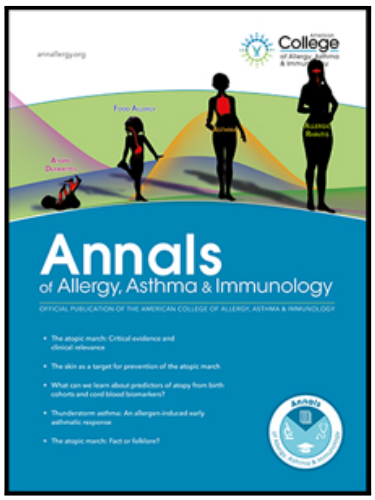
Journal Pre-proof



One year later: What Have We Learned About the Allergenicity and Adverse Reactions Associated with the SARS-CoV-2 vaccines

Ana M Copaescu MD , Jaime S Rosa Duque MD, PhD , Elizabeth J. Phillips MD

PII: S1081-1206(22)00290-3
DOI: https://doi.org/10.1016/j.anai.2022.03.030
Reference: ANAI 3904

To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 20 January 2022
Revised date: 24 March 2022
Accepted date: 25 March 2022

Please cite this article as: Ana M Copaescu MD , Jaime S Rosa Duque MD, PhD , Elizabeth J. Phillips MD , One year later: What Have We Learned About the Allergenicity and Adverse Reactions Associated with the SARS-CoV-2 vaccines, *Annals of Allergy, Asthma Immunology* (2022), doi: https://doi.org/10.1016/j.anai.2022.03.030

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc.

Journal Pre-proof

Review for Annals of Allergy, Asthma and Immunology
https://www.annallergy.org/content/authorinfo

One year later: What Have We Learned About the Allergenicity and Adverse Reactions Associated with the SARS-CoV-2 vaccines

Ana M Copaescu, MD[1,2], Jaime S Rosa Duque, MD, PhD[3], Elizabeth J. Phillips, MD[4,5]
[1]Department of Medicine, Division of Allergy and Clinical Immunology, McGill University Health Center
[2]The Research Institute of the McGill University Health Centre, McGill University, Montreal, Quebec, Canada
[3]Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China
[4]Center for Drug Safety and Immunology, Vanderbilt University Medical Center, Nashville, TN, USA
[5]Institute for Immunology & Infectious Diseases, Murdoch University, Murdoch, Western Australia, Australia

Corresponding Author:
Elizabeth J. Phillips, MD
John A. Oates Chair in Clinical Research
Center for Drug Safety and Immunology
Vanderbilt University Medical Center
e-mail: Elizabeth.j.phillips@vumc.org

Key Messages

- The current vaccines for SARS-CoV-2 currently approved for use by different international jurisdictions and in clinical phase I-III development are whole virus, protein subunit, nucleic acid (RNA and DNA), and viral vector vaccines.
- The adverse reactions associated with the COVID-19 vaccines can be broadly classified as reactogenic or allergic. They are further classified as local or systemic, immediate or non-immediate, and immune or non–immune-mediated reactions.
- Initial reports of allergic reactions led to a risk management strategy that triaged patients based on their prior history of a potential reaction to a vaccine or a component of the existing (mRNA) vaccines.
- Now with a mature understanding of risk, and the reassurance of the very low risk of a pre-existing allergy history impacting the safety of COVID-19 vaccination, we have pivoted to a different approach. This risk management approach focuses on those who have had an allergic

Journal Pre-proof

or other serious reaction to a COVID-19 vaccine and provides support for the completion of primary and booster vaccinations.

- Anaphylaxis to excipients used in the manufacturing process of mRNA vaccines such as polyethylene glycol used to stabilize the lipid nanoparticle (LNP) appears to occur rarely. This means that most individuals known to be allergic to PEG will usually tolerate mRNA vaccines. However, the flip side of this is that tolerance of mRNA vaccines does not confirm tolerance of PEG. Those that tolerate mRNA vaccines can still be susceptible to severe reactions to PEG and they should be worked up for caution applied to hidden ingredients in other products such as bowel preparations and injectable corticosteroids.

Keywords: COVID-19, SARS-CoV-2, mRNA, vaccine, allergy, allergenicity, immunogenicity, risk stratification, polyethylene glycol; polysorbate

Abbreviations/Acronyms:
CDC, Centers for Disease Control and Prevention; COVID-19, Coronavirus disease 2019; FDA, Food and Drug Administration ; MHRA, Medicines and Healthcare Products Regulatory Agency; PEG, Polyethylene glycol; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; VAERS, Vaccine Adverse Event Reporting System

Journal Pre-proof

Introduction

Since the first described case of coronavirus (COVID-19) disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) described in December 2019, the scientific community has united in a common battle against its associated global threats, morbidity, and the astounding 5 million deaths [1]. **(Figure 1).** Supportive care, corticosteroids, monoclonal antibodies and other immunosuppressive and antiviral medications are being trialed and used since the beginning of this pandemic [2]. While patients that have recovered from the COVID-19 disease produce robust humoral and cellular responses, the appropriate memory CD4 -cell response is most effectively attained with an optimal vaccination strategy [3]. Currently there are 139 SARS-CoV-2 vaccines in clinical development, and different types of vaccines have been developed and rolled out in the last year using various strategies to generate an immune system response[1] **(Table 1).** We aim to describe the evolution and the development of the new vaccines for SARS-CoV-2. Furthermore, we will give the context of what is known about the background of vaccine allergy and propose and provide an understanding of the classification and mechanisms of allergic reactions associated with the COVID-19 vaccines. We will synthesize the known information to provide a risk-based management approach for those with immediate and delayed hypersensitivity reactions associated with vaccination as well as other vaccine-related adverse events.

Search strategy and selection criteria

We searched *PubMed* for peer-reviewed articles published between January 1st 2019 and December 4th 2021 (date of last search) with the following key terms: ("SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "COVID-19") AND ("vaccine" OR "mRNA" OR "Pfizer-BioNTech" OR "BNT162b2" OR "Moderna" OR "mRNA-1273" OR "PEG" OR "polyethylene glycol" OR "AstraZeneca" OR "AZD1222" OR "Johnson & Johnson" OR "Ad26.COV2.S" OR "JNJ-78436735") AND ("allergy" OR "anaphylaxis" OR "allergenicity" OR "adverse reaction" OR "immune response" OR "immunogenicity").

Articles published in English were selected and reviewed. We focused on articles classified as "clinical trials" and "meta-analysis". This search provided 116 articles. The first screening was based on titles and abstracts followed by a second round of screening performed by reviewing the full-text articles for selected studies. This was performed by the first and last author. We also identified several new references from the ones listed in the reviewed articles. Finally, we researched the *ClinicalTrials.gov* website to identify current trials on the allergenicity of the SARS-CoV-2 vaccines. The aim of this study was to provide a narrative review and future systematic reviews are required to establish the allergenicity and adverse reactions associated with SARS-CoV-2 vaccines.

HISTORY OF ALLERGIC REACTIONS AND ADVERSE REACTIONS ASSOCIATED WITH VACCINES

Over the last century of vaccine development, allergic reactions to vaccines have been an infrequent but measurable effect that may in some circumstances have led to exclusion from future vaccination [4-6]. Most information gained about vaccine adverse events in the United States has been through the Vaccine Adverse Event Reporting System (VAERS) that was established in 1990 and is managed both by the Centers for Disease Control (CDC) and the Food and Drug Administration. VAERS is a passive surveillance system and relies on individual reports of adverse experiences. A recent publication highlighted that from 1990-2016 and from 467,960 reports, 828 met Brighton collaboration case definition or a physician's diagnosis of anaphylaxis. Of the 42% of reports from adults, 80% were women, 41% had no history of hypersensitivity, and the majority were associated with influenza vaccination [7]. One of the largest studies to date used healthcare data from vaccine safety datalink (VSD).[8] VSD is a collaborative effort between the CDC immunization safety organization and nine health care organizations that is updated weekly since 1990 specifically to answer important vaccine safety questions in larger populations. This study confirmed 33 cases of anaphylaxis after 25, 173,965 vaccines doses to give the vaccine rate of anaphylaxis that we most commonly quote today of 1.31 per million vaccine doses. Interestingly this study also set the context for events to follow with COVID-19 mRNA

vaccines as it suggested that the majority (85%) of those who developed vaccine associated anaphylaxis had pre-existing atopic disease. Although there has been much interest in excipients being the culprits for vaccine-associated immediate reactions and anaphylaxis, there have only been a few case reports to support immunological cross-reactivity between vaccines and/or drugs on the basis of shared common excipients such as the polysorbates [4,9]. For other vaccines, the rates of anaphylaxis have been modified by reduction or elimination of factors such as gelatin and latex [4].

ALLERGIC REACTIONS ASSOCIATED WITH SARS-CoV-2 VACCINES

Shortly after the first administered Pfizer-BioNTech COVID-19 mRNA vaccine in the United Kingdom, anaphylaxis and other allergic reactions were reported on December 8, 2020. This led to the initial recommendation of the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom to exclude from vaccination any person with a history of food, drug or vaccine anaphylaxis and initiating the threat of a vaccine hesitancy movement for patients with known allergies worldwide. This recommendation was later lifted after an additional review on December 30, 2020 that recommended continued mRNA vaccine avoidance in anyone with a history of an allergic reaction to components of the vaccine but allowed those with unrelated allergies (e.g. food allergy) to receive COVID-19 mRNA vaccines. In the United States, the first cases were reported in healthcare workers in December 16, 2020. This led the US Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) to reinforce the recommendation against vaccination in individuals with a history of allergic reactions to any of the vaccine components, a recommendation instigated by the MHRA and all the other allergy associations worldwide [10,11] (**Figure 1**). Of note, the clinical trials performed for the mRNA vaccines had excluded patients with a possible allergic reaction to any vaccine component as well as a past medical history of a severe adverse reaction with any type of vaccine [12,13]. The initial report from the VAERS monitoring database of the Pfizer-BioNTech (BNT 162b2) mRNA COVID-19 vaccine

Journal Pre-proof

between December 14, 2020 and December 23, 2020, 1,893,360 doses of the vaccine were administered and 21 cases of anaphylaxis (Brighton criteria) were reported giving a rate of 11.1/million[14]. As a more diverse group of individuals was vaccinated, the reported rates of anaphylaxis decreased to 2.5 to 5.1 events per million[11,15]. One must also consider that there are various definitions of anaphylaxis and that the Brighton collaboration case definition has recently been reported to overestimate the prevalence of anaphylaxis compared to other criteria such as the National Institute of Allergy and Infectious Disease (NIAID) 2005 and World Allergy Organization (WAO) 2020.[16] Various ongoing trials are aspiring to understand the mechanisms of these reactions focusing on possible risk factors such as patients with multiple allergies or mast cell disorders (clinicaltrials.gov NCT04761822, NCT04977479). Furthermore, recent evidence also shows that patients that presented an allergic reaction to their 1st dose can safely tolerate their 2nd dose[17].

Epidemiology of Allergic Events and Vaccine Rollout of SARS-CoV-2 Vaccines

The initial anaphylaxis reported reactions occurred within 15 minutes of vaccination and primarily in women with a previous history of self-reported allergic reactions [14]. Further insights came from individual healthcare systems that had full ascertainment of vaccine allergic reactions such as the Mass General Brigham (MGB)[18]. MGB employees receiving their first dose from 12/16/2020-2/12/2021 were studied through follow-up on 2/18/2021. Overall acute allergic reactions occurred within 15 minutes of vaccine administration in 2.10%; more commonly with the Moderna vaccine and in women with prior histories of allergic reactions. Approximately 1/3 (31%) had a history of prior anaphylaxis. No individual who experienced anaphylaxis required resuscitation or endotracheal intubation. At Vanderbilt University Medical Center, 23,094 health care workers were screened for history in the vaccine hall prior to vaccination with Pfizer-BioNTech COVID-19 mRNA vaccine [19]. Among the 31 identified with higher risk histories, 28 went onto safe vaccination based on tolerance of PEG or polysorbate containing

medications or vaccines. Shavit et al conducted an 8-week prospective cohort study where they risk stratified potentially allergic patients prior to vaccination. Those considered highly allergic were monitored for 2 hours after vaccination in a specialized setting and those at low risk for 30 minutes in a routine setting.[20,21] They did not vaccinate patients with a history of allergy to polyethylene glycol (PEG) and/or 2 or more injectable drugs. Of the 429 patients deemed highly allergic and observed for 2 hours, 9 patients, all women (2.1%) had immediate reactions of which most were mild and 3 (0.7% overall) experienced anaphylaxis which resolved with epinephrine and without hospitalization[20]. A more recent study reviewed 391,123 members at the Kaiser Permanente Southern California who received at least one dose of a COVID-19 mRNA vaccine between 12/15/2020 and 3/11/2021[22]. Overall, 104 (0.028%) with 85% women, had a first dose reaction and only 2 of these (0.00033%) were consistent with anaphylaxis. Less than 10% of those with first dose reactions had any reaction to the second dose. Similar to other studies, those who received treatment for a first and/or second dose reaction were more likely to be younger women with a pre-existing history of another allergy. To date, no clear risk factors for the COVID-19 vaccines have been definitively proven considering that the group that has safely tolerated the vaccine has not been described in the majority of the studies and that the atopic comorbidity data derives from self-reports.

Journal Pre-proof

Classification of Allergic Reactions to SARS-CoV-2 Vaccines

The adverse reactions associated with the COVID-19 vaccines can be classified as immediate or non-immediate, local or systemic and immune or non–immune-mediated reactions (**Figure 2**).[5]

Immediate reactions

Systemic reactions – *Immune-mediated.* Various described cases fall into the category of anaphylaxis with multi-system involvement. This raised concern that these reactions could be IgE- mediated with

allergen cross-linking on mast cells and rapid improvement following epinephrine administration [23]. If this was the case reactions would be expected to repeat and intensify on subsequent reactions which fortunately was not the case. However, at the time these reactions were initially reported, distinguishing between an IgE mediated reaction and a non-IgE mediated reaction on history alone was a complex task in the acute clinical setting vaccination rollout in the healthcare setting where allergist and immunologist were not in close proximity. Indeed, in the case of a mast-cell activation non-triggered by IgE linking, it is considered that the reactions are caused by direct and indirect mast cell and basophil degranulation by activation of Mas-Related G Protein-Coupled Receptor-X2 (MRGPRX2)[24] or complement activation-related pseudoallergy (CARPA). [25] Mortality has not been reported following an allergic reaction associated with one of the SARS-CoV-2 vaccines,[26] with higher anaphylaxis rates for mRNA vaccines compared with adenoviral vector and inactivated virus vaccines [11]. As we will discuss in the allergenicity and management section, second dose reactions in those with first dose reactions are uncommon. This is evidence against an IgE-mediated mechanism [21].

Systemic reactions - *Non-immune mediated.* Vasovagal reactions are relatively common following vaccine administration and unless fastidiously documented can be confusing retrospectively. It is thus essential for a clinician to be able to recognize these reactions and to distinguish them from anaphylaxis. Important considerations for vasovagal reactions are (1) timing, with reactions occurring in the first seconds to minutes, (2) blood pressure that can transiently drop as well as pulse that is slow and weak, (3) slow breathing and possible apnea as well as (4) marked pallor and diaphoresis that can be observed in the patient's skin [27]. The differential diagnosis for immediate reactions also includes the anxiety-related symptoms such as vocal cord dysfunction and panic attacks that can manifest by stridor and dyspnea and globus sensation [28]. In this context, the World Health Organization (WHO) has defined a condition called "Immunization stress-related response" and has defined this as a stress related

response that can include a variety of symptoms such as fainting, hyperventilation or a dissociative neurological symptom reaction [29] . This is also confirmed by looking at reports of adverse reactions to placebo where more than 35% of the participants in the placebo arms have reported systemic adverse reactions [30]. Furthermore, reports have indicated that among previously reported severe allergic reactions, up to 50% were non-anaphylactic in nature [31]. These can be challenging for allergists to recognize if the history is not well documented since allergists are typically not present to observe the initial vaccine reaction.

Delayed reactions

Local reactions. Local non-immediate reactions, that are not allergenic but possibly a consequence of an innate immune system activation, are common and may include swelling, soreness and erythema at the injection site [10,32,33]. Furthermore, delayed indurated-erythematous reactions have been reported following the administration of RNA vaccines [34,35]. The manifestations known as "COVID-arm" which have been more commonly associated with the Moderna mRNA-1273 SARS-CoV-2 vaccine are considered based on supportive histopathology from the site of the reaction, possible T-cell mediated cutaneous hypersensitivity reactions [36,37]. These more significant local reactions occurred in 0.8% after dose 1 of an mRNA vaccine and 0.2% after dose 2 [34] **(Table 2)**.

Systemic reactions – *Immune-mediated.* Various maculopapular and morbilliform benign skin eruptions have been reported both with mRNA and adenoviral vector vaccines [11,38]. Although most of these are benign rashes (morbilliform and urticarial reactions), acute generalized exanthematous pustulosis, erythema multiforme, and other blistering rashes have been described. Further, a full spectrum of delayed phenotypes described include bullous-pemphigoid like, dermal hypersensitivity reactions, lichen planus, pernio, neutrophilic dermatosis, leukocytoclastic vasculitis, granuloma annulare, and tatoo and sarcoidal reactions [39]. Currently, it has been proposed that delayed reactions be divided into robust

(papulovesicular), moderate (pityriasis-like) and mild (papulosquamous sub-phenotypes). Also, a flare of chronic spontaneous urticaria, as well as new-onset acute urticaria, has been described in the days or weeks following the COVID-19 vaccine [33,38]. Several case reports of reactivation of Varicella-Zoster virus (VZV) after the mRNA and adenoviral vector vaccines, as well as Herpes simplex virus reaction, have been described [40-44]. Another paper found no evidence of oropharyngeal shedding of human herpes viruses before or after vaccination with the Pfizer-BioNTech COVID-19 mRNA vaccine in Israel [45]. The potential mechanism of human herpesvirus (HHV) reactivation is not known. Further, given that this HHV reactivation occurs soon after the first dose and infrequently after the second dose raises the question of whether cross-reactive HHV responses triggered with the initial vaccine dose cause a compensatory regulatory response leading to reactivation. A more recent study which was a retrospective cohort study using aggregated health records from 63 health care organizations that included over 70 million patients and a control population without COVID-19 vaccination did not show a difference in VZV reactivation between those who had received a COVID-19 mRNA vaccine within 28 days compared to the historical control and contemporary cohort [46,47]. Given this may be affecting specific risk groups, the jury is still out as to whether this is a true association. In addition, clouding the picture is that COVID-19 infection itself has been associated with VZV reactivation in case reports[47].

Other systemic delayed reactions. Other delayed reactions may range from those that interestingly mimic the symptoms and signs of COVID-19 disease such as anosmia, fever, fatigue, headache as well as musculoskeletal pain 24-48 hours following a vaccine dose [12,48]. Lymphadenopathy is now a prevalent reactogenic symptoms that is more common following the third-dose booster and may last for up to 3 months. For cancer patients it is recommended that vaccination occur contralateral to any known adenopathy or tumor pathology [49,50]. Studies have also reported neuropsychiatric symptoms with significant morbidity and mortality such as depression, anxiety and altered mental status [48]. In very rare

instances (around 1%), ischaemic and haemorrhagic stroke as well as seizures have been reported [48]. Guillain-Barré Syndrome (GBS) has been more prevalently linked to the viral vector vaccines such as the J&J/Janssen COVID-19 vaccination at a rate of 305 preliminary reports of GBS identified in VAERS after more than 18.1 million doses [26]. Of note GBS may be associated with other vaccines such as influenza and past GBS with influenza is not a contraindication to vaccination with a SARS-CoV-2 vaccine[4]. Thrombosis with thrombocytopenia has been associated with the viral vector vaccines with Astra Zeneca ChAdOx COVID-19 vaccine appearing to have a higher risk than the Janssen Ad26.COV2S (Johnson & Johnson). This appears to have an immunopathogenesis similar to heparin-induced thrombocytopenia in the absence of heparin. The case definition includes a COVID adenoviral vector vaccine 4-42 days prior to symptom onset, any venous or arterial thrombosis (cerebral and abdominal prevalent), thrombocytopenia (platelets <150 x 10^9/L), positive platelet factor 4 ELISA (HIT assay), and elevated D-dimer (>4 x upper limit normal). This should be suspected when there are severe headaches, visual changes, abdominal pain, back pain, shortness of breath, leg swelling or pain, easy bruising or petechiae occurring 4-42 days following vaccination[51]. A small case series of 20 patients with a prior history of heparin-induced thrombocytopenia tolerated the Astra Zeneca ChAdOx COVID-19 adenoviral vector vaccine[52]. Myocarditis has been reported primarily after the second dose of the mRNA vaccines and more prevalently in men < 30 years of age[53-55]. One study of interest suggested that this might be more common with the traditional 3- or 4-week interval between mRNA vaccines versus the extended 12-16-week interval in the rollout in Canada. In addition, heterologous vaccination (e.g. Moderna mRNA-1273 vaccine following another vaccine) may also be associated with a heightened risk. Myocarditis has also been a prevalent feature of COVID-19 natural infection[43]. The incidence of COVID-19-associated myocarditis and cardiac injury is of 1,000–4,000/ 100,000 people versus 0.3–5.0/ 100,000 after COVID-19 mRNA vaccination [56].

Journal Pre-proof

Allergenicity of vaccine components

There are multiple vaccine components that could be responsible for allergic reactions such as the active vaccine antigen, the residual non-human proteins, the excipients such as preservatives or stabilizers in the vaccine formulation as well as other inactive products such as gelatin or latex [23,57] (**Figure 2**). Contrary to drug hypersensitivity reactions, the majority of reactions to vaccines have traditionally been thought to be associated with excipients contained in the formulation and not by the active ingredient[4]. For the mRNA vaccines, concern was initially raised about the polyethylene glycol-2000-lipid component of the mRNA BNT162b2 Pfizer-BioNTech and mRNA-1273 Moderna vaccines that stabilizes the lipid nanoparticle that carries the mRNA spike protein construct[5]. This concern led to special care being taken during the rollout to risk stratify individuals who historically may have had a history of reaction to a vaccine (many of which contain a PEG like sorbitan polysorbate 80 but not PEG) or PEG itself [31]. Polyethylene glycols (PEG) are synthetic agents used as excipients in various medicinal and cosmetic products[31,58]. Although this agent is commonly associated with a good safety profile and pharmacokinetic studies of PEG-3350 following laxative administration show a minimal systemic absorption [59], cases of anaphylaxis and severe immediate hypersensitivity reactions have been described [11,60]. The mRNA-1273-Moderna mRNA vaccine as well as the newly formulated BNT162b2-Pfizer COVID-19 vaccine for > 12 years of age (gray top vial) and that for children (5-11 years) (orange top vial) is tris rather than PBS buffered (contains tromethamine). The original adult BNT162b2-Pfizer COVID-19 mRNA equivalent vaccine does not PBS buffered (purple top vial) and did not contain tromethamine [57]. The allergenic potential of this excipient is not known at this time and has been reported as a possible cause of anaphylaxis in two patients: (1) a patient receiving a gadolinium-based contrast agent [61] and (2) a case report of a 45 year old woman who presented an urticarial reaction following the Moderna mRNA-1273 vaccine and was positive on intradermal testing to an MRI contrast agent gadobutrol which contains tromethamine and negative to gadoteric acid which does not [62]. The viral vector vaccines contain

polysorbate 80 [31] and this commonly used excipient has also been linked to allergic reactions [57]. Despite polysorbate 80 being an excipient in many vaccines and monoclonal antibodies as well as other injectable drugs, it causes surprisingly few adverse events. Since excipients are not strictly regulated, the specific concentration present in drugs and vaccinations is often not precisely stated. Polysorbate 80 contains a lower molecular form of PEG (880 g/ml) and the evidence of cross-reactivity is through skin testing only [60].

Lack of Evidence to support excipients as the culprits of allergic reactions to COVID-19 mRNA Vaccines

Currently there is a general lack of evidence to support that the prevalent immediate reactions associated with mRNA COVID-19 vaccines are related to an antigen-specific IgE-mediated reaction to an excipient component such as PEG [63]. Most reactions were occurring on the first dose of the mRNA vaccines in primarily women with a history of other allergic reactions. The reactions have rarely recurred on the second or subsequent dose and most patients were tolerant [64,65]. The vast majority of people who experience these reactions have mild to moderate reactions that resolve without epinephrine. Tryptase levels, when done, have been normal compared to baseline [65]. Those who have been rechallenged with a second or subsequent vaccine dose were largely without symptoms and antihistamine administration pre- and post-dosing seems to help [64,65]. This tolerance of the second and subsequent doses is very reassuring and is strongly suggestive against PEG or another excipient being the culprit of an antigen specific IgE mediated reaction. However, there may be rare patients who warrant risk mitigation and specific work-up. Several studies now suggest that specific testing for excipients such as PEG and PEG derivatives is not helpful to risk stratify patients before first or second dosing [63]. Also, several studies have suggested that patients with immediate reactions to specific drugs containing PEG or PEG derivatives such as pegaspargase of taxanes are tolerant of the mRNA vaccines [66-69]. In addition, patients with known PEG anaphylaxis have tolerated the Janssen and Astra Zeneca

vaccines containing the PEG derivative polysorbate 80, despite being intradermal skin test positive to polysorbate 80 in 3/10 cases [70,71]. Patients known to have PEG anaphylaxis have also tolerated the mRNA vaccines despite being skin test positive to polysorbate 80 and/or the mRNA vaccine [72]. Importantly, tolerance of an mRNA vaccine in those with histories of PEG anaphylaxis does not suggest tolerance of PEG reagents. It appears that following tolerance of an mRNA vaccine, patients can still have anaphylaxis to PEG 3,350 and higher molecular weight PEG products [72]. Therefore, the role of detailed excipient testing in an individual who has a history of anaphylaxis to a non-COVID-19 vaccine-related PEG product is really to test the safety of administering PEG and other PEG derivatives and products unrelated to the COVID-19 vaccines in the future [58,60]. It may be that the PEG 2,000 in the vaccines is too low a molecular weight to be antigenic or that through the intramuscular injection of the vaccine it is rapidly taken up by the reticuloendothelial system and not bioavailable to induce an immune response. Since mRNA technologies are now of great promise for vaccines and other therapeutics, this has great practical implications for the future. It is of interest that the epidemiology of PEG anaphylaxis, which occurs equally in men and women without prior allergic histories, is associated with PEG IgE and positive prick tests to PEG [60,73]. PEG anaphylaxis intensifies over time and is often severe and initially requires repeat dosing of epinephrine. This is quite different from the COVID-19 vaccine allergy reactions which occur primarily in women with previous allergic histories and reactions typically remit with no treatment or antihistamines alone and do not intensify over time [60].

SUMMARY OF MANAGEMENT OF ALLERGIC REACTIONS ASSOCIATED WITH SARS-CoV-2 VACCINES

Following the potentially life-threatening allergic reactions reported, allergists have responded rapidly during this period of high need to help risk stratify and manage patients based on the reported history of allergic reactions [27]. An abundance of caution was taken during the first few weeks to months of the rollout of the COVID-19 vaccines and, after the billions of doses now given globally, these have now

proven to be safe. Months after the beginning of the vaccination campaign, we are now reassured that any allergic potential of the mRNA vaccines is largely benign and that the vast majority of patients can be safely re-dosed without fear of a repeat reaction. Despite the fear that a component of the vaccines could be an allergen, there is clear evidence that even for the rare individuals confirmed allergic to PEG these vaccines can be safely administered [72]. In this context, investigations for possible PEG or polysorbate allergy prior to the vaccination are now not routinely suggested. Furthermore, we can be reassured that for those who tolerated the first and second dose of the vaccine, the chance of any subsequent reactions appears minimal and the longer observation periods initially recommended for those with an underlying allergy can now be relaxed for those with proven tolerance.

Overall, the confirmation of an allergic mechanism such as an IgE-mediated reaction should this occur rarely is suggested by *in vivo* investigations such as prick and intradermal testing or the detection of antigen-specific IgE antibodies [60]. In the acute setting, it is recommended to test for tryptase, a biomarker that is elevated in anaphylaxis and repeat this at minimum 24 hours later or at baseline. A suggested management strategy is described in **Figure 3**.

Skin testing

The evolving literature on skin testing in the last year has allowed us to progress from the recommendation of performing PEG skin testing [31], despite absent information on sensitivity and specificity to avoiding routine skin testing with the vaccine or its excipients [11]. Some study protocols have involved skin testing with 1:1 mRNA vaccine dilution with negative results in all patients confirmed by a negative mRNA vaccine challenge [74-76]. The previous guidelines for vaccine allergy testing have recommended performing skin prick testing and the undiluted vaccine followed by intradermal with a 1:100 dilution if the initial SPT was negative [77]. Despite absence of international guidelines, non-irritating concentrations for vaccine excipients and standardization across different centers based on trialed

concentrations including for PEG testing, polysorbate 80 and tromethamine are available [60,74]. Currently, there is little evidence to support using excipient skin tests to risk-stratify patients prior to vaccination and it appears that the vast majority of patients can go straight to first or subsequent mRNA vaccine dosing without testing. Indeed, the initial recommendation formulated for skin testing was based on a conservative expert recommendation derived from the 2012 vaccine anaphylaxis parameter guidance[6]. Even if the positive predictive value of PEG SPT is not well described, this provides useful information in those with a high pretest probability of a PEG allergy in the context of a history of anaphylaxis to PEG [31].

The PEG derivatives should be tested in individuals who have underlying suspected PEG anaphylaxis despite having tolerated an mRNA vaccine since tolerance of an mRNA vaccine does not reassure that the patient will tolerate the wide array of PEG products.

Vaccine Challenge

For patients with a history of anaphylaxis to any allergen, the recommendation is to offer a 30-minute observation period following the administration of the COVID-19 vaccine in a monitored area. The vaccinations sites should have the equipment necessary to treat possible anaphylactic reactions. A shared decision-making approach is favored and, in most cases, it appears that a single dose vaccine rechallenge can be carried out in the setting of an immediate reaction the first COVID-19 vaccine dose [11]. Following previous cohort studies, it is now suggested that patients that are known for previous severe allergic reaction to a non-vaccine component can safely tolerate the COVID-19 vaccine [72,74]. Various graded dosing [78] or desensitisation[79] protocols have been suggested. As mentioned above, oncology patients that presented immediate reactions to paclitaxel that contains polyoxyl-35 castor oil and pegaspargase, a multidrug chemotherapy regimen containing PEG 5,000, have safely received the mRNA COVID-19 vaccines [67-69]. Furthermore, evidence is emerging that patients that reported an immediate

reaction and even anaphylaxis to the 1st mRNA vaccine dose can safely tolerate their 2nd dose [17,64,65], supporting non-IgE mediated mechanisms.

Follow-up and Long-term advice

Currently we have an incomplete understanding of the immune correlates of protection for SARS-CoV-2 and this impacts our ability to understand the response to vaccines. It is clear that SARS-CoV-2 vaccines have the largest impact on reduction of illness severity, hospitalization, and death and the very high effectiveness in preventing these primary outcomes in clinical trials has meant that it has not been easy to define the immune correlates of failure.

Newer therapies such as tixagevimab co-packaged with cilgavimab (Evusheld ™) have been approved for pre-exposure prophylaxis with administration every 6 months. This agent is a SARS-Cov-2 monoclonal antibody combination reserved for the moderately to severely immune-compromised patients who may not mount an adequate response to vaccines. However, this drug should not replace vaccination event in the immunocompromised individuals. Another use for this antibody cocktail is listed as being those who have had a severe adverse reaction to a SARS-CoV-2 vaccine where future vaccination is precluded. A severe allergic reaction is listed as an example however we now know that it would be an extremely rare event for an allergic reaction to preclude future vaccination. Ideally all patients with suspected allergic reactions associated with SARS-CoV-2 vaccines such as the mRNA vaccines should be assessed by an allergist with work-up and observed vaccination as indicated. Interventions such as prophylactic monoclonal antibodies, a precious resource, should ideally be reserved for immunocompromised patients such as those with primary immunodeficiency or transplantation. Following vaccine assessment, the patient needs to be provided with a clear management plan regarding future same type vaccine administration as well as the likelihood of safely receiving other vaccines. One year following vaccine rollout, it is clear that allergy consultations continue to represent important guidance for risk

Journal Pre-proof

assessment and vaccine guidance. We would suggest that the role of the allergist and immunologist is not to provide vaccine exemptions but to provide evidence-based confidence and reassurance to the patient who may be hesitant because of a reaction to a previous vaccine, drug or a COVID-19 vaccine. Most immediate and delayed reactions appear to not recur on the second and subsequent doses. Over the next year, we will learn more about mechanisms, however, to date the chance of tolerance with subsequent vaccination is excellent and the chance of harm is minimal.

Conclusion

Further research is needed to identify vaccine components that are responsible for immune-mediated hypersensitivity reactions as well as to understand the underlying mechanisms of vaccine reactions. This will shed light on the immunogenicity, reactogenicity, and allergenicity of current and future SARS-CoV-2 vaccine constructs. The use of effective vaccines is part of the long-time management strategy for SARS-CoV-2 and may continue to be important as the virus moves from a pandemic to an endemic infection. The risk of a reaction compared to the benefit of protection from severe illness and hospitalization is extremely small, and we can be reassured that although there are still many unanswered questions and controversies there is already a very sound approach to ensure safe COVID-19 vaccination even in those with anaphylactic first-dose reactions (Table 3). As the pandemic and the number of SARS-CoV-2 viral variants evolve in the near future, new vaccines built on an adapted mRNA construct but the same delivery method and platform will rollout. The Allergy and Immunology community plays an enormous role in the education, clinical care and research outputs that will result in optimized individual and public health.

Journal Pre-proof

Funding Information/Author Disclosure: EJP reports grants from National Institutes of Health (P50GM115305, R01HG010863, R01AI152183, U01AI154659, R13AR078623, UAI109565) and from the National Health and Medical Research Council of Australia. She receives Royalties from Uptodate and consulting fees from Janssen, Vertex, Biocryst and Regeneron. She is co-director of IIID Pty Ltd that holds a patent for HLA-B*57:01 testing for abacavir hypersensitivity, and has a patent pending for Detection of Human Leukocyte Antigen-A*32:01 in connection with Diagnosing Drug Reaction with Eosinophilia and Systemic Symptoms without any financial remuneration and not directly related to the submitted work. Funders played no role in any aspect of this Review.
AMC receives support from the Montreal General Hospital Foundation and Research Institute of the McGill University Health Centre (RI-MUHC) and was awarded *The Anna Maria Solinas Laroche Career Award in Immunology* and the *Anita Garbarino Girard/Anna Maria Solinas/Dr. Phil Gold Award of Distinction.*

Table 1 - Approved vaccines for SARS-CoV-2
Table 2 – Immediate and Delayed adverse reactions to SARS-CoV-2 Vaccines
Table 3 - Questions on How to Manage Those with a History of Anaphylaxis to a Vaccine Component or Anaphylaxis following an mRNA Vaccine
Figure 1 – Timeline of COVID-19 Vaccines and Therapeutics
Figure 2 – Classification of COVID-19 vaccine reactions
Figure 3 – Management approach

Journal Pre-proof

References

1. World Health Organization. WHO Coronavirus (COVID-19). 2021. https://covid19.who.int/2021).
2. Copaescu A, Smibert O, Gibson A, Phillips EJ, Trubiano JA. The role of IL-6 and other mediators in the cytokine storm associated with SARS-CoV-2 infection. *J Allergy Clin Immunol* 2020; **146**(3): 518-34 e1.
3. Hou H, Zhang Y, Tang G, et al. Immunologic memory to SARS-CoV-2 in convalescent COVID-19 patients at 1 year postinfection. *J Allergy Clin Immunol* 2021.
4. Stone CA, Jr., Rukasin CRF, Beachkofsky TM, Phillips EJ. Immune-mediated adverse reactions to vaccines. *Br J Clin Pharmacol* 2019; **85**(12): 2694-706.
5. Castells MC, Phillips EJ. Maintaining Safety with SARS-CoV-2 Vaccines. *N Engl J Med* 2020.
6. Kelso JM, Greenhawt MJ, Li JT, et al. Adverse reactions to vaccines practice parameter 2012 update. *J Allergy Clin Immunol* 2012; **130**(1): 25-43.
7. Su JR, Moro PL, Ng CS, Lewis PW, Said MA, Cano MV. Anaphylaxis after vaccination reported to the Vaccine Adverse Event Reporting System, 1990-2016. *J Allergy Clin Immunol* 2019; **143**(4): 1465-73.
8. McNeil MM, Weintraub ES, Duffy J, et al. Risk of anaphylaxis after vaccination in children and adults. *J Allergy Clin Immunol* 2016; **137**(3): 868-78.
9. Badiu I, Geuna M, Heffler E, Rolla G. Hypersensitivity reaction to human papillomavirus vaccine due to polysorbate 80. *BMJ Case Rep* 2012; **2012**.
10. Sampath V, Rabinowitz G, Shah M, et al. Vaccines and allergic reactions: The past, the current COVID-19 pandemic, and future perspectives. *Allergy* 2021; **76**(6): 1640-60.
11. Greenhawt M, Abrams EM, Shaker M, et al. The Risk of Allergic Reaction to SARS-CoV-2 Vaccines and Recommended Evaluation and Management: A Systematic Review, Meta-Analysis, GRADE Assessment, and International Consensus Approach. *J Allergy Clin Immunol Pract* 2021; **9**(10): 3546-67.
12. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020; **383**(27): 2603-15.
13. Jackson LA, Anderson EJ, Rouphael NG, et al. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. *N Engl J Med* 2020; **383**(20): 1920-31.
14. Team CC-R, Food, Drug A. Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine - United States, December 14-23, 2020. *MMWR Morb Mortal Wkly Rep* 2021; **70**(2): 46-51.
15. Shimabukuro TT, Cole M, Su JR. Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US-December 14, 2020-January 18, 2021. *JAMA* 2021.
16. Hourihane JO, Byrne AM, Blumchen K, Turner PJ, Greenhawt M. Ascertainment Bias in Anaphylaxis Safety Data of COVID-19 Vaccines. *J Allergy Clin Immunol Pract* 2021; **9**(7): 2562-6.
17. Chu DK, Abrams EM, Golden DBK, et al. Risk of Second Allergic Reaction to SARS-CoV-2 Vaccines: A Systematic Review and Meta-analysis. *JAMA Intern Med* 2022.
18. Blumenthal KG, Robinson LB, Camargo CA, Jr., et al. Acute Allergic Reactions to mRNA COVID-19 Vaccines. *JAMA* 2021; **325**(15): 1562-5.
19. Krantz MS, Stone CA, Jr., Rolando LA, et al. An academic hospital experience screening mRNA COVID-19 vaccine risk using patient allergy history. *J Allergy Clin Immunol Pract* 2021; **9**(10): 3807-10.
20. Shavit R, Maoz-Segal R, Iancovici-Kidon M, et al. Prevalence of Allergic Reactions After Pfizer-BioNTech COVID-19 Vaccination Among Adults With High Allergy Risk. *JAMA Netw Open* 2021; **4**(8): e2122255.
21. Phillips EJ. Allergic Reactions After COVID-19 Vaccination-Putting Risk Into Perspective. *JAMA Netw Open* 2021; **4**(8): e2122326.

Journal Pre-proof

22. Macy E, Pandya S, Sheikh J, et al. Population-based incidence, severity, and risk factors associated with treated acute-onset COVID-19 mRNA vaccination-associated hypersensitivity reactions. *J Allergy Clin Immunol Pract* 2021.
23. Castells MC, Phillips EJ. Maintaining Safety with SARS-CoV-2 Vaccines. *N Engl J Med* 2021; **384**(7): 643-9.
24. Porebski G, Kwiecien K, Pawica M, Kwitniewski M. Mas-Related G Protein-Coupled Receptor-X2 (MRGPRX2) in Drug Hypersensitivity Reactions. *Front Immunol* 2018; **9**: 3027.
25. Zhang B, Li Q, Shi C, Zhang X. Drug-Induced Pseudoallergy: A Review of the Causes and Mechanisms. *Pharmacology* 2018; **101**(1-2): 104-10.
26. Centers for Disease Control and Prevention. Selected adverse events reported after COVID-19 vaccination. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html (accessed January 2 2022).
27. Banerji A, Wickner PG, Saff R, et al. mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current Evidence and Suggested Approach. *J Allergy Clin Immunol Pract* 2020.
28. Gold MS, MacDonald NE, McMurtry CM, et al. Immunization stress-related response - Redefining immunization anxiety-related reaction as an adverse event following immunization. *Vaccine* 2020; **38**(14): 3015-20.
29. World Health Organization. Immunization stress-related response (ISRR) - A synopsis. 2019. https://www.who.int/immunization/sage/meetings/2019/april/2_A_synopsis_of_ISRR_Draft_SAGE.PDF (accessed 15.02 2022).
30. Haas JW, Bender FL, Ballou S, et al. Frequency of Adverse Events in the Placebo Arms of COVID-19 Vaccine Trials: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2022; **5**(1): e2143955.
31. Banerji A, Wickner PG, Saff R, et al. mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current Evidence and Suggested Approach. *J Allergy Clin Immunol Pract* 2021; **9**(4): 1423-37.
32. Catala A, Munoz-Santos C, Galvan-Casas C, et al. Cutaneous reactions after SARS-CoV-2 vaccination: a cross-sectional Spanish nationwide study of 405 cases. *Br J Dermatol* 2021.
33. McMahon DE, Amerson E, Rosenbach M, et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases. *J Am Acad Dermatol* 2021; **85**(1): 46-55.
34. Blumenthal KG, Freeman EE, Saff RR, et al. Delayed Large Local Reactions to mRNA-1273 Vaccine against SARS-CoV-2. *N Engl J Med* 2021; **384**(13): 1273-7.
35. Hoff NP, Freise NF, Schmidt AG, et al. Delayed skin reaction after mRNA-1273 vaccine against SARS-CoV-2: a rare clinical reaction. *Eur J Med Res* 2021; **26**(1): 98.
36. Askenase PW. Rare Skin Reactions after mRNA Vaccination, Similar to Jones-Mote Basophil Responses. *N Engl J Med* 2021; **385**(18): 1720-1.
37. Johnston MS, Galan A, Watsky KL, Little AJ. Delayed Localized Hypersensitivity Reactions to the Moderna COVID-19 Vaccine: A Case Series. *JAMA Dermatol* 2021; **157**(6): 716-20.
38. Niebel D, Novak N, Wilhelmi J, et al. Cutaneous Adverse Reactions to COVID-19 Vaccines: Insights from an Immuno-Dermatological Perspective. *Vaccines (Basel)* 2021; **9**(9).
39. Freeman EE, Sun Q, McMahon DE, et al. Skin reactions to COVID-19 vaccines: An American Academy of Dermatology/International League of Dermatological Societies registry update on reaction location and COVID vaccine type. *J Am Acad Dermatol* 2021.
40. Papasavvas I, de Courten C, Herbort CP, Jr. Varicella-zoster virus reactivation causing herpes zoster ophthalmicus (HZO) after SARS-CoV-2 vaccination - report of three cases. *J Ophthalmic Inflamm Infect* 2021; **11**(1): 28.

Journal Pre-proof

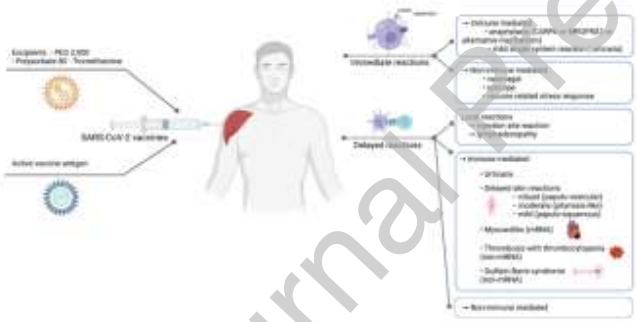
41. Furer V, Zisman D, Kibari A, Rimar D, Paran Y, Elkayam O. Herpes zoster following BNT162b2 mRNA COVID-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: a case series. *Rheumatology (Oxford)* 2021; **60**(SI): SI90-SI5.
42. Katsikas Triantafyllidis K, Giannos P, Mian IT, Kyrtsonis G, Kechagias KS. Varicella Zoster Virus Reactivation Following COVID-19 Vaccination: A Systematic Review of Case Reports. *Vaccines (Basel)* 2021; **9**(9).
43. Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. *N Engl J Med* 2021; **385**(12): 1078-90.
44. Alkhalifah MI, Alsobki HE, Alwael HM, Al Fawaz AM, Al-Mezaine HS. Herpes Simplex Virus Keratitis Reactivation after SARS-CoV-2 BNT162b2 mRNA Vaccination: A Report of Two Cases. *Ocul Immunol Inflamm* 2021: 1-3.
45. Brosh-Nissimov T, Sorek N, Yeshayahu M, et al. Oropharyngeal shedding of herpesviruses before and after BNT162b2 mRNA vaccination against COVID-19. *Vaccine* 2021; **39**(40): 5729-31.
46. Birabaharan M, Kaelber DC, Karris MY. Risk of herpes zoster reactivation after messenger RNA COVID-19 vaccination: A cohort study. *J Am Acad Dermatol* 2021.
47. Algaadi SA. Herpes zoster and COVID-19 infection: a coincidence or a causal relationship? *Infection* 2021.
48. Rogers JP, Watson CJ, Badenoch J, et al. Neurology and neuropsychiatry of COVID-19: a systematic review and meta-analysis of the early literature reveals frequent CNS manifestations and key emerging narratives. *J Neurol Neurosurg Psychiatry* 2021; **92**(9): 932-41.
49. Keshavarz P, Yazdanpanah F, Rafiee F, Mizandari M. Lymphadenopathy Following COVID-19 Vaccination: Imaging Findings Review. *Acad Radiol* 2021; **28**(8): 1058-71.
50. Lam DL, Flanagan MR. Axillary Lymphadenopathy After COVID-19 Vaccination in a Woman With Breast Cancer. *JAMA* 2022; **327**(2): 175-6.
51. Pavord S, Scully M, Hunt BJ, et al. Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis. *N Engl J Med* 2021; **385**(18): 1680-9.
52. Faruqi U, White K, Murray N, Cutler J, Breen K. The impact of COVID-19 vaccination on patients with a history of heparin induced thrombocytopenia. *Br J Haematol* 2022.
53. Husby A, Hansen JV, Fosbol E, et al. SARS-CoV-2 vaccination and myocarditis or myopericarditis: population based cohort study. *BMJ* 2021; **375**: e068665.
54. Patone M, Mei XW, Handunnetthi L, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. *Nat Med* 2021.
55. Heymans S, Cooper LT. Myocarditis after COVID-19 mRNA vaccination: clinical observations and potential mechanisms. *Nat Rev Cardiol* 2021.
56. Heymans S, Cooper LT. Myocarditis after COVID-19 mRNA vaccination: clinical observations and potential mechanisms. *Nat Rev Cardiol* 2022; **19**(2): 75-7.
57. Caballero ML, Quirce S. Excipients as Potential Agents of Anaphylaxis in Vaccines: Analyzing the Formulations of Currently Authorized COVID-19 Vaccines. *J Investig Allergol Clin Immunol* 2021; **31**(1): 92-3.
58. Caballero ML, Krantz MS, Quirce S, Phillips EJ, Stone CA, Jr. Hidden Dangers: Recognizing Excipients as Potential Causes of Drug and Vaccine Hypersensitivity Reactions. *J Allergy Clin Immunol Pract* 2021.
59. Pelham RW, Nix LC, Chavira RE, Cleveland MV, Stetson P. Clinical trial: single- and multiple-dose pharmacokinetics of polyethylene glycol (PEG-3350) in healthy young and elderly subjects. *Aliment Pharmacol Ther* 2008; **28**(2): 256-65.
60. Stone CA, Jr., Liu Y, Relling MV, et al. Immediate Hypersensitivity to Polyethylene Glycols and Polysorbates: More Common Than We Have Recognized. *J Allergy Clin Immunol Pract* 2019; **7**(5): 1533-40 e8.

Journal Pre-proof

61. Lukawska J, Mandaliya D, Chan AWE, et al. Anaphylaxis to trometamol excipient in gadolinium-based contrast agents for clinical imaging. *J Allergy Clin Immunol Pract* 2019; **7**(3): 1086-7.
62. Rama TA, Coutinho RM, Mota D, Moreira A, Cernada J. Hypersensitivity to the Moderna COVID-19 vaccine caused by tromethamine: PEG is not always the culprit excipient. *J Investig Allergol Clin Immunol* 2021: 0.
63. Wolfson AR, Robinson LB, Li L, et al. First-Dose mRNA COVID-19 Vaccine Allergic Reactions: Limited Role for Excipient Skin Testing. *J Allergy Clin Immunol Pract* 2021; **9**(9): 3308-20 e3.
64. Krantz MS, Kwah JH, Stone CA, Jr., et al. Safety Evaluation of the Second Dose of Messenger RNA COVID-19 Vaccines in Patients With Immediate Reactions to the First Dose. *JAMA Intern Med* 2021; **181**(11): 1530-3.
65. Krantz MS, Bruusgaard-Mouritsen MA, Koo G, Phillips EJ, Stone CA, Jr., Garvey LH. Anaphylaxis to the first dose of mRNA SARS-CoV-2 vaccines: Don't give up on the second dose! *Allergy* 2021; **76**(9): 2916-20.
66. Rush C, Faulk KE, Bradley ZK, Turner A, Krumins M, Greenhawt M. The safety of SARS-CoV-2 vaccines in persons with a known history of pegaspargase allergy: A single institution experience. *J Allergy Clin Immunol Pract* 2021.
67. Koo G, Anvari S, Friedman DL, et al. mRNA COVID-19 vaccine safety in patients with previous immediate hypersensitivity to pegaspargase. *J Allergy Clin Immunol Pract* 2021.
68. Mark C, Gupta S, Punnett A, et al. Safety of administration of BNT162b2 mRNA (Pfizer-BioNTech) COVID-19 vaccine in youths and young adults with a history of acute lymphoblastic leukemia and allergy to PEG-asparaginase. *Pediatr Blood Cancer* 2021; **68**(11): e29295.
69. Banerji A, Wolfson AR, Robinson LB, et al. COVID-19 vaccines tolerated in patients with paclitaxel and docetaxel allergy. *Allergy* 2021.
70. Sellaturay P, Gurugama P, Harper V, Dymond T, Ewan P, Nasser S. The Polysorbate containing AstraZeneca COVID-19 vaccine is tolerated by polyethylene glycol (PEG) allergic patients. *Clin Exp Allergy* 2022; **52**(1): 12-7.
71. Bruusgaard-Mouritsen MA, Koo G, Heinrichsen AS, et al. Janssen COVID-19 vaccine tolerated in 10 patients with confirmed polyethylene glycol allergy. *J Allergy Clin Immunol Pract* 2021.
72. Picard M, Drolet JP, Masse MS, et al. Safety of COVID-19 vaccination in patients with polyethylene glycol allergy: A case series. *J Allergy Clin Immunol Pract* 2021.
73. Zhou ZH, Stone CA, Jr., Jakubovic B, et al. Anti-PEG IgE in anaphylaxis associated with polyethylene glycol. *J Allergy Clin Immunol Pract* 2020.
74. Rojas-Perez-Ezquerra P, Crespo Quiros J, Tornero Molina P, Baeza Ochoa de Ocariz ML, Zubeldia Ortuno JM. Safety of New mRNA Vaccines Against COVID-19 in Severely Allergic Patients. *J Investig Allergol Clin Immunol* 2021; **31**(2): 180-1.
75. Marcelino J, Farinha S, Silva R, Didenko I, Proenca M, Tomaz E. Nonirritant concentrations for skin testing with SARS-CoV-2 mRNA vaccine. *J Allergy Clin Immunol Pract* 2021; **9**(6): 2476-7.
76. Pienkowski MM, Pienkowski SM. Evaluation of anaphylaxis risk by skin testing with coronavirus disease 2019 messenger RNA vaccines on patients with anaphylaxis. *Ann Allergy Asthma Immunol* 2022; **128**(1): 101-3.
77. Broyles AD, Banerji A, Barmettler S, et al. Practical Guidance for the Evaluation and Management of Drug Hypersensitivity: Specific Drugs. *J Allergy Clin Immunol Pract* 2020; **8**(9S): S16-S116.
78. Tuong L, Capucilli P, Staicu M, Ramsey A, Walsh E, Mustafa S. Graded Administration of Second Dose of Moderna and Pfizer-BioNTech COVID-19 mRNA Vaccines in Patients With Hypersensitivity to First Dose. *Open Forum Infectious Diseases* 2021; **8**(12).

Journal Pre-proof

79. AlMuhizi F, Ton-Leclerc S, Fein M, et al. Successful Desensitization to mRNA COVID-19 Vaccine in a Case Series of Patients With a History of Anaphylaxis to the First Vaccine Dose. *Frontiers in Allergy* 2022; **3**.



Journal Pre-proof

Review for Annals of Allergy, Asthma and Immunology

Table 1. Approved vaccines for SARS-CoV-2

Journal Pre-proof

Research name	Commercial name	Developer	Vaccine type	Active Ingredient	Relevant details of excipients and formulation*	Dose	Number of doses	Interval doses	Booster Dose**	Efficacy^	Age indication	Storage
BNT162b2 Tozinameran	Pfizer Comirnaty >17 yr	Pfizer-BioNTech (and Fosun)	RNA-based	nucleoside-modRNA encoding viral spike GP SARS-CoV-2	2-[PEG-2000]-N,N-ditetradecylacetamide	0.3 ml IM (30 µg)	2	21 days	>/= 5 months	95%[1]	18 years +	-80°C to -60°C (-112°F to -76°F)
BNT162b2 Tozinameran	Pfizer Comirnaty 12-17 yr	Pfizer-BioNTech (and Fosun)	RNA-based	nucleoside-modRNA encoding viral spike GP SARS-CoV-2	2-[PEG-2000]-N,N-ditetradecylacetamide	0.3 ml IM (30 µg)	2	21 days	>/= 5 months	100% [2]	12-17 years	-80°C to -60°C (-112°F to -76°F)
BNT162b2 Tozinameran	Pfizer Comirnaty 5-11 yr	Pfizer-BioNTech (and Fosun)	RNA-based	nucleoside-modRNA encoding viral spike GP SARS-CoV-2	2-[PEG-2000]-N,N-ditetradecylaacetamide Tromethamine	0.2 ml IM (10 µg)	2	21 days	N/A**	90.7% [3]	5-11 years	-80°C to -60°C (-112°F to -76°F)
mRNA-1273	Moderna Spikevax >17 yr	Moderna and NIAID	RNA-based	mRNA encoding the pre-fusion stabilized spike GP (S) SARS-CoV-2	PEG-2000-DMG Tromethamine	0.5 ml IM (100 µg)	2	28 days	50 mcg >/= 6 months	94.1% [4]	18 years +	-20°C (-4°F)
mRNA-1273	Moderna Spikevax 12-17 yr	Moderna and NIAID	RNA-based	mRNA encoding the pre-fusion stabilized spike GP (S) SARS-CoV-2	PEG-2000-DMG Tromethamine	0.5 ml IM (100 µg)	2	28 days	n/a	100% [5]	12-17 years	-20°C (-4°F)
AZD1222 ChAdOx1-S Vaxzevria	AstraZeneca vaccine COVISHIELD Vaxzevria	AstraZeneca and the University of Oxford	NR Viral Vector	Recombinant, replication-deficient chimpanzee adenovirus vector encoding SARS-CoV-2 spike GP	polysorbate-80	0.5 ml IM (5×10^{10})	2	4-12 weeks	n/a	62%[6]	18 years +	2°C to 8°C (35.6°F to 46.4°F)
JNJ-78436735 Ad26.COV2.S	Johnson & Johnson	Janssen Pharmaceutical Companies (Johnson & Johnson)	NR Viral Vector	recombinant, replication-incompetent adenovirus type 26 expressing SARS-CoV-2 spike protein	polysorbate-80	0.5 ml IM	1	n/a	>/= 2 months	66% (overall) 72% (US) 85% (severe disease)[7]	18 years +	-20°C (-4°F)
NVX-CoV2373	Nuvaxovid	Novavax	protein	SARS-CoV-2 recombinant spike protein	polysorbate-80	0.5 ml IM	2	21 days	n/a	89.7% [8]	18 years +	≤ -60ºC
BBIBP-CorV	Sinopharm	Sinopharm (Beijing)	Inactivated virus	SARS-CoV-2 virus (cultivated in Vero cell line)	n/a	0.5 ml IM	2	21-28 days	n/a	78.1% [9]	18 years +	2°C to 8°C
CoronaVac	CoronaVac	Sinovac	Inactivat	SARS-CoV-2 virus	n/a	0.5 ml IM	2	14-28	n/a	50-91% [10-	18 years +	Room

Journal Pre-proof

PiCoVacc	PiCoVacc		ed virus					days		[12]		Temp.
BBV152 A, B, C	Covaxin	Bharat Biotech	Inactivated virus	SARS-CoV-2 virus	n/a	0.5 ml IM	2	28 days	n/a	77.8% [13]	18 years +	2°C to 8°C

Journal Pre-proof

Abbreviations: GP, glycoprotein; IM, intramuscular; ml, milliliter; modRNA, modified messenger RNA; NIAID, National Institute of Allergy and Infectious Diseases; PEG, polyethylene glycol; PEG-2000-DMG, 1,2-dimyristoyl-rac-glycero3-methoxypolyethylene glycol-2000; RNA, ribonucleic acid; NR, non-replicating; Temp, temperature; US, United States; µg, microgram; yr, years.

* This column only contains the inactive lipids that are considered potential culprit for hypersensitivity reactions associated with these vaccines.

** The recommendation for immunocompromised hosts for the mRNA vaccines is to administer a 3rd dose 28 days after the 2nd dose and a 4th booster dose 5 months after the 3rd dose. For immunocompromised children, a third dose is also recommended 28 days after the 2nd dose but only the Pfizer-BioNTech vaccine has an EUA for 5 to 11-year-old children should this be used. Booster dosing 5 months following primary vaccination has not yet received a EUA. The American College of Rheumatology has recommended adjusting the timing of immunosuppression where possible (e.g. rituximab initiated four weeks prior to primary series or delaying rituximab until 2-4 weeks after completion of the primary vaccination series) [14].
Revaccination with the original series three months following the intervention is recommended following hematopoietic cell transplant or CAR-T therapy [15].

^Refers to efficacy in phase III clinical trials against symptomatic COVID-19 illness. All vaccines have reduced efficacy against the SARS-CoV-2 viral variants although the effectiveness against severe COVID-19 disease, hospitalization and mortality has remained for the Delta and Omicron variants particularly in adults who have received a booster dose with mRNA vaccines. Measurement of SARS-CoV-2 antibody titer or neutralizing antibody should not be measured as there is poor correlation and cellular immunity is likely playing a key role in protection against severe disease associated with newer variants.

Journal Pre-proof

Table 2. Immediate and Delayed adverse reactions to SARS-CoV-2 Vaccines

Clinical Phenotype	Specific type of vaccine	Risk group	Prevalence	Acute Management	Advice for future vaccination
Immediate reactions					
Anaphylaxis	mRNA vaccines	Women > Men History of previous anaphylaxis is prevalent	2.5 to 5.1 events per million [16]	Intra-muscular epinephrine Serum tryptase	Refer to allergy and immunology Increasing reports of tolerance of 2nd and subsequent doses in the setting of anaphylaxis to the first dose suggests a non-IgE mediated mechanism may be prevalent [17,18].
Mild single system reaction	mRNA vaccines	Women > Men	2.1% [19]	Symptomatic management with antihistamines [17,18]	Antihistamine pre-medication prior to subsequent dosing of mRNA vaccine [17,18].
Delayed reactions					
Mild to moderate urticaria	mRNA vaccines	Individuals with underlying urticaria Women > Men	Local reactions 0.8% (dose 1) 0.2% (dose 2) [20]	Symptomatic management with ice (for local reactions) topical steroids and antihistamines	No contra-indication for second and subsequent doses of vaccine Consider antihistamine pre-medication
Injection site		Women < 65 years			
Lymphadenopathy		3rd dose booster > others	Can be >50% lasting up to 10 weeks when sensitive imaging is performed[21]	Symptomatic management	No contra-indication for second and subsequent doses of vaccine (on side contralateral to tumor or other disease process if patient has known pathology for which they are being staged or followed)
Myocarditis	mRNA vaccines	Men < 30 years	more common on 2nd dose (versus 1st dose	Symptomatic management	Consider subsequent dose with mRNA vaccine

Journal Pre-proof

			or booster) Estimated risk 12-29-year-old males – 41 cases/million[22] Moderna>Pfizer in Denmark (4.2/100,000 versus 1.4/100,000 vaccinated)[23]		upon full recovery of all signs and symptoms of myocarditis particularly if patient has co-morbidities or is immunosuppressed. Benefit upon resolution of all symptoms and signs associated with myo-pericarditis
Guillain Barre or transverse myelitis	adenoviral vector vaccines	-	8/millions doses	Symptomatic management	Vaccinate with an alternative vaccine if the conditions is self-limited and resolved
Thrombosis with thrombocytopenia (multiple thrombotic episodes venous and arterial)	adenoviral vector vaccines (AstraZeneca (ChAdOx1) > Johnson & Johnson (Ad26.COV2.S))	Women > Men (69% for J&J; median age <50 for 48% with J&J vaccine)[24] Time course – median 9 days	3.8/million doses for J&J [24]	Avoid heparin Administer thrombin inhibitors IvIg may be of benefit	Administer mRNA vaccine following occurrence. Since December 16, 2021 CDC recommends mRNA vaccines and the Johnson & Johnson vaccine for initial and booster dosing.

Abbreviations: IvIg, intravenous immunoglobulins; J&J, Johnson & Johnson; mRNA, messenger ribonucleic acid.

Journal Pre-proof

Table 3. Questions on How to Manage Those with a History of Anaphylaxis to a Vaccine Component or Anaphylaxis following an mRNA Vaccine

Journal Pre-proof

Question	Pro	Con	General Consensus
Is there a role of skin testing to PEG or PEG derivatives to guide initial or future doses of COVID-19 vaccines?	• If anaphylaxis to PEG exists this will help define what products might be safe and what should be avoided in the future (molecular weight threshold)	• Mounting evidence supports that PEG skin testing is not helpful to determine vaccine tolerance[25] • Patients with PEG anaphylaxis and positive skin tests to PEG have been tolerant of mRNA vaccines	• **<u>There is no role for PEG skin testing prior</u> to administration of a COVID-19 vaccine** • **<u>There is no role for PEG skin testing prior</u> to administration of a COVID-19 vaccine in someone with a history of PEG allergy** • **There is no role for PEG skin testing alone following anaphylaxis to the first dose of a COVID-19 vaccine to guide future vaccine dosing. It is recommended instead that vaccine skin testing be done** • **PEG skin testing should be used in an individual suspected to have PEG anaphylaxis regardless of COVID-19 vaccine exposure or tolerance to help guide PEG containing drugs and products that the individual should avoid.**
Is there a role of skin testing to COVID-19 vaccines to guide initial or future doses of COVID-19 vaccines?	• Prick testing to vaccines is an established procedure to help guide management[26]. • Non-irritating concentrations (undiluted for mRNA vaccines) for prick and intradermal testing have been reported[27,28]. • If testing for more than one COVID-19 vaccine, a positive test to one	• Negative vaccine responses have occurred in those with positive immediate skin tests raising the question of positive predictive value. • Delayed responses (not relevant to an allergic response) at the skin test site may be significant in those who have had at least dose 1 or prior natural infection. • Does not give any indication of tolerance of	• **<u>There is no role for skin testing prior</u> to administration of a COVID-19 vaccine** • It is recommended that COVID-19 vaccine challenge whether it be to the same or different mRNA vaccine or a different vaccine platform (e.g. adenoviral vector) be done under the allergist observation.

Journal Pre-proof

	and negative to another may give a vaccination strategy.	PEG in drugs or injectables and patients with PEG anaphylaxis as they can be negative on skin testing to mRNA vaccines and require additional follow-up and PEG specific testing to determine PEG product avoidance.	
Is there a role for administering a future dose with a different COVID-19 vaccine platform	• Provides a strategy based on those used with vaccine allergy in the past. • Some evidence in small studies to support robust immunologic response using heterologous vaccine platform. • Can be an allergist observed procedure with the decision shared with the patient.	• Data on the efficacy and safety of such procedures has not been established and has typically favored better response with mRNA vaccine following adenoviral vector vaccine. • Vaccination with a new platform or different vaccine (e.g. adenovral vector vaccine) could be associated with age and demographic related adverse events that are not as easily treated as anaphylaxis (e.g. thrombosis with thrombocytopenia with adenoviral vector vaccines or myocarditis with mRNA vaccines).	• Increasing evidence supports that most patients with an mRNA vaccine reaction will tolerate repeat dosing with an mRNA and the decision of whether to administer an alternative mRNA vaccine versus the same mRNA vaccine versus a new platform (e.g. Johnson & Johnson or Astrazeneca) should be shared with the patient.
Is there a role for graded dosing of a COVID-19 vaccine	• This is an established approach that allergists have used with other	• mRNA vaccines are a new vaccine platform and the Pfizer-BioNTech vaccine in	• Shared decision with the patient for rechallenge is recommended. Regardless of how the vaccine is

Journal Pre-proof

	vaccines to challenge in the face of a suspected component or previous vaccine reaction.	particular is low volume. It is not known the impact that graded dosing might have on vaccine efficacy.	administered in the setting of prior anaphylaxis allergist observed vaccination is recommended. Observed full-dose vaccination has been well tolerated even in the setting of first-dose anaphylaxis.
Is there a role to check SARS-CoV-2 antibodies to guide future dosing?	• Antibodies may give some information about a response to vaccine (Spike) or natural infection (Nucleocapsid-RBD).	• Although our knowledge is advancing, the specific immune correlates of protection are not known and include a complex equation of both antibody and T-cell responses. An antibody response does not take into account the importance of T-cell responses. • Antibody responses are not predictably helpful with the presence of new viral variants.	• Measuring antibody responses is generally not helpful to guide initial or future vaccination and could give false reassurance given the importance of booster doses for protection of new viral variants such as Omicron.
Should COVID-19 vaccination be deferred in someone who has had a history of a component reaction or first or second dose reaction?	• COVID-19 monoclonal antibodies have been approved that provide passive immunity giving a buffer of time to make the decision on the safest management.	• COVID-19 monoclonal antibodies approved for pre-exposure prophylaxis (tixagevimab/cilgavimab (Evusheld®) are in short supply and ideally should be reserved for our patients with primary or secondary immunodeficiencies likely to have inferior vaccine response. In addition, they are not a replacement for vaccination and all patients who receive Evusheld®	• With careful allergist assessment there should be no need to unnecessarily delay COVID-19 vaccination either initial series or booster based on a prior reaction. This should be shared with the patient and follow the principles outlined above.

Journal Pre-proof

		should have had vaccination attempted. • Monoclonal antibodies may not be active against future variants. • Most patients with a component reaction tolerate COVID-19 mRNA vaccines. • Most patients with a first or second dose anaphylactic reaction tolerate subsequent dosing.	

Journal Pre-proof

References:

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020; **383**(27): 2603-15.
2. Lutrick K, Rivers P, Yoo YM, et al. Interim Estimate of Vaccine Effectiveness of BNT162b2 (Pfizer-BioNTech) Vaccine in Preventing SARS-CoV-2 Infection Among Adolescents Aged 12-17 Years - Arizona, July-December 2021. *MMWR Morb Mortal Wkly Rep* 2021; **70**(5152): 1761-5.
3. Walter EB, Talaat KR, Sabharwal C, et al. Evaluation of the BNT162b2 Covid-19 Vaccine in Children 5 to 11 Years of Age. *N Engl J Med* 2022; **386**(1): 35-46.
4. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med* 2021; **384**(5): 403-16.
5. Ali K, Berman G, Zhou H, et al. Evaluation of mRNA-1273 SARS-CoV-2 Vaccine in Adolescents. *N Engl J Med* 2021; **385**(24): 2241-51.
6. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021; **397**(10269): 99-111.
7. Sadoff J, Gray G, Vandebosch A, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. *N Engl J Med* 2021; **384**(23): 2187-201.
8. Heath PT, Galiza EP, Baxter DN, et al. Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. *N Engl J Med* 2021; **385**(13): 1172-83.
9. Al Kaabi N, Zhang Y, Xia S, et al. Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial. *JAMA* 2021; **326**(1): 35-45.
10. Jara A, Undurraga EA, Gonzalez C, et al. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Chile. *N Engl J Med* 2021; **385**(10): 875-84.
11. Tanriover MD, Doganay HL, Akova M, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet* 2021; **398**(10296): 213-22.
12. Fadlyana E, Rusmil K, Tarigan R, et al. A phase III, observer-blind, randomized, placebo-controlled study of the efficacy, safety, and immunogenicity of SARS-CoV-2 inactivated vaccine in healthy adults aged 18-59 years: An interim analysis in Indonesia. *Vaccine* 2021; **39**(44): 6520-8.
13. Ella R, Reddy S, Blackwelder W, et al. Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial. *Lancet* 2021; **398**(10317): 2173-84.
14. American College of Rheumatology. COVID-19 Vaccine Clinical Guidance Summary for Patients with Rheumatic and Musculoskeletal Diseases. 2021. https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf.
15. Centers for Disease Control and Prevention. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States. 2021. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html.
16. Greenhawt M, Abrams EM, Shaker M, et al. The Risk of Allergic Reaction to SARS-CoV-2 Vaccines and Recommended Evaluation and Management: A Systematic Review, Meta-Analysis, GRADE Assessment, and International Consensus Approach. *J Allergy Clin Immunol Pract* 2021; **9**(10): 3546-67.
17. Krantz MS, Kwah JH, Stone CA, Jr., et al. Safety Evaluation of the Second Dose of Messenger RNA COVID-19 Vaccines in Patients With Immediate Reactions to the First Dose. *JAMA Intern Med* 2021; **181**(11): 1530-3.

Journal Pre-proof

18. Krantz MS, Bruusgaard-Mouritsen MA, Koo G, Phillips EJ, Stone CA, Jr., Garvey LH. Anaphylaxis to the first dose of mRNA SARS-CoV-2 vaccines: Don't give up on the second dose! *Allergy* 2021; **76**(9): 2916-20.
19. Shavit R, Maoz-Segal R, Iancovici-Kidon M, et al. Prevalence of Allergic Reactions After Pfizer-BioNTech COVID-19 Vaccination Among Adults With High Allergy Risk. *JAMA Netw Open* 2021; **4**(8): e2122255.
20. Blumenthal KG, Freeman EE, Saff RR, et al. Delayed Large Local Reactions to mRNA-1273 Vaccine against SARS-CoV-2. *N Engl J Med* 2021; **384**(13): 1273-7.
21. Lam DL, Flanagan MR. Axillary Lymphadenopathy After COVID-19 Vaccination in a Woman With Breast Cancer. *JAMA* 2022; **327**(2): 175-6.
22. Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices - United States, June 2021. *MMWR Morb Mortal Wkly Rep* 2021; **70**(27): 977-82.
23. Husby A, Hansen JV, Fosbol E, et al. SARS-CoV-2 vaccination and myocarditis or myopericarditis: population based cohort study. *BMJ* 2021; **375**: e068665.
24. See I. Updates on Thrombosis with Thrombocytopenia Syndrome (TTS). 2021. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-12-16/02-COVID-See-508.pdf2022).
25. Picard M, Drolet JP, Masse MS, et al. Safety of COVID-19 vaccination in patients with polyethylene glycol allergy: A case series. *J Allergy Clin Immunol Pract* 2022; **10**(2): 620-5 e1.
26. Broyles AD, Banerji A, Castells M. Practical Guidance for the Evaluation and Management of Drug Hypersensitivity: General Concepts. *J Allergy Clin Immunol Pract* 2020; **8**(9S): S3-S15.
27. Marcelino J, Farinha S, Silva R, Didenko I, Proença M, Tomaz E. Nonirritant concentrations for skin testing with SARS-CoV-2 mRNA vaccine. *J Allergy Clin Immunol Pract* 2021; **9**(6): 2476-7.
28. Pienkowski MM, Pienkowski SM. Evaluation of anaphylaxis risk by skin testing with coronavirus disease 2019 messenger RNA vaccines on patients with anaphylaxis. *Ann Allergy Asthma Immunol* 2022; **128**(1): 101-3.

Journal Pre-proof