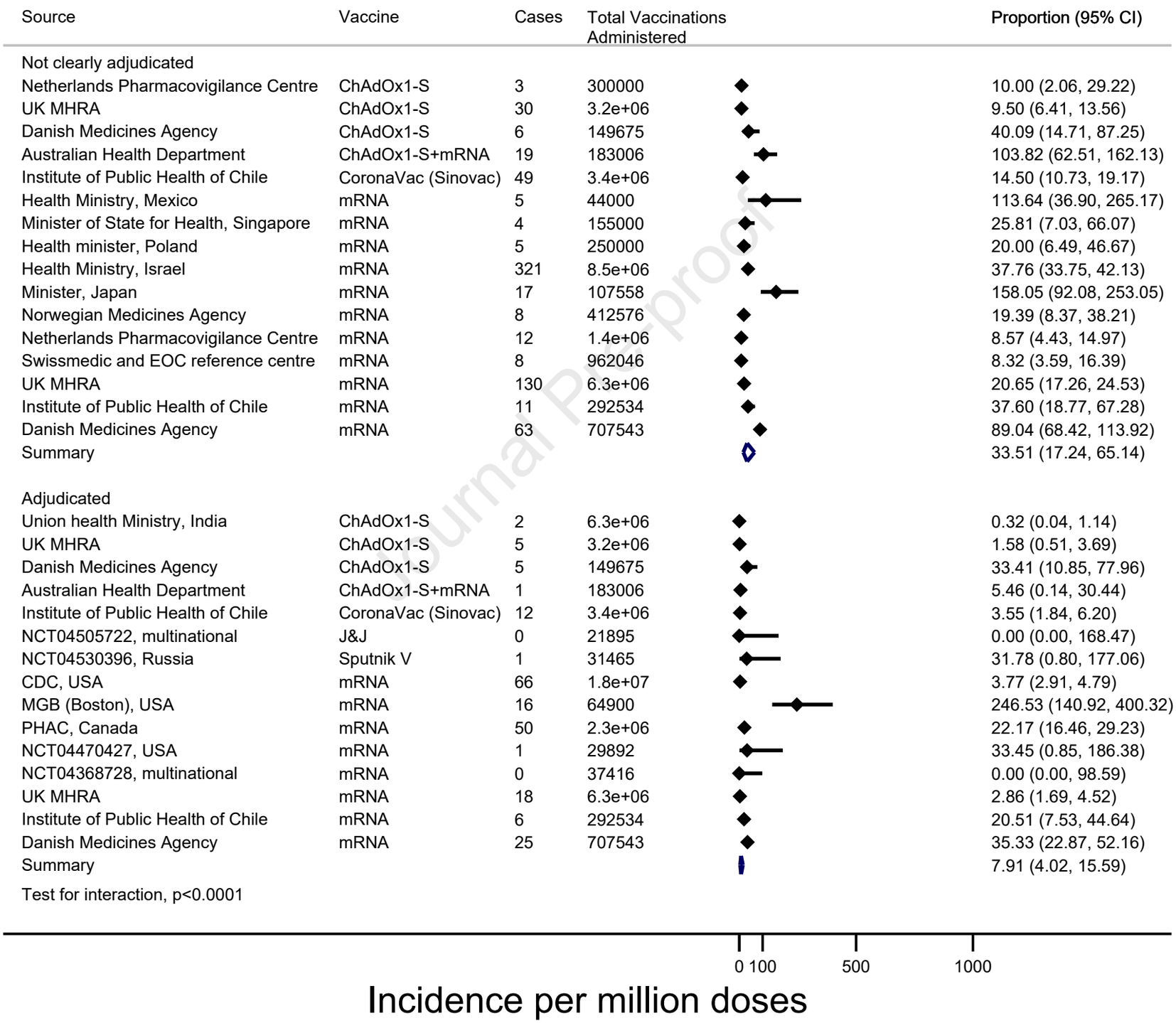
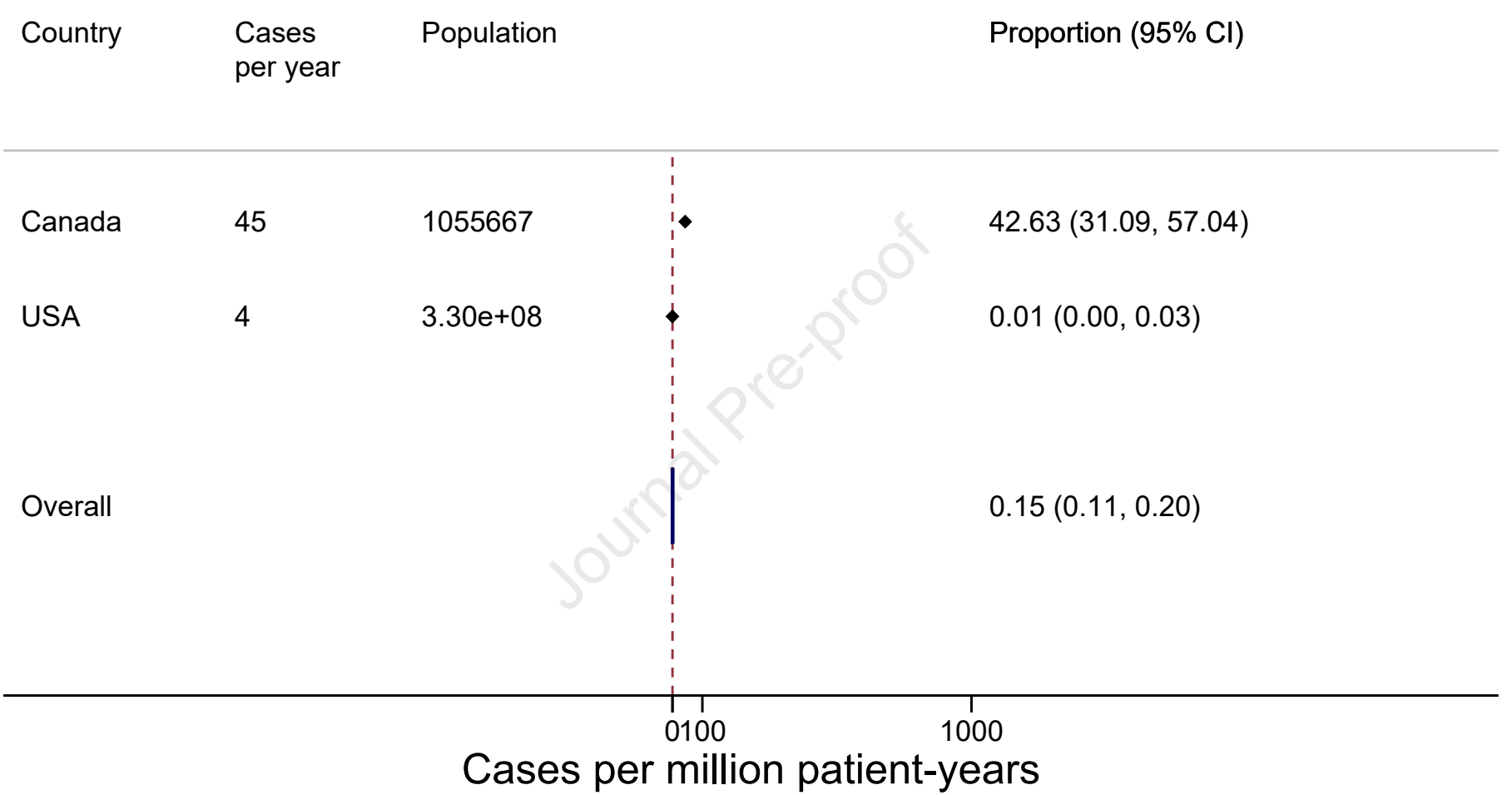


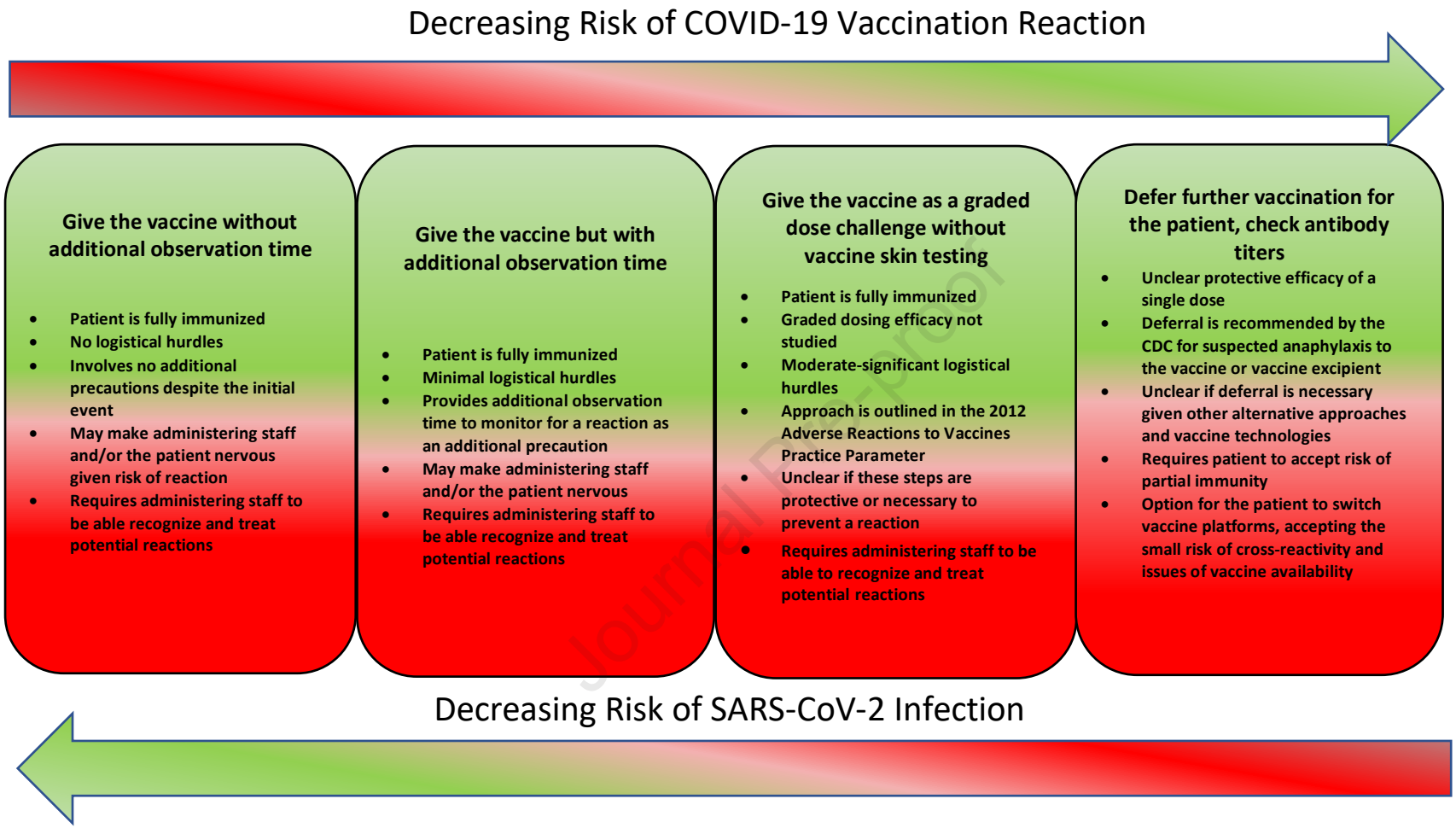
Figure 3:

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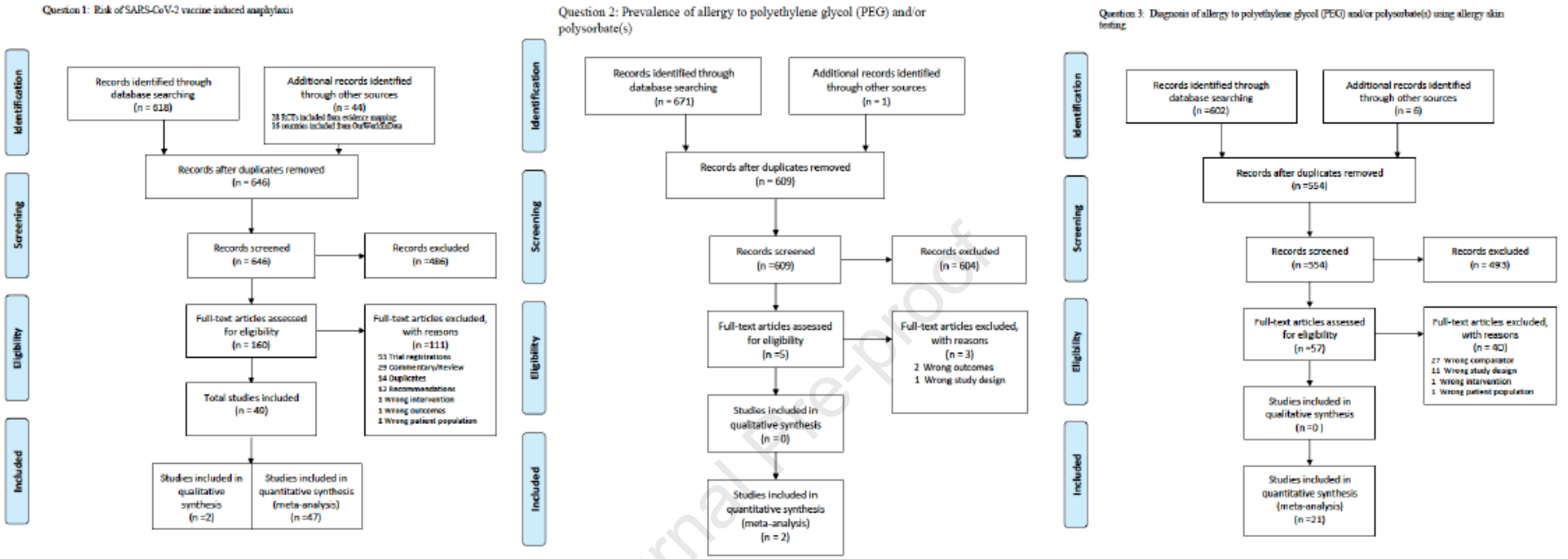
Figure 4:



These options are also considerations for patients wishing to receive a second dose of a SARS-CoV-2 mRNA vaccine without graded dosing. The green to red color gradient across and within each choice represents gradually increasing risk. There is no single best-choice approach to vaccinating an individual with a suspected history of an allergic reaction to a SARS-CoV-2 vaccine. There is a trade-off between potential subsequent risk of a reaction and the ability that can be safely managed, the risk of reduced efficacy from splitting the vaccine dose into two or more steps that may require dilution, and the risk of contracting SARS-CoV-2 infection as a result of having partial immunity resulting from deferring additional vaccine doses. The risks, benefits, and trade-offs should be thoroughly and carefully discussed with the patient, and the selected approach be made through a shared decision-making process. *Alternative vaccine platforms may encourage use of options to give the vaccine with or without additional observation time, although use of combination SARS-CoV-2 vaccine platforms has not been well studied.* Consult published guidance regarding how to interpret antibody titers or other immune markers post-vaccination.

***All of the approaches outlined are only intended for consideration in a specialist's office, who has been trained in the diagnosis and management of allergic reactions, including anaphylaxis.**

Figure E1: PRISMA Diagrams



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Figure E2: Risk of Bias Assessment for Question 1

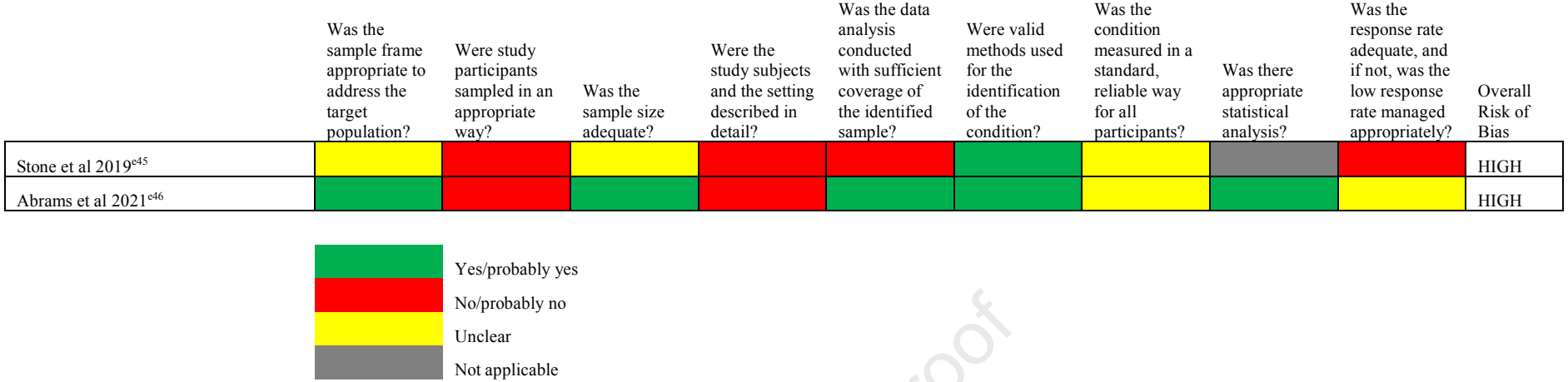
	Was the sample frame appropriate to address the target population?	Were study participants sampled in an appropriate way?	Was the sample size adequate?	Were the study subjects and the setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were 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 Risk of Bias
UK MHRA [e1]										HIGH
UK MHRA [e1]										HIGH
UK MHRA [e1]										LOW
UK MHRA [e1]										LOW
Institute of Public Health of Chile [e2]										LOW
Institute of Public Health of Chile [e2]										LOW
Institute of Public Health of Chile [e2]										HIGH
Institute of Public Health of Chile [e2]										HIGH
Australia Health Department [e3]										HIGH
Australia Health Department [e3]										LOW
Mexico Heath Ministry [e4]										HIGH
Singapore Health Ministry [e5]										HIGH
USA CDC VAERS [e6]										LOW
MGB (Boston) [e7]										HIGH
India Health Ministry [e8]										LOW
Public Health Agency of Canada [e9]										LOW
Poland Health Ministry [e10]										HIGH
USA NCT04405076 [e11]										HIGH
Australia and the United States NCT04368988 [e12]										HIGH
USA NCT04537208 [e13]										HIGH
South Africa NCT04444674 [e14]										HIGH
South Africa NCT04533399 [e15]										HIGH
USA NCT04436276 [e16]										HIGH
USA NCT04470427 [17]										LOW
Australia NCT04495933 [e18]										HIGH
China NCT04412538 [e19]										HIGH
India NCT04471519 [e20]										HIGH
India NCT04471519 [e21]										HIGH

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Multiple NCT04505722 [e22]										LOW
Australia NCT04368988 [e23]										HIGH
Russia NCT04530396 [e24]										LOW
Multiple NCT04368728 [e25]										LOW
China NCT04412538 [e26]										HIGH
Australia NCT04405908 [e27]										HIGH
UK, Brazil and South Africa Multiple registrations [e28]										HIGH
USA NCT04368728 [e29]										HIGH
USA NCT04368728 [e29]										HIGH
Canada NCT04450004 [e30]										HIGH
China NCT04383574 [e31]										HIGH
China ChiCTR2000032459 [e32]										HIGH
China ChiCTR2000031809 [e33]										HIGH
China NCT04466085 [e34]										HIGH
China NCT04445194 [e35]										HIGH
China NCT04352608 [e36]										HIGH
China NCT04341389 [e37]										HIGH
Israel Health Minister [e38]										HIGH
Japan Health Minister [e39]										HIGH
Norwegian Medicines Agency [e40]										HIGH
Romania [e41]										HIGH
Romania [e41]										HIGH
Netherlands Pharmacovigilance Centre [e42]										HIGH
Netherlands Pharmacovigilance Centre [e42]										HIGH
Swissmedic [e43]										HIGH
Danish Medicines Agency [e44]										LOW
Danish Medicines Agency [e4]										LOW
Danish Medicines Agency [e44]										HIGH
Danish Medicines Agency [e44]										HIGH

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Figure E3. Risk of Bias, Question 2



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Figure E4. Risk of Bias, Question 3

		Risk of Bias				Applicability		
Author	Agent	Could Patient Selection Have Introduced Bias	Could the conduct or interpretation of the index test have introduced bias	Could the reference standard, its conduct, or its interpretation have introduced bias	Could the patient flow have introduced bias	Is there concern that the included patients do not match the review question	Is there concern that the index test, its conduct, or interpretation differ from the review question	Is there concern that the target condition as defined by the reference standard does not match the review question
Setullarnay 2000 [e47]	PEG							
Stone 2019 [e45]	PEG							
Wenande 2016 [e48]	PEG							
Sanchez Moreno 2015 [e49]	PEG							
Extremera Ortega 2018 [e50]	PEG							
Shah 2013 [e51]	PEG							
Pizzimenti 2014 [e52]	PEG							
Kim 2018 [e53]	PEG							
Sohy 2008 [e54]	PEG							
Giangrande 2019 [e55]	PEG							
Bommarito 2011 [e56]	PEG							
Hryr 2006 [e57]	PEG							
JoverCerda 2019 [e58]	PEG							
AntonGirones 2008 [e59]	PEG							
Badiu 2015 [e60]	PEG							
Perez-Perez 2011 [e61]	PS							
Wagner 2018 [e62]	PS							
Badiu 2012 [e63]	PS							
Shelly 1995 [e64]	PS							
Coors 2005 [e65]	PS							
Limaye 2002 [e66]	PS							

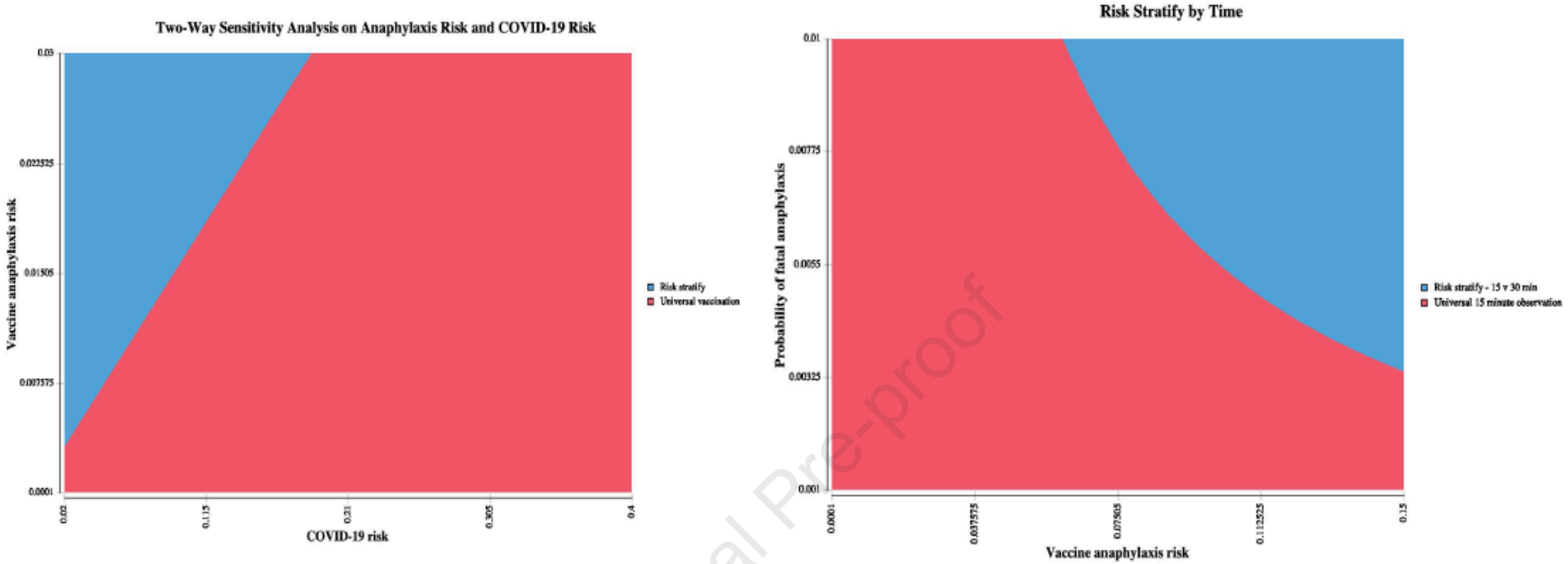
Low
High
Unclear

PEG= polyethylene glycol
PS= polysorbate

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Figure E5: Sensitivity Analysis of SARS-CoV-2 Vaccine Deferral and Post-Vaccination Wait-Time



Legend:
Panel A: Two-way sensitivity analysis of anaphylaxis risk and COVID-19 risk. As risk of COVID-19 increased, cost-effectiveness of a risk-stratified required vaccine deferral at higher anaphylaxis risk thresholds. Red area shows where universal vaccination is the optimal strategy, and blue area shows where risk stratification is the optimal strategy.

Panel B: Two-way sensitivity analysis of risk-stratification by time. Evaluating risk stratification of anaphylaxis risk by observation time, a universal approach of 15 minute observation was preferred until risk of anaphylaxis and anaphylaxis case-fatality rates rose significantly (red area). However, if a 1% anaphylaxis case-fatality was assumed, a risk-stratified approach of 30 minute (vs 15 minute) observation became cost-effective when vaccine anaphylaxis exceeded 6% (WTP = 10,000,000 per death prevented) (blue area)

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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	

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Table E2: GRADE Evidence Certainty Tables

Question 1: Risk of severe allergic reaction, including anaphylaxis, after SARS-CoV-2 vaccination

№ of studies	Certainty assessment						Effect			Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of events	№ of individuals	Rate (95% CI)		
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

Explanations

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.

Question 2: Screening compared to no screening for diagnosing PEG allergy in the general population

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
2	observational studies	serious [a]	not serious	not serious	serious [b]	publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect [c]	Between 2 studies reviewing US and Canadian drug allergy case reports to a federal reporting system (FDA Adverse Event Reporting System Canadian Primary Care Sentinel Surveillance Network repository) a total of 163 cases out of 1,582,377 entries were consistent with a PEG/Polysorbate allergy or to a medication containing PEG/Polysorbate as an excipient. This is a prevalence rate of 0.01% (100 cases per million)	⊕◯◯◯ VERY LOW	CRITICAL

Explanations

a. It is possible that cases are underreported due to unrecognized cases of reactions to non-identified excipients. b. There were only two studies. c. Patients with idiopathic anaphylaxis may go undiagnosed without evaluation to diagnose PEG/Polysorbate allergy

Question 3: Should PEG skin testing be used to diagnose SARS-CoV-2 vaccine allergy in persons with suspected PEG allergy?

Sensitivity	0.59 (95% CI: 0.44 to 0.72)
Specificity	0.99 (95% CI: 0.98 to 1.00)

Prevalences	0.001%	1%	10%

Outcome	№ 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 of 0.001%	pre-test probability of 1%	pre-test probability of 10%	
True positives (patients with COVID-19 vaccine allergy)	15 studies 296 patients	cohort & case-control type studies	very serious [a]	very serious [b]	very serious [c]	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)	⊕◯◯◯ VERY LOW
False negatives (patients incorrectly classified as not having COVID-19 vaccine allergy)								0 (0 to 0)	4 (2 to 9)	36 (24 to 95)	
True negatives (patients without COVID-19 vaccine allergy)								995 (977 to 999)	985 (967 to 989)	896 (879 to 899)	-
False positives (patients incorrectly classified as having COVID-19 vaccine allergy)								5 (1 to 23)	5 (1 to 23)	4 (1 to 21)	

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 test
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 report

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Table E3. Summary of the Modified Delphi Panel Results

Question	% Agreement and Mean Score[a,b]	Free text comments
Recommendation 1: For patients with no history of a previous allergic reaction to a SARS-CoV-2 vaccine or its excipients, the risk of SARS-CoV-2 vaccine-induced anaphylaxis is very rare and we recommend vaccination over no vaccination based on this risk. Strong Recommendation; High Certainty of Evidence	100% Mean score: 4.98	Strongly agree; Survey of Canada, very low numbers; Excellent section!
Recommendation 2: For patients with no history of a previous allergic reaction to a SARS-CoV-2 vaccine or its excipients the requirement for additional observation beyond standard wait time (e.g., recommended by local health authorities for the general population) provides a minimal absolute risk reduction in severe anaphylaxis outcomes and may also contribute to vaccine hesitancy. Therefore, we suggest against prolonged observation in those with a history of anaphylaxis unrelated to a SARS-CoV-2 vaccine or excipient. Conditional Recommendation; Low Certainty of Evidence	90.7% Mean score: 4.53	This may provide some patients with peace of mind and reassurance; I admit this is more art than science, but would not favor this recommendation, although qualified as conditional. When I have done this for selected patients (e.g., someone with venom anaphylaxis, not a patient with pollen-fruit syndrome) they do not view this as a burden, but seem to welcome the recommendation to prolong the wait time to 30 minutes; strongly agree; Is there evidence that longer wait contributes to vaccine hesitancy; Consider deleting word "also" so it reads "provides a minimal absolute risk reduction in severe anaphylaxis outcomes and may contribute to vaccine hesitancy""; The words "no history of anaphylaxis" in Question 1 could be replaced by "no history of allergic reactions" to be consistent with what reported in both Recommendation 1 and 2; They are not at increased risk; I have had patients who will only get the vaccine because they can wait and others ask if they really have to stay; If it makes some patients safer to receive the vaccine this way, it can be recommended to increase vaccine compliance (i.e. SDM)
Recommendation 3: In patients with no history of anaphylaxis to SARS-CoV-2 vaccines or its excipients, we suggest against vaccine or vaccine excipient testing prior to vaccination prior to vaccination in an attempt to predict the rare individual who will have a severe allergic reaction to vaccination.. Strong recommendation; Low Certainty of Evidence.	94.4% Mean score: 4.82	There are patients who have had anaphylaxis to a chemotherapeutic agent who I would judge as meriting skin testing -- are they included in this statement?; strongly agree; Please note that in Table 4, the description of the Jonhson and Jonhson vaccine seems to be missing; For table 4, I do not recall seeing the Johnson and Johnson vaccine listed but maybe I missed it. For figure 2, would it be clearer to say incidence per ten thousand "reports" on the x axis? Otherwise, it may seem like there are a lot more people with PEG allergy?
Recommendation 4: We suggest against the clinician routinely performing skin or in vitro testing using SARS-COV-2 vaccines or excipients outside of the research setting for the purposes of vaccine withholding, given such testing has unknown sensitivity/specificity in predicting severe allergic reactions, including anaphylaxis, to SARS-CoV-2 vaccines. Conditional recommendation; Low Certainty of Evidence	88.9% Mean score: 4.51	The key word here is "routinely"; strongly agree; What is clear based on the literature is that anaphylaxis with confirmed sensitization to PEG is possible, can be demonstrated by skin testing and serum IgE. Just because PEG allergy is a relatively rare event, does not mean there is no value in doing testing if it can be done. It is hard to establish testing validity for rare events and apply it to more widely--unless testing on those who have had anaphylaxis were to actually be done on a wider level (which would help establish its validity). This data should be collected as part of a research protocol, which isn't the same as saying don't do it at all.?; Given that Recommendation 4 is "conditional with low certainty of evidence" and that (line 473-474) "there is no elaboration on how the allergy specialist should evaluate these patients to determine whether vaccination is advisable and how to proceed" and that (Line 392-393) "testing may be considered as a preference sensitive option.." Figure 3 should report this option somewhere either in the box on the right or in the footnote (something like Can consider skin testing to vaccine or excipient(s) however, predictive value of this testing is not known and is recommended to be limited to research contexts). Please note that in Table 2 there is a mistake as the Recommendation Strength is reported as "Strong" while in the main manuscript is reported as "Conditional"; This statement is too strong in my view. In many countries and clinical settings this recommendation is hard to implement. It is fairly mentioned in the manuscript that ASCIA and WAO consider skin testing to the vaccine or its components an option. In the light of available evidence my suggestion would be to change the statement to "we cannot suggest for or against..." There is a sentence in the manuscript "While testing may be considered as a preference-sensitive option in shared decision-making, options for cautious administration of vaccine (Figure 3) or the use of an alternative vaccine with a different platform and excipient may be more practical choices" which also somehow contradicts recommendation in its' current form. ASCIA and WAO; NB: Table 2 has "strong" recommendation; in specialized units this may be performed even though there is no formal research project and may add to knowledge; For figure 3, it seems like boxes 1 and 2 only differ by 15 minute wait so risk of SARS-COV-2 are essentially the same. Should we add lack of availability of vaccines to specialist offices in this figure?; "Routinely" makes this question a "1" but feel this should be discussed, along with limits of sensitivity/specificity, with patient and some may wish to have testing. Routinely the answer is clearly a 1.
Recommendation 5: We recommend a shared decision-making paradigm of care favoring vaccination through full or graded dosing (with or without additional observation time post-vaccination) or changing vaccine platforms to another agent over no vaccination because there is no single best approach to assessment and management of the patient with a suspected SARS-CoV-2 mRNA or adenovirus vector vaccine reaction, or the patient with an allergy to an excipient	96.3% Mean score: 4.71	I'm on the fence with this one based on wording. Not sure whether we're talking about anaphylaxis when you say "generalized systemic allergic reaction"; I've had patients with urticaria who have gone on to receive round 2 with pretty much the same (and not more serious) reaction. Also, the statement states "suspected" vaccine reaction rather than actual reaction. Let me know if you wanna discuss this further; strongly agree; Figure 3: I would keep the red/green colors only in the 2 arrows, because the different colors in the 4 graphs create confusion and make it difficult to read the lines. Also in the last graph it is stated "Unclear protective efficacy of a single dose". It should

in either of these vaccines who has not yet been vaccinated. Strong Recommendation; Moderate Certainty of Evidence		be specified that this refers to the 2 doses vaccine and not the single dose (eg. Jonhson and Jonhson); For table 5, if we are using shared decision making, how can you blind a placebo dose for someone with anxiety?; Statement is too vague; For those with previous reactions to excipients, physicians should see if these excipients were tolerated in other vaccines or medicine too; Many physicians want a straightforward, "cookbook" answer and flow diagram on what to do with vaccine reactions. It is emphasized very well that individual physician judgment is essential and vital.
Recommendation 6: In patients with suspected immediate allergic reaction to SARS-CoV-2 vaccine whose standard schedule requires more than one dose, we recommend referral to an allergist for assessment of additional vaccination over no/deferred vaccination Strong Recommendation; Moderate Certainty of Evidence	98.1% Mean score: 4.82	Strongly agree; In my opinion the recommendation as currently stated allows for wide interpretation in terms of the type of patient that is appropriate for referral to an allergist; Recommendation 6 and 8 seems very similar with regards to allergic reaction to SARS-COV2 vaccine; We allergists/immunologists are indeed the experts.
Recommendation 7: In patients with a suspected or confirmed but remote history of reaction to a vaccine excipient, we recommend referral to an allergist for assessment of additional vaccination over no vaccination/vaccination being withheld. In resource limited settings where specialist referral is not readily available, alternatives may be presented in a shared decision-making context to provide assessment and opportunity for vaccination by remote consultation, use of alternative vaccine products, or delay in vaccination until a solution can be determined. Strong Recommendation; Moderate Certainty of Evidence	98.1% Mean score: 4.78	Strongly agree; What do you mean by remote? Do you mean a non-local reaction? If so, suggest wording is changed to "with a suspected or confirmed systemic reaction to a vaccine excipient"; In my opinion the recommendation as currently stated allows for wide interpretation in terms of the type of patient that is appropriate for referral to an allergist; My only concern is that many allergists really may not know what to do; Strongly agree with statement but we options for the specialist are limited other than a shared-decision making discussion. This is particularly a problem if the specialist does not have access to the vaccine.
Recommendation 8: In patients with a definite/confirmed recent allergic reaction to SARS-CoV-2 vaccine and/or excipient, we recommend referral to an allergist for assessment of additional vaccination over no vaccination/vaccination being withheld. In resource limited settings where specialist referral is not readily available, alternatives may be presented in a shared decision-making context to provide assessment and opportunity for vaccination by remote consultation, use of alternative vaccine products, or delay in vaccination until a solution can be determined. Strong Recommendation; Low Certainty of Evidence	98.1% Mean score: 4.82	Strongly agree; Despite the clarified definition of allergic reaction as generalized and systemic I still believe that that the recommendation is open to wide interpretation. I thought the phrase used in earlier version was more appropriate : ": We recommend that an allergist-immunologist evaluation be considered as a possible path in support of such patients being vaccinated,"; the strong likelihood here is that no further vaccine will be given
Recommendation 9: While all vaccines should be administered in facilities capable of treating anaphylaxis, particularly for individuals with a prior immediate systemic allergic reaction to a SARS-CoV-2 vaccine or vaccine excipient, we recommend the clinician should administer SARS-CoV-2 mRNA or adenovirus vector vaccine in a setting equipped to manage anaphylaxis (e.g. hospital, mass immunization clinic, specialist office), under the supervision of personnel trained in the recognition and management of anaphylaxis. In resource limited settings where specialist referral is not readily available, alternatives may be presented in a shared decision-making context to provide assessment and opportunity for vaccination by remote consultation, use of alternative vaccine products, or delay in vaccination until a solution can be determined. Strong Recommendation; Moderate Certainty of Evidence	94.4% Mean score: 4.80	Patients who are candidates for the vaccine can be stratified such that higher risk patients observe this recommendation. For individuals in the gen'l population without risk factor(s), this is not necessary and would interfere with efforts to vaccinate rapidly to achieve herd immunity; If this is routine vaccination, this is not needed as we state the risk is so low. Probably need to reword if this in regards to prior vaccine reactors; strongly agree; should make the wording clearer to explain this is just for those with definite or confirmed reactions; I am not sure about the e.g. specialist part since most Covid vaccines are not given by specialists and most allergists I know cannot obtain vaccine for their offices. If we want to emphasize the specialist, we may need to emphasize making vaccine available to allergy specialist offices (maybe add somewhere in lines 501-512); Routine vaccination should not require a specialist but the staff should be equipped to treat reactions. The "e.g." confused me as to the intent of question; Only in those with a history of anaphylaxis
Recommendation 10: We suggest against routine H1-antihistamine or systemic corticosteroid pre-medication prior to vaccination as it has low certainty evidence in preventing anaphylaxis, and theoretically corticosteroid pre-medication could diminish the immune response. Conditional Recommendation; Low Certainty of Evidence	98.1% Mean score: 4.75	I believe this is more than "theoretical"; strongly agree; What saves this statement is the use of the word "routine". In the text can state if a high risk person needs vaccine and has reacted to first dose, this is sdm based on precedent for prevention of complement mediated reactions. As much evidence for this as graded challenges to vaccines being recommended; We studied this for DT vaccine years ago, some effect on primary, no significant effect of OCS on booster; one could argue H1 antihistamine is a VERY low risk med to use. Would have considered changing to strong rec against for steroids only; this leaves latitude to pretreat with an H1 antihistamine in anxious patients; True with regard to anaphylaxis, but may have value in decreasing local and non-anaphylactic reactions/side effects.
Recommendation 11: We recommend in favor of globally coordinated research studies being conducted to address i) vaccine and vaccine excipient testing diagnostic accuracy for allergy to SARS-CoV-2 vaccines; ii) administration of the vaccine to individuals with prior anaphylaxis to the vaccine or vaccine excipient; iii) the necessity of graded vaccine administration in the context of a patient with possible SARS-CoV-2 vaccine allergy; iv) the safety, efficacy, and necessity of mixing SARS-CoV-2 vaccine platforms; and v) the incremental benefit of additional doses of an mRNA or certain adenovirus-vector vaccines	100% Mean score: 4.96	Great job with this!!!; strongly agree; Line 342 in manuscript should be sensitivity not specificity. Recommendations 4 and 10 need some more elaboration in the text of the document; Good to work towards these studies; Outstanding, clinically relevant points.

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following an initial dose; Research Recommendation		

[a]Voting scale: 1=strongly disagree, 2= disagree, 3=neutral, 4=agree, 5=strongly agree. Higher mean score indicates stronger agreement.
[b]Based on n=54 votes and 2 rounds of voting. Of 63 total authors, 3 did not vote due to strictly methodological roles, and 2 voted in the first round but not the 2nd as their IT systems repeatedly blocked the voting email. Four authors were added right as the second round of voting started, and these individuals were asked to rate their agreement outside of the voting, given we had already reached agreement threshold on the first vote (the second vote was to affirm minor wording changes) and worst-case scenario sensitivity analysis of these 6 authors noted no effect on reaching the agreement threshold (>75% voting "agree" [4] or avove).

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Table E4: Comparison of Criteria for the Grading of Anaphylaxis

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Brighton Collaboration Criteria	NIAID Criteria (2005)	WAO Criteria (2020)*
For all levels of diagnostic certainty Anaphylaxis is a clinical syndrome characterized by • sudden onset AND • rapid progression of signs and symptoms AND • involving multiple (≥2) organ systems, as follows Level 1 of diagnostic certainty • ≥1 major dermatological AND • ≥1 major cardiovascular AND/OR ≥1 major respiratory criterion Level 2 of diagnostic certainty • ≥1 major cardiovascular AND ≥1 major respiratory criterion OR • ≥1 major cardiovascular OR respiratory criterion AND • ≥1 minor criterion involving ≥1 different system (other than cardiovascular or respiratory systems) OR • (≥1 major dermatologic) AND (≥1 minor cardiovascular AND/OR minor respiratory criterion) Level 3 of diagnostic certainty • ≥1 minor cardiovascular OR respiratory criterion AND • ≥1 minor criterion from each of ≥2 different systems/categories <u>Major criteria</u> *Dermatologic or mucosal* • generalized urticaria (hives) or generalized erythema • angioedema*, localized or generalized • generalized pruritus with skin rash *Cardiovascular* • measured hypotension • clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following: • tachycardia • capillary refill time >3 s • reduced central pulse volume • decreased level of consciousness or loss of consciousness *Respiratory* • bilateral wheeze (bronchospasm) • stridor • upper airway swelling (lip, tongue, throat, uvula, or larynx) • respiratory distress—2 or more of the following: • tachypnea • increased use of accessory respiratory muscles (sternocleidomastoid, intercostals, etc.) • recession • cyanosis • grunting *Not hereditary angioedema. <u>Minor criteria</u> *Dermatologic or mucosal* • generalized pruritus without skin rash • generalized prickle sensation • localized injection site urticaria • red and itchy eyes *Cardiovascular* • reduced peripheral circulation as indicated by the combination of at least 2 of	Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled: 1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia (collapse], syncope, incontinence) 2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula) b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) 3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours): a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline Reference: Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, 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;117:391-7.	Anaphylaxis is highly likely when any one of the following 2 criteria are fulfilled: 1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING: a. Respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (e.g. hypotonia [collapse], syncope, incontinence) c. Severe gastrointestinal symptoms (e.g. severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens 2. Acute onset of hypotension* or bronchospasm or laryngeal involvement after exposure to a known or highly probable allergen for that patient (minutes to several hours), even in the absence of typical skin involvement. *Criteria are co-endorsed by 50 global allergy societies, but not AAAAI or EAACI Reference: Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J 2020;13:100472.

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• tachycardia and • a capillary refill time of >3 s without hypotension • a decreased level of consciousness *Respiratory* • persistent dry cough • hoarse voice • difficulty breathing without wheeze or stridor • sensation of throat closure • sneezing, rhinorrhea *Gastrointestinal* • diarrhea • abdominal pain • nausea • vomiting *Laboratory* • Mast cell tryptase elevation > upper normal limit Reference: Ruggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007;25:5675-84.		

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Table E5: Simulation model-based guidance for SARS-CoV-2 vaccine second dose deferral.

First dose protection	Second dose protection	Anaphylaxis risk threshold*
Very high overall vaccine protection (95%)		
90%	5%	0.13%
75%	20%	1.27%
50%	45%	5.72%
30%	65%	11.57%
5%	90%	21.72%
High overall vaccine protection (75%)		
70%	5%	0.38%
50%	25%	3.18%
30%	45%	8.01%
5%	70%	16.02%
Moderate overall vaccine protection (50%)		
45%	5%	0.70%
30%	20%	3.56%
5%	45%	10.88%
Low overall vaccine protection (30%)		
25%	5%	0.96%
5%	25%	6.05%

This table demonstrates the anaphylaxis risk threshold projected using different modeled scenarios considering efficacy of the first dose and increase in second dose protection against symptomatic COVID-19 infection. The degree to which first and second dose offer protection to others was not specifically modelled and could increase the anaphylaxis threshold at which second dose deferral would be cost-effective.

*Evaluation of cost-effectiveness threshold (willingness to pay: $10,000,000 per death prevented) of anaphylaxis risk for a second dose of an mRNA SARS-CoV-2 vaccination from a societal perspective. Anaphylaxis risk threshold represents the value at which second vaccine deferral is cost-effective in an at-risk population who has received some degree of durable protection from a first vaccination for the ensuing 12 months.

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Table E6: PEG and Polysorbate Content Conversion Chart for SARS-CoV-2 mRNA Vaccines

	Methylprednisolone acetate 40mg/ml	**Methylprednisolone acetate 4mg/ml**	**Methylprednisolone acetate 0.4mg/ml**	**Pfizer mRNA vaccine**	**Moderna vaccine**
PEG 3350	29.1 mg per ml	0.058 mg per 0.02 ml	0.0058 mg per 0.02ml	-	-
PEG 2000	-	-	-	0.05 mg per dose	not stated
Polysorbate	1.94 mg per ml	0.0039 mg per 0.02ml	0.00039mg per 0.02ml	-	-

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Author Roles:
Matthew Greenhawt, Elissa Abrams, Marcus Shaker, Derek Chu, David Khan, David Golden: development of the literature search questions, literature search, abstract review and data abstraction, data analysis, development of the primary iterative critical review of the manuscript, questions and recommendations

Antonio Bognanni, Anna Whalen-Brown: development of the literature search terms, literature search, abstract review and data abstraction, data analysis.

Timothy E. Dribin: conducting of the Delphi panel, iterative critical review of the manuscript

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Supplemental Methods: Systematic Review Question Development, Protocol, and Search Strategies

1) ***Question Development***

Prior to initiating a systematic review, 3 pre-specified questions were formulated for search, using the PICO (Population, Intervention, Comparator, Outcomes) format. The populations for study included published data for patients without known SARS-CoV-2 vaccine reaction or vaccine excipient allergy seeking vaccination (questions 1 and 2) and patients with known (or suspected) SARS-CoV-2 vaccine reaction or vaccine excipient allergy seeking vaccination (question 3). The questions developed included the following:

Question 1: What is the risk of a severe allergic reaction, including anaphylaxis, to a SARS-CoV-2 vaccine in a patient with no history of a severe allergic reaction to a SARS-CoV-2 vaccine or its excipients?
Population: Patients without known SARS-CoV-2 vaccine reaction or vaccine excipient allergy seeking vaccination
Intervention: SARS-CoV-2 vaccination
Comparator: Defer SARS-CoV-2 vaccination
Outcome: Allergic reaction to a SARS-CoV-2 vaccine

Question 2: In patients without a history of a severe allergic reaction, including anaphylaxis, to a SARS-CoV-2 vaccine or its excipients, should allergy skin testing to SARS-CoV-2 vaccines or its excipients be performed?
Population: Patients without known SARS-CoV-2 vaccine reaction or vaccine excipient allergy seeking vaccination
Intervention: Allergy skin testing to SARS-CoV-2 vaccines or its excipients (PEG, polysorbate 80)
Comparator: Not performing allergy skin testing to SARS-CoV-2 vaccines or its excipients (PEG, polysorbate 80)
Outcome: Allergic reaction to a SARS-CoV-2 vaccine

Question 3: In patients with a history of a severe allergic reaction, including anaphylaxis, to a SARS-CoV-2 vaccine or its excipients, should allergy skin testing to SARS-CoV-2 vaccines or its excipients be performed to determine if vaccine withholding is needed?

Population: Patients with a known SARS-CoV-2 vaccine reaction or vaccine excipient allergy seeking vaccination
Intervention: Allergy skin testing to SARS-CoV-2 vaccines or its excipients (PEG, polysorbate 80)
Comparator: Not performing allergy skin testing to SARS-CoV-2 vaccines or its excipients (PEG, polysorbate 80)
Outcome: Allergic reaction to a SARS-CoV-2 vaccine

A 4th question was formulated within the PICO search for question 3, but not analyzed with meta-analysis. This was based on investigator pre-specified determination that this literature was evolving in real-time and at the time the search was initiated, that no known literature to answer this question existed.

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

2) *Protocol*

Protocol version 2021-03-16

Anaphylaxis to SARS-CoV2 vaccines, excipients, and diagnostic test accuracy

Derek Chu, Matthew Greenhawt, Marcus Shaker, David Golden, Elissa Abrams, Antonio Bognanni, Anna Whalen-Browne

Review question

1. What is the risk of anaphylaxis to SARS-CoV2 vaccination?
2. What is the risk of polyethylene glycol and polysorbate allergy?
3. What is the diagnostic test accuracy of polyethylene glycol and polysorbate skin testing to diagnose allergy to these respective molecules?

Searches

The following data bases will be searched since inception (date of search, 19 Mar, 2021)
1. MEDLINE
2. Embase
3. WHO Global Coronavirus database
4. COVID NMA Vaccine RCT evidence map

We will also use Web of Science (all databases) forward and backward citation analysis of any relevant study. We will also search government websites and press releases for 50 countries with most vaccinations per OurWorldInData

No restrictions in language and period.

Types of study to be included

For risk of anaphylaxis and excipient allergy:
RCTs and observational studies, including adverse event reporting systems

For diagnostic test accuracy:
Any study design

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Condition or domain being studied

People at risk for anaphylaxis to SARS-CoV2 vaccines

Participants/population

General public

Intervention(s), exposure(s)

SARS-CoV2 vaccine

Comparator(s)/control

For risk of vaccine anaphylaxis or excipient allergy: Those not receiving SARS-CoV2 vaccine, though we anticipate that the majority of the data to answer this question optimally will come form adverse event reporting systems, which do not have a control arm.

For diagnostic test accuracy: 2x2 tables will be generated for true positives, true negatives, false positives and false negatives.

Context

Worldwide

Main outcome(s)

Respectively per question
1. Risk of vaccine induced anaphylaxis
2. Risk of excipient allergy
3. Sensitivity and specificity

Measures of effect

For questions 1 and 2, absolute measures of risk
For question 3, sensitivity and specificity

Additional outcome(s)

None

Measures of effect

None

Data extraction (selection and coding)

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

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Data extraction
Data extraction will occur independently and in duplicate. Any disagreement will be resolved by discussion, and if needed, a third author. We will extract, apart from the outcome measures, study characteristics including Author, year, country (ies), study design, definition of anaphylaxis (including adjudicated versus not).

Risk of bias (quality) assessment

Risk of bias assessment will use done per question using the most appropriate tool. For questions 1 and 2 addressing risk, we will use the JBI risk of bias tool for prevalence studies. For the diagnostic test accuracy question, we will use QUADAS-2.

Strategy for data synthesis

Given that we anticipate the events to be rare and of risks, we will meta-analyze proportions by logistic-normal random effects. Statistical heterogeneity will be assessed using the GRADE approach, as I^2 will likely be misleading in pooling large observational studies. Given the likelihood for sparse data for diagnostic test accuracy with zeros in the more than one cell of the 2x2 table, we anticipate specificity to be falsely high, and will report raw pooled sensitivity specificity across trials. Supplemental analyses may use a Bayesian approach. Analysis will be done using Stata 14.3. We will use the GRADE approach (GRADE Working Group. GRADE home. Available from: http://www.gradeworkinggroup.org) will be used for rating the overall quality of evidence.

Analysis of subgroups or subsets

1. Anaphylaxis to be higher among studies with no clear adjudication of anaphylaxis, as there are many mimickers of anaphylaxis.
2. mRNA vaccines are more likely than other types of vaccines to cause anaphylaxis.

All subgroup analyses will employ tests for interaction.

Type and method of review

Intervention, Meta-analysis, Systematic review

Anticipated or actual start date

19 March 2021

Anticipated completion date

26 March 2021

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Funding sources/sponsors

None

3) *Literature Selection and Search Strategy*

Five reviewers screened records independently and in duplicate using Covidence, for initial inclusion, full text inclusion, and final inclusion for data extraction. A total of two reviewers were minimally required to render a decision for any abstract, and a threshold of 2 votes to include or exclude a particular abstract was used. Conflicts were resolved by direct discussion between the conflicting reviewers. Search terms were generated by DC, AB, and AWB. Inclusion criteria included human studies only, clinical studies of >20,000 patients for reporting allergic reactions to SARS-CoV-2 or vaccination data from country specific datasets reporting >500,000 vaccines, for any type of SARS-CoV-2 vaccine platform (question 1); clinical studies or data reporting sources detailing a patient or physician reported national level dataset for drug allergy to PEG of any molecular weight and in any form or any form of polysorbate (question 2); and any study or case series reporting skin testing (prick, percutaneous, and/or intradermal testing) to any molecular weight and concentration of PEG or polysorbate in which negative controls were also tested, and where true/false negatives as well as true/false positives were reported, inclusive of any testing threshold to denote sensitization. Exclusion criteria for question 1 included reports/studies smaller than the pre-specified threshold; for question 2 included case reports or case series not derived from large, centralized data collection systems or from single centers; and for question 3 included studies and series that did not report negative control subjects were also tested, did not report the size of the test, that described atopy patch testing for contact dermatitis, or that related to testing of a reaction to PEGalated chemotherapy where it was not distinctly clear that the PEG or the chemotherapy were the provoking agent.

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Specific Search Strategies

1) Question 1: Incidence of allergic reactions to SARS-CoV-2 vaccines

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

We evaluated all studies mapped as of March 19, 201: https://covid-nma.com/vaccines/

We searched for "[country name] vaccine adverse event", "[country name] vaccine allergy" , and "[country name] vaccine anaphylaxis" for all countries reporting more than 500,000 vaccinations according to OurWorldInData as of March 19, 2021

2) **Question 2: Prevalence of allergic reactions to PEG and Polysorbate**

We searched MEDLINE and EMBASE and used all databases in Web of Science forward and backward citation analysis:

C1 - Database: Embase <1974 to 2021 March 18>

Search Strategy:

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1 exp polysorbate/ or exp polysorbate 20/ or exp polysorbate 40/ or exp polysorbate 60/ or exp polysorbate 80/ (14044)

2 exp macrogol/ or exp macrogol 10000/ or exp macrogol 200/ or exp macrogol 2000/ or exp macrogol 20000/ or exp macrogol 3000/ or exp macrogol 3350/ or exp macrogol 400/ or exp macrogol 4000/ or exp macrogol 6000/ or exp macrogol 8000/ (56209)

3 polyethyl*.mp. (86262)

4 polysorb*.mp. (14808)

5 1 or 2 or 3 or 4 (130803)

6 sensitiv:.tw. (1817668)

7 diagnostic accuracy.sh. (262948)

8 diagnostic.tw. (1044645)

9 6 or 7 or 8 (2786336)

10 exp allergy/ or allerg*.mp. (379550)

11 exp hypersensitivity/ or hypersens*.mp. (668129)

12 exp anaphylaxis/ or anaphyla*.mp. (67077)

13 10 or 11 or 12 (747829)

14 5 and 9 and 13 (299)

15 from 14 keep 1-299 (299)

16 prevalence.mp. or exp prevalence/ (1146429)

17 incidence/ or incidence.mp. (1283613)

C1 - Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

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1 exp Polysorbates/ or polysorb*.mp. (5783)

2 exp Polyethylene Glycols/ or polyethyl*.mp. (129452)

3 1 or 2 (130582)

4 exp "Sensitivity and Specificity"/ (601394)

5 "Predictive Value of Tests"/ (209185)

6 accuracy*.ti,ab. (430142)

7 sensitiv*.ti,ab. (1443027)

8 predictive.ti,ab. (335826)

9 value*.ti,ab. (1981860)

10 8 and 9 (151359)

11 4 or 5 or 6 or 10 (1020739)

12 7 or 11 (2163390)

13 3 and 12 (11228)

14 exp Hypersensitivity/ or allerg*.mp. (435804)

15 exp Anaphylaxis/ or anaphyla*.mp. (38255)

16 14 or 15 (444274)

17 13 and 16 (99)

18 incidence.mp. or exp Incidence/ (892660)

19 exp Prevalence/ or prevalence.mp. (749006)

Diagnosis of allergy to polyethylene glycol (PEG) and/or polysorbate(s):

3) Question 3: Diagnostic testing precision for allergy testing to PEG and Polysorbate

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We searched MEDLINE and EMBASE and used all databases in Web of Science forward and backward citation analysis:
C1 - Database: Ovid MEDLINE(R) ALL <1946 to March 18, 2021>

Search Strategy:

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1 exp Polysorbates/ or polysorb*.mp. (5783)

2 exp Polyethylene Glycols/ or polyethyl*.mp. (129455)

3 1 or 2 (130585)

4 exp "Sensitivity and Specificity"/ (601394)

5 "Predictive Value of Tests"/ (209185)

6 accuracy*.ti,ab. (430193)

7 sensitiv*.ti,ab. (1443114)

8 predictive.ti,ab. (335849)

9 value*.ti,ab. (1981983)

10 8 and 9 (151364)

11 4 or 5 or 6 or 10 (1020791)

12 7 or 11 (2163514)

13 3 and 12 (11228)

14 exp Hypersensitivity/ or allerg*.mp. (435813)

15 exp Anaphylaxis/ or anaphyla*.mp. (38257)

C1 - Database: Embase <1974 to 2021 March 18>

Search Strategy:

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1 exp polysorbate/ or exp polysorbate 20/ or exp polysorbate 40/ or exp polysorbate 60/ or exp polysorbate 80/ (14044)

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2 exp macrogol/ or exp macrogol 10000/ or exp macrogol 200/ or exp macrogol 2000/ or exp macrogol 20000/ or exp macrogol 3000/ or exp macrogol 3350/ or exp macrogol 400/ or exp macrogol 4000/ or exp macrogol 6000/ or exp macrogol 8000/ (56209)

3 polyethyl*.mp. (86262)

4 polysorb*.mp. (14808)

5 1 or 2 or 3 or 4 (130803)

6 sensitiv:.tw. (1817668)

7 diagnostic accuracy.sh. (262948)

8 diagnostic.tw. (1044645)

9 6 or 7 or 8 (2786336)

10 exp allergy/ or allerg*.mp. (379550)

11 exp hypersensitivity/ or hypersens*.mp. (668129)

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E Figure Legends:

Figure E1: PRISMA Diagrams
Legend: Outlines of the literature searches

Figure E2: Risk of Bias Assessment for Question 1
Legend: Risk of Bias Assessment Using the JBI risk of bias tool for prevalence studies

Figure E3: Risk of Bias Assessment for Question 2
Legend: Risk of Bias Assessment Using the JBI risk of bias tool for prevalence studies

Figure E4: Risk of Bias Assessment for Question 3
Legend: Risk of Bias Assessment Using the QUADAS-2 Criteria

Figure E5: Sensitivity Analysis of SARS-CoV-2 Vaccine Deferral and Post-Vaccination Wait-Time
Legend: Panel A: Two-way sensitivity analysis of anaphylaxis risk and COVID-19 risk. As risk of COVID-19 increased, cost-effectiveness of a risk-stratified required vaccine deferral at higher anaphylaxis risk thresholds. Red area shows where universal vaccination is the optimal strategy, and blue area shows where risk stratification is the optimal strategy.
Panel B: Two-way sensitivity analysis of risk-stratification by time. Evaluating risk stratification of anaphylaxis risk by observation time, a universal approach of 15 minute observation was preferred until risk of anaphylaxis and anaphylaxis case-fatality rates rose significantly (red area). However, if a 1% anaphylaxis case-fatality was assumed, a risk-stratified approach of 30 minute (vs 15 minute) observation became cost-effective when vaccine anaphylaxis exceeded 6% (WTP = 10,000,000 per death prevented) (blue area)

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E References

e1 https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions. Accessed March 20, 2021.
e2 https://www.ispch.cl/wp-content/uploads/2021/03/INF-FARMACOVIGILANCIA.pdf. Accessed March 20, 2021.
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e4 https://mexiconewsdaily.com/news/coronavirus/covid-vaccinations-have-produced-110-allergic-reactions. Accessed March 20, 2021.
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