Title: Vaccines and Allergic reactions: the past, the current COVID-19 pandemic, and future perspectives

Short title: Vaccination and allergic reactions

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Abstract

Vaccines are essential public health tools with a favorable safety profile and prophylactic effectiveness that have historically played significant roles in reducing infectious disease burden in populations, when the majority of individuals are vaccinated. The COVID-19 vaccines are expected to have similar positive impacts on health across the globe. While serious allergic reactions to vaccines are rare, their underlying mechanisms and implications for clinical management should be considered to provide individuals with the safest care possible. In this review, we provide an overview of different types of allergic adverse reactions that can potentially occur after vaccination and individual vaccine components capable of causing the allergic adverse reactions. We present the incidence of allergic adverse reactions during clinical studies and through post-authorization and post-marketing surveillance and provide plausible causes of these reactions based on potential allergenic components present in several common vaccines. Additionally, we review implications for individual diagnosis and management and vaccine manufacturing overall. Finally, we suggest areas for future research.

Keywords*:* allergy, anaphylaxis, COVID-19, SARS-CoV-2, vaccine

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Introduction

The rapid development and the launch of several novel COVID-19 vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an extraordinary and remarkable accomplishment of modern science. The Pfizer-BioNTech BNT162B2 was the first vaccine to be granted temporary authorization for emergency use by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the U.K for the treatment of COVID-19 on Dec 2, 2020.[1] Soon after, on Dec 11, 2020, it also received emergency use authorization (EUA) by the U.S. Food and Drug Administration (FDA).[2] EUA is a mechanism to facilitate the availability of vaccines during public health emergencies, such as the current COVID-19 pandemic. Under an EUA, the FDA may allow the use of unapproved medical products (including vaccines) to prevent serious or life-threatening disease when certain statutory criteria have been met and no adequate and/or approved alternatives are available. The authorization of BNT162B2 was followed by an EUA for a second COVID-19 vaccine, the Moderna mRNA-1273 on Dec 18, 2020.[3] This was followed by the authorization of mRNA-1273 for use by other regulatory agencies such as the European Commission, UK MHRA, Israel Ministry of Health, and others.[4] On December 30, a third COVID-19 vaccine, the Oxford/AstraZeneca recombinant adenoviral AZD1222 or ChAdOx1-S was authorized for use by the UK MHRA.[5] In addition to the above authorized COVID-19 vaccines, a number of other novel COVID-19 vaccines are currently in different phases of clinicals development. Currently used platforms in COVID-19 vaccines include RNA- and DNA-based, viral vectors (nonreplicating), protein subunits, virus like particles and inactivated viral platform (**Table 1**).[6, 7]

With the authorization of COVID-19 vaccines, vaccination campaigns have been initiated in many areas throughout the world. Within the first few days of public vaccinations, however, BNT162b2 was associated with a few severe cases of anaphylaxis.[8] While severe allergic reactions may pose a potential risk with any vaccine (or systemic medications), the benefits of vaccination outweigh the potential risks of receiving the vaccine for the vast majority of individuals. However, the fear of allergic reactions may lead to vaccine hesitancy, which could compromise herd immunity and limit efforts to sustain the pandemic. It is therefore critical that we understand the risk of severe allergic reactions and their mechanisms in order to improve individual safety and issue proper guidance with the goal of vaccinating the maximum number of individuals. Here, we review adverse events associated with vaccine-related allergic and non-allergic reactions to COVID-19 and other vaccines, mechanisms associated with allergic adverse reactions, and rates of severe allergic reactions with existing vaccines and with the novel COVID-19 active vaccines currently being administered to large parts of the world.

Section I: Vaccine-associated allergic vs non-allergic reactions

Vaccines are associated with the potential for adverse events. An adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.[9] Adverse events can present as local or systemic, immediate or non-immediate, and immune or non-immune mediated reactions. While all allergic reactions are immune-mediated, not all immune-mediated reactions are allergic. Local non-immediate reactions that are not allergenic are common and may include swelling and erythema at the injection site. These reactions can occur hours or days after administration and are not always mediated through the immune system. Systemic non-

allergic reactions include mild fever and vasovagal reactions such as hypotension, nausea, and syncope are also relatively common and neither the local reactions or the vasovagal reactions pose any serious risk. Although some of these reactions are immune-mediated, they are not allergic reactions. Rather, soreness at the injection site or fatigue are consequences of activation of the innate immune system.[10-13]

Adverse events, including allergic reactions, are graded according to severity as mild, moderate, and for purposes of this review, serious. Typical signs of an allergic reaction include bronchoconstriction, conjunctivitis, rhinorrhea, gastrointestinal symptoms, and/or characteristic skin lesions such as generalized urticaria and/or angioedema. These can occur in combination or alone, and onset can be immediate, within minutes, or up to several hours post-vaccination. Examples of mild allergic reactions are swelling with itching at the injection site, conjunctivitis, or rhinorrhea. Examples of moderate allergic reactions are bronchoconstriction that can be adequately treated with nebulized beta-agonists or generalized urticaria that may be treated with an antihistamine. Serious adverse events (SAE) are those events that are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, cause a persistent or significant incapacity or substantial disruption in the ability to conduct normal life functions, a congenital anomaly/birth defect, or death. Two examples of SAE that are allergic reactions are bronchospasm that requires intensive treatment and life-threatening anaphylaxis.[9, 14]

Anaphylaxis, an immediate systemic multi-organ reaction, is rare but can be life-threatening. Organs affected include the cutaneous, gastrointestinal, respiratory, and cardiovascular systems. Anaphylaxis can be either immunological, non-immunological,

or idiopathic. Idiopathic anaphylaxis is diagnosed through exclusion of other known causes and may mask a clonal mast cell disorder.[15-20] Non-immunological anaphylaxis was previously termed anaphylactoid reactions, but the World Allergy Organization (WAO) in 2004 suggested replacing anaphylactoid reactions with non-immunological anaphylaxis.[21] The change in terminology is to reinforce the risk and potential fatality of all types of anaphylaxis, regardless of the underlying mechanism. All three mechanisms of anaphylaxis produce the same clinical picture. (see **Section IV** on mechanisms below). Distinguishing between systemic vasovagal reactions and anaphylaxis during immunization is critical to ensure that appropriate and immediate treatment can be administered (**Table 2**). Vasovagal reactions usually occur immediately or up to 30 minutes of vaccine administration. Similar to anaphylaxis, organs affected include the cutaneous, gastrointestinal, respiratory, neurological, and cardiovascular systems.[22, 23]

Anaphylactic reactions are considered adverse events of special interest (AESI)[24], i.e. adverse events that are of significant medical and scientific concern for which immediate medical action with ongoing monitoring and rapid communication by the investigator or sponsor is required. AESI reporting is a critical aspect of pharmacovigilance for characterization of the safety profile of a drug or vaccine in context of previous reports of the vaccine or of other vaccines with similar manufacturing processes, formulation, immunogenicity, and novelty, AESIs alert regulators to potential risks. Particularly in mass vaccination programs where a large number of adverse reactions may be reported, identification and assessment of AESIs are a high priority because they highlight potential risks that may alter risk-benefit profile and may require

immediate investigation, regulatory action, and prompt communication with the public.[25, 26] **Table 3** lists Pharmacovigilance Practices that follow authorization of a vaccine.

Section II: Allergic reactions to vaccines

In the last 120 years, global vaccination programs have eradicated or vastly reduced the incidence of debilitating infectious diseases such as smallpox, polio, and measles.[27] According to the Institute of Medicine, epidemiologic and mechanistic evidence support a causal relationship between anaphylaxis and several vaccines, including those for measles, mumps, and rubella (MMR), varicella, influenza, hepatitis B, meningococcus, human papillomavirus, and the combined diphtheria, tetanus, pertussis (DTaP or TdaP) vaccine. Although approved vaccines have been rigorously tested for safety, anaphylactic reactions, although rare, can occur in individuals.[28] An analysis of reported anaphylaxis to the Vaccine Adverse Reporting System (VAERS) in the United States over a 26-year period found that out of the almost 500,000 reports to VAERS, only 828 were classified as anaphylaxis based on either on physician's diagnosis or in according to the Brighton Collaboration case standards.[29] A 2003 study analyzing over eight million routine vaccinations in the Vaccine Safety Datalink (VSD) Project[30] found the risk of anaphylaxis ranged between 0.65 cases/million doses and 1.53 cases/million doses. They also noted that most anaphylactic episodes occurred when multiple vaccines were administered during the same visit.[31] Similarly, a 2016 study used health data from VSD and found 33 confirmed cases of anaphylaxis after 25,173,965 vaccine doses or an anaphylaxis rate of 1.31 per million vaccine doses.[32] The study also found that 85% of cases of anaphylaxis had pre-existing atopic disease, which was consistent with earlier reports emphasizing coexisting atopic disease, particularly asthma, as being clinical risk

factors for anaphylaxis.[33] In Asian children, analysis of a large-linked database found risk of anaphylaxis to be 1.21 cases/million doses.[34] A study conducted in Australia found that estimated incidence rate of anaphylaxis for DTaP vaccines was 0.36 cases per 100,000 doses, and 1.25 per 100,000 doses for MMR vaccines.[35] Overall, rates of reported anaphylaxis occurs at a rate of about 1 per 100,000 to one per 1,000,000 depending on the vaccine.[36] **Figure 1** and **Table 4** shows the frequency of anaphylaxis for specific vaccines. **Table 5** provides population-specific considerations for common vaccines.[37-40]

Section III: Allergic reactions to COVID-19 vaccines

Development of the SARS-CoV-2 mRNA vaccine occurred in record time. So far, three candidate vaccines (mRNA BNT162B2, mRNA-1273 and adenovirus vectored ChAdOx1) have been authorized for COVID-19 in the European Union and the United Kingdom. Of these, mRNA BNT162B2 and mRNA-1273 are authorized for emergency use in the United States. Additional candidates have entered or are completing the pivotal stage of clinical development programs. At the time of this review, there are 64 vaccines in several stages of clinical development and 173 in pre-clinical development worldwide.[41] Details of their composition, mode of action, and developmental stage can be found in the review by Rodriguez−Coiraet al.[42]

Even after formal authorization, vaccine rollout in the United Kingdom, United States, and European Union has been and continues to be challenging. Navigating complex distribution logistics, determining ethical allocation of a limited resource, and de-mystifying widespread news coverage of anaphylactic events that perpetuate vaccine hesitancy are among the most pressing. While anaphylaxis after routine vaccination is

very rare, it is important for the scientific community to be informed and prepared to treat adverse vaccine reactions to increase safety and acceptability. During the COVID-19 pandemic, vast quantities of vaccine are expected to be administered over a very short period of time, with increased public awareness and surveillance. In this situation, the probability of reporting anaphylaxis likely increases without the added context of the denominator, which is the millions of individuals receiving the vaccine.

Of the vaccines authorized for use in Europe and the US, the first vaccine to be administered and distributed was the mRNA BNT162B2 vaccine in the UK. Following two reports of allergic reactions in the UK on December 8, 2020, the MHRA updated its guidelines to state that individuals should not receive the vaccine if they have had previous anaphylaxis to a vaccine, medicine, or food. In addition, MHRA recommended that individuals who experience anaphylaxis after their first dose of the mRNA BNT162B2 vaccine should not receive the second dose, and that everyone should be monitored for a minimum of 15 minutes after vaccination. However, on Dec 30, after a review of additional data, the guidelines were further updated to indicate that anyone with a previous history of allergic reactions to the ingredients of the vaccine should not receive it, but those with any other allergies such as a food allergy can receive the vaccine.[43]

A CDC report of the VAERS monitoring database indicates that between December 14–23, 2020, 1,893,360 first doses of the mRNA BNT162B2 COVID-19 vaccine were administered, and 21 cases of anaphylaxis were reported (11.1 cases per million doses). Seventy one percent of these reactions occurred within 15 minutes of vaccination.[44] Similarly, the CDC reported that between December 21, 2020–January 10, 2021, 10 cases of anaphylaxis were reported after administration of 4,041,396 first doses

of the mRNA-1273 vaccine (2.5 cases per million doses administered). In nine cases, onset occurred within 15 minutes of vaccination. No anaphylaxis-related deaths were reported.[45] This suggests that the incidence of anaphylaxis in the mRNA BNT162B2 (11.1 cases per million doses) and mRNA-1273 COVID-19 vaccines (2.5 cases per million doses) may be about 2 to 8.5 times as high as the incidence reported in the 2016 VSD study for all vaccines (1.31 per million doses). The US FDA authorized labeling currently lists past severe allergic reactions (e.g. anaphylaxis) to any component of the vaccine as a contraindication to the mRNA BNT162B2 vaccine. Yet, the CDC also recommends that individuals with a history of immediate allergic reactions to other vaccines weigh their risk of exposure, risk of severe disease or death due to COVID-19, and consider whether they were previously infected with COVID-19 (because of lower rates of reinfection in the three-month period after infection), when deciding whether to delay or forego vaccination.[46, 47]

After the mRNA BNT162B2 vaccine received central European marketing approval on December 21, 2020, the Paul-Ehrlich-Institut, Federal Institute for Vaccines and Biomedicines in Germany, and the European Medicines Agency (EMA) released its own guidance for vaccination of people with allergies. These guidelines recommended that only individuals in the European Union with an allergy to a specific vaccine component not receive the vaccine.[48] The European Academy of Allergy and Clinical Immunology (EAACI) position paper on diagnosis, management, and prevention of severe allergic reactions to the COVID-19 vaccines states that the vaccines are contraindicated only when there is an allergy to one of the vaccine components or if there was a severe allergic reaction to the first dose. The paper also provides a simplified

algorithm of prevention, diagnosis and treatment of severe allergic reactions and a list of recommended medications and equipment for vaccine centers.[49]

Section IV. General mechanisms in pathways of immune-mediated and non-immune-mediated reactions.

Immunological hypersensitivity is either IgE-medicated (hypersensitivity reaction type 1),[50] IgG- mediated (hypersensitivity reaction type 2), or immune complex and/or complement-mediated (hypersensitivity reaction type 3) or cell-mediated (hypersensitivity reaction type 4).[51] The mechanisms underlying IgE-mediated hypersensitivity are best understood. Individuals with IgE-mediated allergic reactions first undergo an initial sensitization phase during which allergen specific IgE antibodies bind to high affinity FcεRI receptors on mast cells and basophils. Subsequent allergen exposure can cross-link the cell-bound IgE antibodies and triggers degranulation of mast cells and/or basophils, with subsequent release of histamine and other inflammatory chemical mediators (cytokines, interleukins, leukotrienes, and prostaglandins) into the surrounding tissue causing several systemic effects, such as vasodilation, mucous secretion, tissue eosinophilic infiltration, and airway smooth muscle contraction.[52]

Type II IgG-mediated immune vaccine reactions are rare but have been observed with an MMR vaccine containing dextran before those preparations were taken off the market.[53] The occurrence of large, local injection-site reactions with TdaP vaccines have been reported to be due to a local immune complex type III hypersensitivity reaction.[54] Type IV hypersensitivity reactions occur when an individual's T cells provoke an inflammatory response against allergens, leading to T cell activation and the release of

cytokines and chemokines.[55] Type IV reactions to vaccines induce local eczema, which may start between 2 hours to up to 2 days after vaccinations. These reactions are typically observed following vaccines containing thimerosal, aluminum and anti-microbial agents. The occurrence of such an event is not a contraindication for further vaccinations.[56]

Non-immunologic anaphylaxis is caused by agents or events that induce sudden, massive mast cell and/or basophil degranulation in the absence of immunoglobulins. These reactions may be due to activation of complement by nanoparticles, colloidal solutions, or liposomes without immune complex formation, commonly termed complement-activation-related pseudoallergy or CARPAs[57] (e.g., medications containing Cremophor EL[58]), direct mast cell and basophil activation resulting in histamine release (vancomycin[59] and opiate medications[57]), or other mechanisms (activation of the kallikrein-kinin pathway[60]). Nonsteroidal anti-inflammatory drugs (NSAIDs)[61], local anesthetics[62], monoclonal antibodies, and chemotherapeutic agents have also been reported to induce non-immunologic anaphylaxis. Recently, transient receptor potential cation receptor, subfamily V (TRPV4) channel has been implicated as a driver of IgE-independent mast cell-dependent bronchospasm via cysteinyl leukotrienes release.[63] While radiocontrast agents have traditionally been considered to be non-immunologic, some of the newer, low-osmolar agents may induce IgE-mediated reactions.[18]

Although the clinical presentations of both IgE-mediated anaphylaxis and non-immunologic anaphylaxis are similar, measurements of tryptase and SC5b-9 may assist in differentiating the two types.[64] Tryptase is a marker of mast cell activation which is released following mast cell degranulation while SC5b-9 is a marker of complement activation and is a terminal complement complex.[64, 65] As both tryptase and SC5b-9 are

transiently elevated soon after an anaphylaxis episode, blood should ideally be collected between 30 and 90 minutes after the onset of reaction.[64] Acute serum total tryptase should be at least 20% plus 2 ng/ml over the baseline tryptase level.[65] Another novel emerging biomarker is hereditary α-tryptasemia which is present in mastocytosis and may be useful for determining the individual patient´s risk of developing severe anaphylaxis.[66] **Figure 2** depicts the mechanisms of IgE-mediated and non-immunological anaphylaxis.[67-73]

Section V: Proven and suspected allergenic components of vaccines

Anaphylaxis to vaccines is rare and occurs primarily among individuals who have histories of allergies to the components of the vaccines.[16] Allergic reactions after vaccination can be due to any of the vaccine components such as antigens, adjuvants, stabilizers, preservatives, emulsifiers, leached packaging components, residual antibiotics, cell culture materials, and inactivating ingredients (**Box 1**).[74] **Table 6** lists components that have been implicated in allergenic reactions and related adverse events. Here we discuss some of the most common allergenic or potentially allergenic components of vaccines.

Many vaccines contain small amounts of the egg protein ovalbumin. Influenza, yellow fever, and rabies vaccines tend to have higher concentrations of ovalbumin because they are cultured in embryonated chicken eggs.[75] Vaccines cultured in chicken embryo fibroblasts, such as the MMR vaccine, have lower concentrations of egg protein than those cultured in embryonic eggs.[76] While egg allergy is common in childhood, studies have shown that vaccinating egg-allergic children with MMR and influenza vaccines is well tolerated and risk of an allergic reaction is similar in the general

population.[77, 78] Specifically, egg-allergic children, including those who have had anaphylaxis, were successfully vaccinated with yellow fever[79] vaccines with no serious adverse events reported. Since severe allergic reactions to egg-based influenza vaccines are rare, the CDC and its Advisory Committee on Immunization Practices (ACIP) guidelines state that individuals with mild egg allergy can receive any licensed and recommended age-appropriate flu vaccine and no longer need to be observed for 30 minutes after receiving the vaccine. However, in those with severe egg allergy, the vaccines should only be given under the supervision of a health care provider who is capable of recognizing and managing serious allergic conditions.[80, 81]

Gelatin, a protein derived from bovine or porcine sources, is added to both live and inactivated vaccines as a stabilizing agent.[56] Sensitivity to gelatin was confirmed with both skin-prick tests and by immunoassay in a 17-year old female who had an anaphylactic reaction to an MMR vaccine.[82] A retrospective case-control study which interviewed and collected sera from individuals who had suffered anaphylaxis after receiving MMR found that 27% of them had anti-gelatin IgE. In comparison, anti-gelatin IgE was not detected in any of the vaccinated subjects who did not present with adverse events.[83] It was subsequently shown that patients who have anaphylaxis to MMR were sensitized to gelatin present in the DTaP vaccine[84, 85], and that cellular immunity to gelatin from the DTaP vaccine can persist for more than three years.[86] However, sensitization may also persist due to exposure to gelatin in foods or through cross-reactivity to other allergens such as egg, chicken and cow's milk [87]. Gelatin is also a source of alpha-gal, an carbohydrate allergen that causes meat allergy.[88] Anaphylaxis was observed after

423 vaccination with MMR, Varicella, and DTaP/IPV in pediatric subjects with alpha-gal
424 allergy.[89]

425 Milk proteins are used as stabilizers in DTaP and Tdap vaccines. Although bovine
426 casein is present in nanogram quantities in these vaccines, they rarely cause anaphylaxis.
427 Kattan et al reported eight children with severe cow's milk allergy who reacted with
428 anaphylaxis to the booster dose of DTaP or Tdap vaccine and suggested casein present in
429 the vaccines may play role in the induction of anaphylaxis in atopic children.[90,
430 91]However, the methods used in this report were questioned[91] and to our knowledge, there
431 have been no subsequent data that support a causative role for DTaP or Tdap vaccines in
432 the induction of allergic disease. It is the position of EAACI (or subcommittee) that these
433 vaccines do not contribute to the pathogenesis of allergic disease and that atopy is not a
434 contraindication to these vaccines.[92]

435 As stated above, dextran present in one preparation of MMR vaccine was
436 responsible for numerous cases of anaphylaxis, but this brand of MMR vaccine has since
437 been withdrawn from the market.[93] It was used as a medium nutrient or as a stabilizer.
438 Similarly, during Brazil's national MMR vaccination campaign in 2004, the rate of
439 hypersensitivity following MMR vaccination was unexpectedly high while its case-
440 control study showed no association with a history of allergy.[94] However, subsequent
441 studies implicated dextran as the likely cause of these hypersensitivity events.[95]

442 Many vaccines contain antigens that are created in cell lines. For example,
443 hepatitis B vaccines and the human papillomavirus (HPV) vaccines contain antigens that
444 are recombinant proteins expressed in Baker's yeast.[96] Purification removes most of the

cellular material, but it is impossible to remove all trace components. Between 1990 and 2004, only 15 reports were identified of probable or possible anaphylaxis following vaccination of individuals with a reported history of yeast allergy. Eleven of these occurred after administration of the hepatitis B vaccine, which contains trace amounts of yeast proteins. Because these subjects were not tested for yeast allergy, it cannot be confirmed that sensitivity to yeast caused these adverse reactions. These data indicate that recombinant yeast-derived hepatitis B vaccine poses minimal risk of allergic reactions in yeast-sensitive individuals. Therefore, evaluation by an allergist is recommended for people who have a history of severe yeast allergy before administration of hepatitis B and HPV vaccines.[96] According to VAERS, there were 107 reports of adverse events in those with a history of yeast allergy present prior to vaccination; of these 11 recipients of hepatitis B vaccine had probable or possible anaphylaxis events.[97] By contrast, another study found no episodes of anaphylaxis in a large cohort of women who had positive skin tests to yeast extract after the HPV vaccine.[98]

Antibiotics such as neomycin, streptomycin, polymyxin B, kanamycin and gentamicin are well known to cause mild to life-threatening allergic reactions. An individual receiving an MMR vaccine containing neomycin was reported to have experienced anaphylaxis shortly after vaccination.[99] Although a skin test to neomycin alone could not be performed in this individual due to a lack of a commercial preparation suitable for skin testing, patient history indicated systemic sensitivity on topical application of neomycin during infancy to disrupted skin. In another case, a history of previous reaction and positive skin test to neomycin was not associated with immediate or delayed hypersensitivity reactions following MMR vaccination.[100] In a report of

anaphylaxis after rabies vaccination, the presence of residual kanamycin in the vaccine and a positive kanamycin result to an antibiotic skin sensitivity test suggested that kanamycin was the likely cause of the adverse event.[101] Finally, there is one report of anaphylaxis after applying eye drops containing polymyxin B, an excipient used in DTaP and other vaccines.[39, 102] To our knowledge, no other antibiotics have been associated with vaccine-associated anaphylaxis. 2-Phenoxyethanol is widely used as preservative in cosmetics and vaccines due to its large spectrum of antimicrobial activity, and is considered as one of the most well-tolerated preservatives.[103]

Natural latex allergy is well characterized among healthcare personnel and latex content in vaccines as vial stopper or syringe plunger may pose safety concerns in this population. However, Smith et al could not detect latex allergens in adult vaccines.[104] In 2004, an analysis of VAERS revealed only 28 cases of immediate hypersensitivity with latex allergy in vaccine recipients among 160,000 reports of vaccine-associated adverse events.[105]

Thimerosal, which is approximately 50% mercury by weight, has been one of the most widely used preservatives in vaccines to prevent growth of harmful microbes. All vaccines routinely recommended for children 6 years of age and younger in the U.S. are available in formulations that do not contain thimerosal.[106] A risk assessment study revealed that except for local hypersensitivity reactions, there is no evidence of harm caused by thimerosal in vaccines.[107] Thus, while thimerosal is the most prevalent preservative inducing contact dermatitis, it is considered irrelevant to vaccine-induced anaphylaxis.[108]

Although formaldehyde is only found in residual quantities in vaccine preparation, it has been reported to aggravate eczematous dermatitis following hepatitis B vaccination.[109] It is used to inactivate virus or for the detoxification of bacterial toxin. Formaldehyde-specific contact dermatitis had also been reported following formaldehyde-containing influenza vaccine.[110] It is hypothesized that the introduction of carbonyl groups on antigens by formaldehyde in vaccines profoundly affects its immunogenicity, thus explaining adverse effects due to formaldehyde-containing vaccines.[111, 112]

Adjuvants are incorporated into some vaccines to boost T-cell immunity and increase helper T-cell function. The most commonly used adjuvants in vaccines are aluminum hydroxide and aluminum phosphate. Despite its long-standing use as an adjuvant in vaccines, aluminum has always been the target of controversy. Although no association between direct toxicity of aluminum and vaccines has been established, several delayed type hypersensitivity reactions have been reported.[113-115] In Denmark, 39 out of 42 children with persistent skin reactions following vaccination had positive patch tests for aluminum.[116] In another study, vaccination-induced granulomas and contact allergy to aluminum was reported in 60 out of 63 Swedish children receiving DTP vaccines.[117] In contrast, an *in vivo* study in a mouse model of peanut allergy found that the severity of peanut-hypersensitivity was reduced by an alum/CpG-adjuvanted vaccine while exposure to endotoxin and alum did not influence allergic symptoms.[118] More recently, adjuvants such as AS01, AS03, AS04, CpG ODN, and MF59, are used in FDA-approved vaccines for human use. Details on the mechanism of these and other vaccine adjuvants under clinical investigation are detailed in the review by Shi et al.[119]

Polysorbate 80 is an emulsifier which has been widely used to solubilize agents in foods and medicines, including vaccines. This nonionic detergent induces local and systemic allergic reactions, including IgE-mediated and non-immune anaphylaxis. The hydrophilic polymer polyethylene glycol (PEG) is structurally similar to polysorbate 80 and PEG and its derivatives are frequently found in household products including toothpaste, cosmetics, pharmaceuticals and foods. In addition, PEG is often conjugated to biological therapeutics to form a depot agent. It is now well understood that sensitivity to PEG can cause IgE-mediated anaphylaxis after administration of PEG-conjugated biological therapeutics[120-125], and that severe allergic reactions to PEG have been associated with pre-existing anti-PEG antibodies induced by PEG-containing household products.[126] However, measures of pre-existing anti-PEG antibodies vary widely, range from 0.2% to 72% of healthy individuals.[127] This has become immediately relevant because PEG 2000, a high-molecular weight version of PEG, is a component in two of the three authorized COVID-19 vaccines. The mRNA BNT162B2 and mRNA-1273 COVID-19 vaccines are lipid nanoparticles containing mRNA that codes for the spike protein in the coronavirus.[128] The lipid nanoparticle delivery system prevents premature degradation of the genetic instructions necessary for individuals to eventually become protected against SARS-CoV-2.[129] PEG 2000-lipid is a component of the mRNA-1273 vaccine. The lipid nanoparticles stabilize and improve the aqueous solubility of the two mRNA vaccines, and also act as an adjuvant. While more research is needed to determine the cause of the potentially increased rate of anaphylaxis to COVID-19 compared to other vaccines, based on the experience with PEG-conjugated biologics, PEG 2000 in the vaccines is considered the most likely culprit.[122, 123, 130-135] Therefore, individuals with a

known allergy to PEG should be excluded from vaccination with these vaccines for the time being.[136] In addition to PEG, other excipients present in COVID-19 vaccines, such as distearoyl phosphatidylcholine, tromethamol, polysorbate 80, and EDTA, should also be evaluated as potential allergenic components **Table 7** lists the excipients present in the mRNA and ChAdOx1-S vaccines.[137]

Section V: Management of vaccine allergy

Treatment of anaphylaxis in the setting of vaccine administration is reviewed in Sokolowska et al [138] and Castells et al.[121] Briefly, due to the possibility of an anaphylactic reaction to the vaccine, any professional administering the vaccine must be capable of managing an anaphylactic reaction and should have the necessary medications and tools on hand. There must be a mandatory observation period after vaccine administration of at least 15 minutes for all individuals, to allow for the administration of adrenaline in an adequate dose.[139] Individuals with a suspected allergic reaction to the first dose of the vaccine should be followed up by an allergist so that administration of the second dose can be performed in a specialized setting equipped to treat anaphylaxis. One approach used successfully for many vaccine-allergic individuals, but which has not been evaluated for the COVID-19 vaccines, is to administer the vaccine in incremental doses. Any adverse allergic reactions should be promptly reported including any additional information including individual characteristics.

Section VI: Conclusions

Vaccinations benefit public health and help to reduce the risk of disease across the entire population. Despite early reports of waning of antibody responses over 20 days

following SARS-CoV2 infection, evidence is now accumulating that similarly to other infections, recovered patients develop long-lasting immunity.[140] Recently, Hartley et al. reported that patients who have recovered from SARS-CoV-2 infection have stable virus-specific memory B cells that recognize the spike or nucleocapsid proteins of the SARS-CoV-2 virus for at least eight months post infection.[141] Another study found that neutralizing antibody titers against the SARS-CoV-2 spike protein persisted for at least 5 months after infection.[142] These findings support optimism that the currently licensed vaccines will be efficacious despite the emergence of highly infectious mutant viruses and are consistent with the limited reports of natural reinfection after confirmed illnesses. Moreover, research by Pfizer and researchers from the University of Texas have determined that antibodies from 20 recipients of the mRNA BNT162B2 vaccine can neutralize the mutant strains *in vitro* (as yet not peer reviewed).[143]

It is crucial that further research is conducted to better understand to which components of the currently available vaccines individuals are reacting and how to identify individuals who may be at risk of an adverse allergic reaction (Box 2). Individuals who may be at risk for an allergic response or who have a history of allergic responses to vaccinations (or their components) should be evaluated by an allergist.[56]

The best mechanism to further our understanding is to study individuals who have had reactions through a variety of *in vitro* experiments and clinical testing. *In vitro* experiments including analysis of plasma IgE markers as well as, basophil and mast cell line activation tests can help to better characterize potential allergens and identify individuals at risk of an anaphylaxis. Clinical testing, including skin prick and intradermal tests can also help identify allergens and at-risk individuals. All of these tests

can involve testing the individual components of the vaccine to determine the reaction-inducing antigen. However, the critical and pragmatic evaluation of these tests' results in relationship to particular patient's clinical problems remains crucial.

Increased understanding of vaccine-related allergies will help to further improve the manufacturing processes and safety of vaccines. Specifically, through identifying specific vaccine components that cause allergic reactions, vaccine manufacturers can either try to remove or create replacements for those components. This also has an impact on the management of vaccine distribution, specifically with regards to ensuring that those who need vaccination will not have an allergic reaction.

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Table 1: COVID-19 vaccine platforms and developers currently in phase 3 clinical trials[7]

Vaccine Platform	Developers
Inactivated virus	• Sinovac Research and Development Co., Ltd • Sinopharm + China National Biotec Group Co + Wuhan Institute of Biological Products • Sinopharm + China National Biotec Group Co + Beijing Institute of Biological Products • Institute of Medical Biology + Chinese Academy of Medical Sciences • Research Institute for Biological Safety Problems, Rep of Kazakhstan • Bharat Biotech International Limited
Viral vector (non-replicating)	• AstraZeneca + University of Oxford • CanSino Biological Inc./Beijing Institute of Biotechnology • Gamaleya Research Institute ; Health Ministry of the Russian Federation • Janssen Pharmaceutical
Protein subunit	• Novavax • Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences • Clover Biopharmaceuticals Inc./GSK/Dynavax • COVAXX + United Biomedical Inc
RNA-based	• Moderna + National Institute of Allergy and Infectious Diseases (NIAID) • Pfizer/BioNTech + Fosun Pharma • CureVac AG
DNA-based	• Inovio Pharmaceuticals + International Vaccine Institute + Advaccine (Suzhou) Biopharmaceutical Co., Ltd • AnGes + Takara Bio + Osaka University • Cadila Healthcare Ltd.
Virus-like particle	• Medicago Inc.

Table 2: Differentiating features of vasovagal episode vs. anaphylaxis[22, 23]

Vasovagal Episode	Anaphylaxis
Onset	
Immediately or up to 30 minutes after vaccine administration	Can be immediate or within minutes or up to several hours after vaccine administration
Respiratory	
Normal respiration - may be shallow, but not laboured	Cough, wheeze, stridor, hoarseness, rhinorrhea Signs of respiratory distress (tachypnoea, cyanosis, rib recession) Upper airway swelling (lip, throat, tongue, uvula or larynx)
Cardiovascular	
Bradycardia – weak/absent peripheral pulse- but with strong central pulse (carotid) Hypotension – usually transient and corrects in supine position Loss of consciousness – improves once supine or head- down position	Tachycardia, weak/absent central pulse Hypotension – sustained and no improvement without specific treatment (in infants and young children, limpness and pallor are signs of hypotension) Loss of consciousness – no improvement once supine or in head-down position
Skin	
Generalised pallor, cool clammy skin	Urticaria, angioedema, pruritus, erythema
Gastrointestinal	
Nausea or vomiting	Abdominal cramps, diarrhea, nausea or vomiting
Neurological	
Nausea or vomiting	Feels faint, light-headed, headache, dizziness blurred vision, restless, seldom: seizures

Table 3: General pharmacovigilance practices for monitoring vaccine reactions[144]

Goal	Steps
Observed vs. expected (O/E) analysis of AESIs during a mass vaccination program	-Collect background incidence rates of AESIs -Create system to process and display real-time vaccination data
Routine pharmacovigilance	-Provide AESI standard case definitions -Present age-stratified data on AESI incidence rate in target population
Follow-up for an adverse reaction	Collect data on: -Patient -Adverse reaction -Vaccination history -Vaccination and diluent (including manufacturer, batch number, batch release specifications, expiry date, laboratory test results about the batch) -Route of administration -Storage and handling conditions

Table 4: **Frequency of anaphylaxis after vaccines.**

Vaccine	Anaphylaxis rate per 10^6 doses	Comment	Reference
Rabies	55.43 – 86.1		McNeil et al. JACI 2016[32]
HPV	1.29 – 26	Different rates according to the type of HPV vaccine	Brotherton et al. 2008[145] Erlewyn-Lajeunesse et al. 2012[146] McNeil et al. JACI 2016[32]
TBE	20	Polygeline-free TBE vaccine with lower rate of anaphylaxis	Zent et al. 2003[147]
MMRV	19.8		McNeil et al. JACI 2016[32]
BNT162b COVID-19	11		CDC MMWR 2021[44]
Varicella	1.2 – 10.3	Gelatin-free varicella vaccine with lower rate of anaphylaxis	Sakaguchi et al. 2000[148] Ozaki et al. 2005[149] Su et al. 2016[29]
Herpes zoster	6.16 – 9.6		McNeil et al. JACI 2016[32]
Pandemic A/H1N1 vaccine	6.8 – 8	Increased risk of anaphylaxis compared to seasonal influenza vaccines	Rouleau et al. 2013[150]
Yellow fever	7.6		Kelso et al. 1999[151]
MMR	0.6 – 5.14	Egg allergens no longer clinically relevant	D'Souza et al. 2000[152] Pool et al. Pediatrics 2002[83] McNeil et al. JACI 2016[32] Su et al. 2016[29]
MCV4	6.16		McNeil et al. JACI 2016[32]
HAV	3.34		McNeil et al. JACI 2016[32]
DTaP	0.51 - 3.6	During last two decades, the content of gelatin in this type of vaccine	Cheng et al. 2015[35]

		decreased followed by decreased frequency of anaphylaxis	
PPSV23	0.2 – 2.48		McNeil et al. JACI 2016[32] Su et al. 2016[29]
Influenza	0.1 – 1.83	No significant differences by types of vaccine or manufacturer 2-fold higher rate for LAV compared to IIV regarding immediate hypersensitivity reactions	Kawai et al. 2014[153] Ropero-Alvarez et al. 2015[154] McNeil et al. JACI 2017[32] Halsey et al. 2013[155] Su et al. 2016[29]
HBV	0 – 1.67		McNeil et al. JACI 2016[32] Duclos. 2003[156]
Japanese encephalitis	0 – 0.26	Anaphylaxis reported in live attenuated vaccine	Li et al. 2014[157] McNeil et al. JACI 2016[32]
Hib	0	Very rare event	McNeil et al. JACI 2016[32]
PCV13	0	Very rare event	McNeil et al. JACI 2016[32]
Rotavirus vaccines	0	Very rare event	McNeil et al. JACI 2016[32]

BNT162b2 – mRNA vaccine against COVID-19
DTaP – diphtheria-tetanus-acellular pertussis vaccine
HAV – hepatitis A vaccine
Hib – *Haemophilus influenza* type b vaccine
IIV – inactivated influenza vaccine
LAIV – live attenuated influenza vaccine
MCV4 – 4-valent meningococcal conjugated vaccine
MMR – measles-mumps-rubella vaccine
MMRV- measles-mumps-rubella-varicella vaccine
PCV13 – pneumococcal conjugated 13-valent vaccine
PPSV23 – 23-valent pneumococcal polysaccharide vaccine
TBE – tick-borne encephalitis vaccine

Table 5: Population-specific considerations for vaccination[37-40]

Population	Considerations
Healthy	A. Follow routine guidelines/schedule for vaccination. B. Monitor mRNA vaccine recipients for 15-30 minutes per local guidelines.
History of food allergies	*Egg:* Proceed with vaccination under supervision. *Yeast:* Seek allergist evaluation prior to Hepatitis A, B, HPV, DTaP, Meningococcal, Pneumococcal vaccines. *Gelatin:* Seek allergist evaluation prior to MMR, Zoster, Influenza, Rabies, Yellow fever, Typhoid vaccines.
History of immunosuppression	A. Defer live vaccination. B. Administer vaccine prior to immunosuppression if possible.
History of vaccine, drug, or antibiotic allergy	A. Refer to allergist. B. Identify specific components that may be similar in other vaccines. C. Graded administration of vaccine/drug after discussion of risks and benefits.

Table 6: Major components, function, and allergic reactions**

Component	Function	Vaccine	Allergic reactions
Gelatin	Stabilizer	MMR, Zoster, Influenza Rabies, Yellow fever, Typoid	Anaphylaxis, Urticaria, Local
Albumin (egg protein, bovine/calf/fetal serum)	Residual médium, Stabilizer	Yellow fever, MMR, Influenza, Rabies, Influenza	Anaphylaxis
Casein	Medium nutrient	DTaP, Meningococcal, Hib, Tdap, Influenza	Anaphylaxis
Aluminum	Adjuvant	Adenovirus Antrax, DTaP, Hib, Hepatitis A/ B, HPV, Japanese Encephalitis Meningococcal Pheumococcal, Tdap	Local
2-Phenoxyethanol	Stabilizer, Preservative	DTaP, Influenza, Polio, Tdap	Local
Thimerosal	Preservative	Influenza, Td	Local
Yeast	Medium nutrient	Hepatitis A, B, HPV, DTaP, Meningococcal, Pneumococcal, Typhoid	Anaphylaxis
Natural latex	Pharmaceutical closure	Tdap, Meningococcal, Anthrax, Hepatitis A, B, Influenza, DTaP, Rotavirus, Td, Yellow fever	Anaphylaxis, Urticaria
Neomycin	Antimicrobial	Polio, DTaP, Hepatitis A, Influenza, MMR, Rabies, Polio, Smallpox, Varicella, Zoster	Anaphylaxis
Polymyxin B	Antimicrobial	DTaP, Influenza, Polio, Smallpox	NA
Streptomycin	Antimicrobial	DTaP, Polio	NA
Kanamycin	Antimicrobial	Meningococcal, Influenza	Anaphylaxis
Gentamicin	Antimicrobial	Influenza	NA
Amphotericin B	Antimicrobial	Rabies	NA
Dextran	Stabilizer Medium nutrient	MMR*, Rotavirus	Anaphylaxis
Formaldehyde	Inactivation of virus, Detoxification of bacterial toxin (Inactivating agent)	Polio, DTaP, Hib, Hepatitis B, Influenza, Japanese Encephalitis, Meningococcal, Tdap,	Local

		Thypoid	
Peptone (soy)	Medium nutrient	Pneumococcal Hepatitis B	
Polysorbate 80	Surfactant	DTaP, Hepatitis A, B, HPV, Influenza, Meningococcal, Pneumococcal, Rotavirus, Tdap, Zoster	Non-immunological anaphylaxis, Local
Polyethylene glycol	Surfactant of mRNA	COVID-19	Anaphylaxis

*Currently, MMR vaccines containing Dextran not on the market.

** All reasonable efforts have been made to ensure the accuracy of this information, but manufacturers can change product contents before that information is reflected here.

Table 7: Excipients in the COVID-19 vaccines mRNA BNT162B2, mRNA-1273, and ChAdOx1-S and their functions.

Type of Excipient	Excipient	Vaccine
Lipid nanoparticles: stability and transport of mRNA		
PEGylated lipids	((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0159)	mRNA BNT162B2
	1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000 DMG)	mRNA-1273
Phospholipids	1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)	mRNA BNT162B2, mRNA-1273
lipids	((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)	mRNA BNT162B2
	lipid SM-102 (patented ionizable lipid)	mRNA-1273
	Cholesterol	mRNA BNT162B2, mRNA-1273
Buffer: stability of lipid nanoparticles / radical oxidation inhibition		
phosphate buffer	potassium dihydrogen phosphate/disodium phosphate dihydrate)	mRNA BNT162B2
Tromethamol	tromethamol / tromethamol hydrochloride	mRNA-1273
acetic acid/acetate	acetic acid / sodium acetate trihydrate	mRNA-1273
histidine	L-histidine / L-histidine hydrochloride monohydrate	ChAdOx1-S
Other stabilisers: Ionic strength, surfactant, metal-ion chelates		

	potassium chloride	mRNA BNT162B2
	sodium chloride	mRNA BNT162B2, ChAdOx1-S
	magnesium chloride hexahydrate	ChAdOx1-S
	Ethanol	ChAdOx1-S
	disodium edetate dihydrate (EDTA)	ChAdOx1-S
	polysorbate 802	ChAdOx1-S
Thermostabilisation		
	Sucrose	mRNA BNT162B2, mRNA-1273 ChAdOx1-S

Adapted from: Borgsteede S, Tjerk G, Tempels-Pavlica Z, Other excipients than PEG might cause serious hypersensitivity reactions in COVID-19 vaccines. Allergy. Accepted Jan 2021. In Press., (2021).

Figure Legends

Figure 1: Vaccination-triggered anaphylaxis rates for major vaccines[16]

Figure 2: Immunological (IgE-mediated) and non-immunological anaphylaxis

Box 1: Description of common components and contaminants present in vaccine formulations[39, 74, 158, 159]

Vaccine Component Category	Function
Antigen or its genetic code (DNA, RNA)	Molecules of the pathogen that cause the formation of antibodies and development of specific immune protection (humoral, cellular)
Adjuvants	To stimulate, broaden and optimize immune response
Stabilizers	To keep the vaccine potent and safe during storage and transportation
Preservatives	To prevent contamination
Residual antibiotics	To prevent contamination by bacteria during the vaccine manufacturing process
Residual cell culture materials	To grow enough of the virus or bacteria to make the vaccine
Residual inactivating ingredients	To kill viruses or inactivate toxins during the manufacturing process
Latex	Found in the vial and syringes used to contain and administer the vaccine. It is a potential contaminant.

BOX 2: Future Safety Research Objectives	
General	COVID-19
-Develop individualized prediction algorithms to determine risk of a vaccine reaction. -Refine reaction reporting guidelines for continued accurate vaccine pharmacovigilance. -Identify vaccine components that mediate allergic reactions. -Understand mechanisms for reactions to various vaccine components. -Develop better adjuvants	-Compare various COVID-19 vaccines to each other to understand key differences in safety and efficacy, stratified by patient age and health status. -Compare intradermal PEG tests to oral challenges in evaluating PEG sensitization.