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Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273) COVID-19 mRNA vaccines and hypersensitivity reactions

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Abstract: The SARS-CoV-2 Virus (COVID-19) is responsible for over 239 million cases and 4.8 million deaths globally (Data source WHO COVID-19 Dashboard accessed on October 14, 2021). It continues to surge and ravage countries, leaving healthcare systems in constant struggle and uncertainty. A variety of vaccines were developed to combat the spread of the COVID-19 Virus. Reports of possible allergic reactions with COVID-19 vaccines are a significant cause of public concern, especially among those with a known history of a severe allergic reaction (e.g., anaphylaxis). Here we review articles relevant to COVID-19 vaccines and their excipients (especially PEG (Polyethylene glycol) and hypersensitivity reactions associated with COVID-19 vaccines (including clinical features, pathophysiology, special populations receiving COVID-19 vaccinations, potential diagnostic tests, and preventive measures that can be taken to minimize the risks of hypersensitivity reactions with COVID-19 vaccines).

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INTRODUCTION

One of the significant advancements in scientific research and development is the creation of vaccines. Undoubtedly, most countries are free from many common life-threatening diseases due to vaccines. Fundamentally, several vaccinations against meningitis and polio have been a breakthrough for the health and well-being of the pediatric population.¹ However, anything administered into a human body as an atopic or external stimulus or even ingested may result in an allergic reaction. It could be mild or intense and can be considered a side effect. The same is true for vaccines. This review summarizes the COVID-19 vaccines currently being used in many countries, the types of hypersensitivity reactions, and provide an understanding of the ingredients of the vaccines and the potential causality of COVID-19 vaccine-associated allergic reactions.

METHODS

The review was designed based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol. We searched systematically in PubMed and Google Scholar using the keywords "SARS-CoV-2", "COVID-19", "vaccination," "vaccine," "mRNA Vaccine," "Polyethylene glycol," "PEG," "Hypersensitivity," "Hypersensitivity reactions," "Allergy," "adverse effect," to identify the studies, case reports, official statement from the manufactures of the vaccine candidates and the drug authorities, to identify approximately 72 articles up until October 13, 2021. This review is not all-inclusive and includes articles that deemed appropriate and manageable by the research team.

Hypersensitivity reactions

Hypersensitivity reactions (HR) are immune responses that are exaggerated or inappropriate against an antigen or allergen. While most reactions tend to be self-resolved and rarely life-threatening, on occasions, they may result in serious complications.^{2,3} One could encounter different kinds of allergies and hypersensitivities. The ingredient responsible for this hypersensitivity reaction is often difficult to ascertain. This article will investigate the types of hypersensitivity reactions, types of the COVID-19 vaccine, clinical features, diagnostic tests, and prevention of hypersensitivity reactions reported after COVID-19 Vaccine administration. Before we better understand allergic reactions concerning the COVID-19 vaccine, we should have some idea about the pathophysiology of vaccine-induced allergic reactions and hypersensitivities. Coombs and Gell classified hypersensitivity reactions into four forms Hypersensitivity type I; type II, type III, and hypersensitivity type IV (delayed hypersensitivity) resulting from foreign bodies/antigens.⁴

Hypersensitivity Type-I

Type 1 is Immunoglobulin type E (IgE) mediated and considered anaphylaxis, which could occur in minutes or up

to 3 to 4 h after exposure to an allergen (vaccination, wasp, or venom). The initial exposure to an allergen can produce allergen-specific IgE by plasma cells.⁵ These IgE then binds to mast cells in the tissues and basophils in the bloodstream. Subsequent re-exposure leads to allergen interaction with cell-bound IgE, resulting in mast cell or basophil degradation and release of chemical mediators (histamine, prostaglandins, leukotrienes, etc.), which could cause life-threatening anaphylactic shock. In late-hour reactions, eosinophils play a significant part in allergic reactions. Certain excipients in the medications/vaccines have been reported to contribute to anaphylaxis reactions. Examples include Asthma and Urticaria.

An excipient is a substance formulated alongside an active ingredient of the medication, which is included for long-term stabilization, bulking up solid formulations that contain potent active ingredients in small amounts, often referred to as fillers, bulking agents, or diluents.

Hypersensitivity type-II

With type II, antibodies bind to a cell surface antigen causing cellular inflammation, dysfunction, and destruction. Most autoimmune diseases fall in this category, like Goodpasture syndrome, Grave's disease, and Myasthenia Gravis.

Hypersensitivity Type-III

Type III includes all three crucial elements of antigen, antibody, and complement interactions. Hypersensitivity III has been seen with many medications; for example, sensitivity is often seen with chimeric monoclonal antibody medications like (Infliximab, etc.)⁶ and non-human immunoglobulins (e.g., venom, antitoxins).⁷ Repeated exposure to monoclonal antibody trigger memory B cells to differentiate into plasma cells which generate a burst of IgG against the monoclonal antibody, activation of the classical component system by IgG. Most of the time, these immune complexes are deposited in various organs. Symptoms could include cutaneous rash, fever, joint pain, and low serum of C3 and C4 complement in 5–14 days after exposure. Examples are serum sickness and Arthus reaction Lupus and post-streptococcal glomerulonephritis.^{2,4}

Hypersensitivity type-iv

Type IV hypersensitivity reactions have two phases: a sensitization phase (which occurs within 10–14 days and includes dendritic cells presenting antigens to MHC-I and MHC-II, activation of CD4+ and CD8+T cells, causing activation and clonal expansion) and an excitation phase (occurring within 2–3 days of re-exposure to the same

antigen, activation of hapten sensitized cells and inflammatory response. Examples include Type 1 Diabetes Mellitus, Steven-Johnsons syndrome, Toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and Behcet's disease.^{4,8}

COVID-19 vaccines and hypersensitivity reactions

There are different kinds of vaccines, i.e., live or attenuated, Inactivated or killed, virus-like particles, toxoid or subunit, DNA and messenger RNA vaccines. Some of the COVID-19 vaccines are listed below. We will be focusing on Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) although there are other vaccines being used as well (Such as Johnson & Johnson (Ad26.COV2.S), Sinopharm(BBIBP-CorV), and Oxford/AstraZeneca vaccine (ChAdOx1/AD1222)

According to a group of researchers at Massachusetts General Hospital (MGH), Allergic reactions occur in 1.31 cases per million vaccine doses. Although the number is small, it has caused significant concern in the general population. Per the Center for Disease Control and Prevention report, out of the 175 possible severe allergic reactions, 49% were non-anaphylactic allergic reactions.²⁷

Mechanism

Allergic reactions to vaccines are rarely attributed to the active vaccine itself, and a majority are non-immunologically mediated, although immunologic and complement-mediated mechanisms are also responsible for these reactions.^{37,38} It is usually the inactive ingredients like synthetic proteins, excipients, or adjuvants which could cause allergy.³⁹ Type 1 hypersensitivity is often seen with vaccines with constituted egg protein, gelatin, formaldehyde, thimerosal, or neomycin that contribute to IgE-mediated reactions.⁴⁰ According to the European medicines agency (EMA), excipients are added to vaccines for a pharmaceutical purpose to maintain the medicine's density, absorption, or solubility, which causes the allergic reaction. It is not the vaccine itself. Excipients could cause allergic reactions from skin rash to life-threatening hypotensive shock. Unfortunately, these excipients are unavoidable as they add to preserve vaccine life, stimulate a robust immune response, or prevent bacterial contamination. However, these excipients are often contributors to the development of specific IgE-mediated and immediate reactions associated with the vaccine.⁸ There are a variety of excipients in vaccines that have the potential to cause an allergic reaction. Polyethylene glycol (PEG) and certain substances having structural or immunogenic similarities to PEG have been high-

lighted extensively in the literature to increase the risk of hypersensitivity reactions when used as excipients in COVID-19 vaccines.³⁷ Some scientists have also proposed complement activation due to PEG molecules in COVID-19 mRNA vaccines.⁴¹ PEG present in many food items and other vaccines has been reported to have cross-reactivity with Polysorbate 80 due to the shared chemical moiety: $-(CH_2CH_2O)_n$. Furthermore, PEG has been mentioned as the possible culprit of these allergic reactions as a study of 1721 serum samples, up to 9% were positive for IgG. Of 948 samples, 6% were positive for IgM, and 9% were positive for IgG.²⁷⁻³⁶ Therefore, skin prick testing and intradermal testing with different dilutions of PEG, basophil activation test, and oral provocation testing are recommended in suspected individuals.

Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273) COVID-19 mRNA vaccines

Pfizer-BioNTech (95% effective against COVID-19 infection) and Moderna mRNA vaccines (94.5% effective against COVID-19 infection)⁴² have been granted emergency approval by FDA (Food and Drug Administration) as the initial vaccines against COVID-19 infection on 11th and 12th December 2020 respectively based on safety and efficacy data demonstrated in randomized placebo-controlled clinical trials.⁴³⁻⁴⁶ PEG and Macrogol are excipients in Pfizer-BioNTech COVID-19 mRNA vaccines. Messenger RNA vaccines have been studied for quite a while, and researchers have used this approach to develop the COVID-19 vaccines.⁴⁷ The mRNA in vaccine transcripts to make a specific protein that stimulates the immune system and triggers an immune response to the Virus. It has certain benefits over other vaccines as it is fast producing and does not contain a live virus. So, there is less risk of causing harm compared to other vaccines. So, how does the Pfizer vaccine work? It is a synthetically created molecule of RNA sequence, which is then transformed into an infected virus and injected into an individual. The infected vaccine mRNA functions as an mRNA inside the immune cell and induces the cell to produce foreign protein, further triggering the immunity system⁴⁸—liposomes transport mRNA into the human cell. In short, mRNA mimics the actual COVID-19 Virus and retains a minimal amount of viral mRNA, which encodes for the required antigen. mRNA vaccine is also far easier to create and faster to produce economically. The mRNA vaccines stimulate both innate and humoral immunity. Storage temperature is vital in maintaining the integrity and potency of these vaccines and must be kept at minus 30 to minus 80° centigrade.^{8,49}

Pfizer vaccine excipients³⁷.

- mRNA encoding the viral spike(S) glycoprotein of SARS-COV 2 and constitutes the active ingredient
- Electrolytes potassium chloride, monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate, dihydrate
- Lipids polyethylene-glycol
- Glucose
- Saline

Side effects reported in Package insert of BNT162b2 Pfizer vaccine⁶⁴: Myocarditis, Pericarditis, Syncope, fatigue, headache, muscle pain, chills, joint pain, fever, and injection site redness and swelling.

Moderna vaccine excipients²⁹.

- mRNA as an active ingredient
- Acetic acid
- Lipids
- Polyethylene glycol
- Sodium acetate
- Glucose
- Tromethamine
- Tromethamine hydrochloride

Side effects reported in Package insert of mRNA-1273 Moderna vaccine⁶⁵: Myocarditis, Pericarditis, Syncope pain at the injection site, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting, axillary swelling/tenderness, fever, swelling at the injection site, erythema at the injection site, and rash

OTHER COVID-19 VACCINES

AstraZeneca COVID-19 vaccines - Adenoviral vector vaccines

Oxford/Astra Zeneca (ChAdOx1/AD1222)⁵⁰ vaccine is among the three vaccines approved in the United Kingdom. Its mechanism of action is inserting the COVID-19 S-protein gene into the viral vector. These viral vectors are from chimpanzees, gorillas, and human adenoviruses. Viral vectors are used to shuttle this gene into a human cell. For the COVID-19 virus, the gene codes the S protein present on the surface of SARS-COV-2. Once inside a cell, the viral vector uses the gene and the cell mechanism to present S protein and display it on the cell surface.⁵¹ The Virus in which DNA is inserted loses its ability to replicate. Most virus-based vaccines are injected intramuscularly, but the medical world started other ways to administer vaccines through the nasal passage or other parts of the body.⁵² Non replicating vectors are used in AstraZeneca, Sputnik Vgam COVID-19 vaccine, and John-

son and Johnson. Polysorbate 80 or Tween 80 are excipients in AstraZeneca and Johnson and Johnson. Polysorbate is structurally similar to polyethylene glycol (PEG). These excipients are primarily responsible for inducing allergic reactions in patients.⁴⁷ The current recommendation from Public Health England in the United Kingdom is that individuals with PEG allergy can receive the AstraZeneca ChAdOx1 vaccine, although it would seem prudent to keep these patients for at least 30min observation post-vaccination and avoid the second dose if there is a history of an allergic reaction to the first dose.

AstraZeneca vaccine excipients³⁸.

- Recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS COV2 spike glycoprotein produced in genetically modified human embryonic kidney (HEK) 293 cells
- Histidine
- L-Histidine hydrochloride monohydrate
- Magnesium chloride hexahydrate
- Polysorbate 80
- Ethanol
- Sugar
- Sodium chloride
- Edetate disodium dihydrate
- Water for injections

Johnson & Johnson (Janssen)(Ad26.COVID.S) adenovirus vectored COVID-19 vaccine

Although not a typical hypersensitivity reaction; some cases of thrombosis with thrombocytopenia syndrome (TTS), Guillain-Barré syndrome (GBS), cerebral venous sinus thrombosis (CVST) have been reported in patients in the USA, leading to a pause in the dispensation of Johnson & Johnson (Janssen) adenovirus vectored COVID-19 vaccine which was initially approved in February 2021 for emergency utilization by FDA.⁵³⁻⁵⁶ However, this topic remains controversial as the data suggest no significant correlation between Cerebral Venous Sinus Thrombosis and Johnson & Johnson (Janssen) adenovirus vectored COVID-19 vaccine.²⁸

Sinopharm vaccine (BBIBP-CorV) inactivated covid –19 vaccine

The Sinopharm vaccine is based on the COVID-19 virus that was inactivated with Beta-propiolactone. This approach is more traditional and practiced in medicine. Inactivated viruses maintain their ability to replicate in vivo with mild or no symptoms. These are viruses killed or inactivated by heat or chemicals, thereby not leading to clin-

ical disease.²⁹⁻³¹ The inactivated viruses stimulate the immune system, induce an intense and persistent immune response, and prevent infection. Interestingly, this immune response is directed against the S protein and SARS-CoV-2 antigens.⁸ This vaccine has several advantages like inexpensive production and a far more thorough attack on antigens without genetic manipulation. However, additional adjuvants are used alongside the active agent within this type of vaccine.³² The rationale behind adding an adjuvant is to stimulate a solid immune system response. There are two very popular adjuvants, which are thimerosal and Aluminum. Thimerosal is a preservative mercury compound added to the vaccines to kill the "live viruses," fungi, and bacteria in a vial. Aluminum (Aluminum hydroxide or Aluminum Phosphate) is an adjuvant in a vaccine to boost the immune system. Both are regarded as metal and regarded as environmental toxins. There are theories and ongoing research on Aluminum and Alzheimer's or metal toxicity and GI concerns. However, this area of knowledge is still uncharted waters and remains controversial.³³

We have been discussing allergies and anaphylaxis reactions. What precisely is anaphylaxis? It could be a severe allergic reaction to the venom, food, or medicine.³⁰ Anaphylaxis could cause a series of reactions, including rash, low pulse, and even shock.³¹ Almost all vaccine components could be considered as potential allergic reaction triggers. It includes killed, live, and fragments like polysaccharides, preserving agents, adjuvants, antimicrobial agents, etc.⁴⁷ However, Pfizer and Moderna COVID-19 vaccines do not contain syringes with latex rubber stoppers, culture-derived proteins from eggs, yeast, or gelatin. All these mentioned components could cause Ig-E mediated hypersensitivity I reactions. The rest of the adjuvants and excipients, which develop along with the vaccines, increase the effect of a robust immune system and maintenance of the vaccine that could cause specific reactions. But, it is challenging to speculate the induced reaction beforehand most of the time. If a person is getting severe reactions after the first shot, it is wise to be cautious and not take the second one without proper consultancy. However, there are case reports where immune reactions are seen with the second dose of the vaccine even if the first dose was well tolerated and uneventful. An example is severe immune thrombocytopenic purpura seen after the second dose of the covid vaccine. With the unpredictable number of mutant variants that might emerge, there is a high possibility that multiple booster doses could be required in the future. There is a potential to develop ITP with any of those boosters despite tolerating the regular doses or prior booster doses without any complications.⁶³

Vasovagal activity vs. allergic reaction

Anaphylactic reactions through vaccines are common. The question is, to what extent patients are experiencing allergic reactions. It could be minor or go to shock or a hypotensive state.³² Another critical factor is sometimes vasovagal symptomatology mimicking allergic reactions. Generally, healthcare providers need to be thorough in their evaluation to recognize the symptoms to see whether it is an anaphylactic reaction or not? A person's fear, anxiety, and nervousness can contribute to abnormal vasovagal activity and masquerade as an allergic reaction due to the vaccine. Flushing, tremor, tachycardia, dizziness, and shortness of breath associated with anxiety may masquerade as an allergic reaction.

Detection via cutaneous provocation testing

Screening for hypersensitivity reactions before COVID-19 vaccines, although not absolutely needed,³⁴ is strongly recommended by the American College of Allergy, Asthma, and Immunology (ACAAI), and an observatory period of 30min is also encouraged after the first dose of COVID-19 mRNA Vaccine.³⁵ Skin testing has presented itself as a potential tool to screen for the early detection and prevention of severe hypersensitivity reactions to any of the ingredients of COVID-19 vaccines.³⁷ It can be utilized following a reaction with an increased suspicion of hypersensitivity after administering the first dose of the COVID-19 mRNA vaccine. A group of researchers from Guy's and St Thomas' Hospital, London, UK, has described an innovative allergy support model for the allergy assessment at COVID vaccination hubs.³⁷ A group of researchers from Rochester, NY, has reported 2 cases where skin testing was utilized to diagnose hypersensitivity to the Moderna mRNA vaccine.³⁶ Multiple sources have proposed PEG (especially with high molecular weight concentrations) as a possible culprit for hypersensitivity reactions caused by COVID-19 vaccines.⁵⁷ By January 18, 2021, 4.7 cases per million and 2.5 cases per million anaphylaxis reactions were reported with Pfizer – BioNTech and Moderna COVID-19 mRNA vaccines. A group of researchers from Minnesota and Arizona reported skin testing procedures for PEG and Polysorbate skin testing completed in 15 individuals who had a history of PEG or Polysorbate allergy ($n = 7$) or reported allergic symptoms after their first dose of mRNA COVID-19 vaccines ($n = 8$). Their work alluded to the potential of using Skin testing as a predictive test to identify individuals at risk for an anaphylactic reaction from COVID-19 vaccines.⁵⁸

Prevention

Most recently, attempts have been made to intervene if a patient has experienced an anaphylactic reaction from the first dose of the COVID-19 vaccine. Dr. Meller's group presented two case reports where the patient experienced an anaphylactic reaction from the first dose of the COVID-19 vaccine and was treated with anti-IgE antibody omalizumab before their second dose COVID-19 vaccine. The first patient was 27-year-old urticaria, the first dose of the mRNA-1273 COVID-19 vaccine.⁵⁹

Recommendation for cancer patients

In patients with a history of cancer or undergoing anti-cancer therapy, hypersensitivity reactions are often observed within the first one or two doses of monoclonal antibodies or within the first 1 to 2 weeks after initiation of therapy with tyrosine kinase inhibitors. Therefore, most patients with solid tumors or hematological malignancies are recommended to receive COVID-19 vaccines except patients receiving a transplant or adoptive cell therapies. In these patients, the COVID-19 vaccines are recommended to be delayed for > 3 months to allow the immune function to achieve homeostasis.⁶⁰

Recommendation for pregnant patients

A group of researchers conducted an observational case-control study from January 2021 to February 2021 on 539 pregnant women to determine the immunogenicity and reactogenicity of the Pfizer/BioNTech COVID-19 vaccine compared to 260 non-pregnant women and to review obstetrical outcomes. Their findings revealed that rates of rash, fever, and severe fatigue after administering the COVID-19 vaccine in pregnant women are similar to non-pregnant women, with significantly fewer occurrences of myalgia, arthralgia, and headache symptoms in pregnant women recipients. The rates of obstetric complications were also significantly low. Rates observed were as follows: uterine contractions (1.3% after the first dose and 6.4% after the second dose), vaginal bleeding (0.3% after the first dose and 1.5% after the second dose), and pre-labor rupture of membranes (0% after the first dose and 0.8% after the second dose). Pregnant recipients had a lower SARS-Cov-IgG level (27.03 vs. 34.35, respectively; $P < 0.001$). Fifty-seven pregnant patients delivered during the observation period, the median gestational age at delivery was 39.5 (interquartile range, 38.7–40.0) weeks, with no cases of preterm birth < 37 weeks, no cases of fetal or neonatal death, and two (3.5%) cases of admission to the neonatal intensive care unit for respiratory support.⁶¹

Reports of generalized anaphylactic and non-anaphylactic reactions associated with COVID-19 vaccines (Table 1)

- Between December 14, 2020, to January 18, 2021, the Center for Disease Control (CDC) identified 66 case reports of anaphylaxis (life-threatening allergic reaction) through Vaccine Adverse Event Reporting System (VAERS), 47 cases associated with the Pfizer-BioNTech vaccine (out of 4.7 cases/million doses administered), and 19 cases associated with Moderna vaccine (out of 2.5 cases/million doses administered).⁹
- A group of researchers from Massachusetts General Hospital reported that among 649,000 employees, 25 929 (40%) received the Pfizer-BioNTech vaccine while 38 971 (60%) received the Moderna vaccine. Acute allergic reactions were observed in 2.20% of Moderna vaccine recipients and 1.95% of Pfizer Vaccine recipients). Anaphylaxis develops in 16 employees (9 with Moderna vaccine versus 7 cases from the Pfizer-BioNTech vaccine.¹⁰
- There were also 2 cases of severe allergic reactions following the Pfizer/BioNTech vaccine administration reported by the National Health Service in England.¹¹ In addition, various orofacial reactions have also been reported because of hypersensitivity reactions from COVID-19 vaccines, such as swelling of the face (occasionally in patients who have had facial cosmetic injections), tongue or throat, temporary one-sided facial drooping (Bell's palsy), acute peripheral facial paralysis.¹²
- A Case report from a group in Mexico reported an interesting case of delirium associated with the first dose of Pfizer/BioNTech BNT162b2 vaccine. It was characterized by confusion, fluctuating attention, anxiety, and inversion of the sleep-wake cycle. On physical examination, he was inattentive and had oscillatory movements of the trunk. Most other causes of delirium were ruled out. Over the next 48 h, the patient showed gradual improvement.¹³
- A group of researchers from Cape Fear Valley Health System, Lillington, North Carolina, randomized, cross-sectional study using an independent online survey questionnaire was conducted to collect responses from healthcare workers. 1116 responses were received, and the most common side effects reported were localized pain, generalized weakness, headache, myalgia, chills, fever, nausea, joint pains, sweating, localized swelling at the injection site,

dizziness, itching, rash, decreased appetite, muscle spasm, decreased sleep quality, and brain fogging. It is atypical for an anaphylaxis reaction to present with such symptoms and this report may represent an adverse reaction rather than an anaphylaxis reaction.¹⁴

- Another group from Poland conducted a questionnaire-based survey on healthcare providers who received the Pfizer-BioNTech vaccine. 1707 individuals responded to the questionnaire, and more Systemic Adverse events were reported after the second dose rather than the first dose in individuals prone to allergic reactions (77.29% vs. 41.06%), 70 cases of anaphylaxis reactions required pharmacological intervention.¹⁵
- A collaboration group from Saudi Arabia and Egypt conducted a Google Form questionnaire-based online survey among the 455 Saudi Arabian native recipients of the Pfizer-BioNTech Vaccine, out of which 85.2% individuals reported the presence of some symptoms after the first dose of this vaccine and 98.4% of individuals reported symptoms after the second dose. In addition, hypersensitivity symptoms were reported by 8% of individuals after the first dose and 14.5% of the individuals after the second dose of Pfizer-BioNTech Vaccine.¹⁶

Table 1: We enumerate the findings of 7 publications related to COVID-19 Vaccine associated Anaphylactic reactions (or Non-anaphylactic reactions) reviewed by our team. Shimabukuro et al. 2021 describes anaphylactic reactions, reported in 1 million vaccine recipients with relatively minor incidence rate (Pfizer 0.00047% and Moderna 0.00025%). Given the larger “n” this data seems to be providing a reliable estimation of incidence of anaphylactic reactions associated with these vaccines. Similarly, Blumenthal et al. 2021 extracts data from approximately 6.5 million recipients of these two vaccines and reporting relatively minor incidence rate (Pfizer 1.95% and Moderna 2.2%). The next two articles (Cirillo N. 2021 and Jongitud LF et al. 2021) report 2 and 1 BNT162b2 associated anaphylactic and non-anaphylactic reactions respectively. Kadali RAK et al. 2021 reported non-anaphylactic local reactions in approx. 98% recipients of mRNA-1273. Nittner-Marszalska M et al. 2021 interestingly reported higher incidence of systemic adverse reactions in the recipients of BNT162b2 and approximately 38% requiring medical interventions. El-Shitany NA et al. 2021 reported BNT162b2-associated anaphylactic reactions in approximately 8% of individuals receiving the 1st dose and approximately 14.5% in 2nd dose recipients.

Table 1. Reports of generalized Anaphylactic and Non-Anaphylactic reactions associated with COVID-19 vaccines:.

Serial Number	Approximate No. of COVID-19 vaccination recipients	Vaccine used: Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273)	Anaphylactic vs Non-Anaphylactic reactions	Pfizer Vaccination related Anaphylactic reaction in percentage actual number and percentage (n(%))	Moderna Vaccine related Anaphylactic reaction cases in percentage actual number and percentage (n(%))	Non-Anaphylactic reactions	References
1	1,000,000	Pfizer, Moderna	Anaphylactic	4.7 cases/million (0.00047%)	2.5 cases/million (0.00025%)	N/A	Shimabukuro et al. 2021
2	649,000	Pfizer, Moderna	Anaphylactic	12,655 (1.95%)	14,278 (2.2%)	N/A	Blumenthal et al. 2021
3	Not reported	Pfizer	Anaphylactic	2	N/A	N/A	Cirillo N. 2021
4	1	Pfizer	Non-Anaphylactic reactions	1 (100%)	N/A	Delirium	Jonguitud LF et al. 2021
5	432	Moderna	Non-Anaphylactic reactions	N/A	425 (98.34%)	Localized pain, generalized weakness, headache, myalgia, chills, fever, nausea, joint pains, sweating, localized swelling at the injection site, dizziness itching, rash, decreased appetite, muscle spasm, decreased sleep quality, and brain fogging	Kadali RAK et al. 2021
6	1808	Pfizer	Anaphylactic	70 (38%)	N/A	N/A	Nittner-Marszalska M et al. 2021
7	455	Pfizer	Anaphylactic	36 (8%) after 1st dose), 66 (14.5%) after 2st dose	N/A	N/A	El-Shitany NA et al. 2021

Table 2. Reports of specific cutaneous reactions associated with COVID-19 vaccines.

Serial Number	Approximate No. of COVID-19 vaccination recipients	Vaccine used: Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273) Corona Vac	Pfizer Vaccination related Cutaneous reactions in percentage actual number and percentage (n(%))	Moderna Vaccination related Cutaneous reactions in percentage actual number and percentage (n(%))	Other Vaccines related Cutaneous reactions in percentage actual number and percentage (n(%))	Cutaneous and other reactions details	References
1	3	Pfizer	3(100%)	N/A	N/A	Purpuric lesions	Mazzatenta C et al. 2021
2	16	Pfizer	15 (93%)	N/A	N/A	Pruritic, painful, and edematous pink plaques	Johnston MS et al. 2021
3	6	Corona Vac	N/A	N/A	4 (66%)	Erythematous plaques associated with weal and angioedema	Akdaş E et al. 2021
4	1	Pfizer	1 (100%)	N/A	N/A	Full body and face diffuse maculopapular rash, Pruritus, shortness of breath, diaphoresis, urticaria, diaphoresis, severe chills, and dysphagia	Daou C AZ et al. 2020
5	1422	Pfizer, Moderna, Other unknown vaccinations	35 (7%)	459 (90%),	16 (3%)	Delayed large local cutaneous reactions	Samarakoon U et al. 2021
6	12	Pfizer, Moderna	1 (9%)	11 (91%)	N/A	"COVID arm": pain, redness, swelling, and itching at the injection site, fever, and chills with mild blistering	Ramos CL et al. 2021
7	1	Pfizer	1 (100%)	N/A	N/A	Morbilloform rash, fevers, headache, and injection site soreness in the deltoid region	Jedlowski PM et al. 2021
8	1	Pfizer	1 (100%)	N/A	N/A	Pruritic edematous skin lesions on the trunk, shortness of breath, and dizziness	Pérez-Codesido S et al. 2021
9	Million plus	Pfizer, Moderna	11.1/million (0.0011%)	2.8/million (0.0028%)	N/A	Anaphylaxis reactions (manifested by skin involvement (Urticaria and Angioedema), GI symptoms, respiratory symptoms (dyspnea) and dizziness, cyanosis, and syncope	Bousque Jet al 2021
10	22	Pfizer, Moderna	Not Reported	Not Reported	N/A	Eczematous dermatitis, interface dermatitis, granulomatous inflammation, and/or lymphocytic vasculitic component, perniosis, pityriasis rosea, pityriasis rubra pilaris, and guttate psoriasis	Magro C et al. 2021

Reports of specific cutaneous reactions associated with COVID-19 vaccines (Table 2)

- 3 Patients have reported purpuric lesions, 1st one 21 and 25 days after Pfizer/BioNTech vaccine. 2nd patient-reported three weeks after the second dose of

the Pfizer/BioNTech vaccine. 3rd patient, ten days after the first dose of Pfizer/BioNTech vaccine.¹⁷

- A group of researchers at Yale University Connecticut, performed a retrospective chart review of 16 patients who developed cutaneous lesions after 2–12 days from the dose after receiving the Moderna vaccine. The reactions at the injection sites were de-

- scribed as s pruritic, painful, and edematous pink plaques. 15 out of 16 reacted to the first dose, and 11/16 developed a reaction after the second dose.¹⁸
- A group of researchers in Turkey reported cutaneous hypersensitivity reactions in 6 recipients of the inactivated vaccine candidate CoronaVac COVID-19 in Phase 1/2 clinical trials described as Erythematous plaques associated with weal and occasionally angioedema. One patient developed maculopapular rash one week after the initial vaccination and another developed erythematous scaly papules along the skin cleavage lines. Three patients presented with urticaria symptoms after the first vaccination and one patient after the second vaccination.¹⁹
 - A group of researchers from Bruit, Lebanon, reported a case of Biphaseic anaphylaxis in a 30-year-old nurse who had a past medical history of allergies to meperidine, amoxicillin-clavulanate acid, pollen, and dust mites, after receiving the COVID-19 Pfizer/BioNTech vaccine. It was described as a full body and face diffuse maculopapular rash within minutes of receiving the first COVID-19 vaccine dose. He also experienced Rash, Pruritus, shortness of breath, and diaphoresis on Day 2, followed by urticaria, diaphoresis, severe chills, and dysphagia on Day 3, leading to resolution of symptoms after four days.²⁰
 - Multiple reports of Delayed cutaneous hypersensitivity reactions (84.2% according to one study) from February 10, 2021, through April 23, 2021, a total of 1422 reports of postvaccination reactions were submitted to a COVID-19 vaccine allergy case registry (<https://allergyresearch.massgeneral.org>. opens in new tab). Of these reactions, 510 (36%) were delayed large local reactions that were reported by patients (64%) and clinicians (36%). The mean (\pm SD) age of the patients was 50 ± 15 years (range, 21 to 91), and the majority were women (472 [93%]). Delayed large local reactions were reported in 459 patients (90%) mRNA-1273 vaccine recipients, 35 (7%) BNT162b2 vaccine recipients and 16 (3%) unknown vaccine recipients.²¹
 - Another group of researchers from San Diego, California, USA, reported 12 cases of delayed injection site reactions of the "COVID arm" to the mRNA COVID-19 vaccines. Symptoms included pain, redness, swelling, and itching at the injection site, fever, and chills with mild blistering at the site for one patient. Some treated these reactions with topical corticosteroids, ice, oral antihistamines, or pain relievers.²²
 - Another group of researchers from Arizona reported a Morbilliform rash after administration of Pfizer-BioNTech COVID-19 mRNA within 24 h, fevers, headache, and injection site soreness in the deltoid region. The rash dissolved within the next 24 h without intervention. The patient again developed fever, myalgias, and a similar rash after the second dose of the vaccine, which also resolved within 24 h of developing without requiring any medical attention.²³
 - Another group of researchers from Madrid has reported a case of a 30-year-old female who experienced an anaphylactic reaction to the first dose of Pfizer COVID-19 vaccine (which manifested as pruritic edematous skin lesions on the trunk, shortness of breath, and dizziness treated with epinephrine, methylprednisolone, and dexchlorpheniramine leading to complete resolution) which was later confirmed by the skin prick test. Skin Prick Test (SPT) protocol at that group consisted of the following ingredients, injected subcutaneously: Polyethylene Glycol (PEG, also called Macrogol) 1500 g/mol (0.5 g/ml); PEG 3350 (0.5 g/ml); PEG 4000 (0.5 g/ml); polysorbate 80 (1 g/ml), and polysorbate 20 (pure) or polysorbate 80. SPT controls with Pfizer SARS COV-2 vaccine were negative in 5 individuals. Some cross-reactivity between Polysorbate 80 PEG (2000 or 3350) was also reviewed by this group.²⁴
 - In the Elderly, anaphylaxis reactions (manifested by skin involvement (Urticaria and Angioedema), GI symptoms, respiratory symptoms (dyspnea), and dizziness, cyanosis, and syncope, which are highly predictive of shock) increase the likelihood of a major cardiovascular event such as LOC and Cardiac arrest. 60% of elderly patients required hospitalization after anaphylactic reactions after mRNA vaccines, and 19% required ICU care. Ring and Messmer classification Grade III (47%) and grade IV (4%) anaphylaxis reactions were more frequent in elderly patients. Management of Anaphylaxis with Adrenaline carries additional cardiovascular risk in elderly patients.²⁵
 - In a study conducted by a group in New York on 22 patients, classic clinical, morphological, and/or histological depictions of type IV cutaneous hypersensitivity with features of eczematous dermatitis, interface dermatitis, granulomatous inflammation, and/or lymphocytic vasculitic component, perniosis, pityriasis rosea, pityriasis rubra pilaris, and guttate psoriasis were observed in biopsy samples from patients experiencing hypersensitivity reactions from COVID-19 vaccines.²⁶

Table 2: We enumerate the findings of 10 publications reviewed by our team. These reports were related to cutaneous reactions reported as associated with COVID-19

vaccinations. Mazzatenta C et al. 2021 reported purpuric lesions in 3 subjects after they received BNT162b2 vaccine. Johnston MS et al. 2021 reported Pruritic, painful, and edematous pink plaques in 15/16 subjects (93%) after receiving BNT162b2 vaccine. Akdaş E et al. 2021 reported Erythematous plaques associated with weal and angioedema in 6 recipients of Corona Vac COVID-19 vaccine. Daou C AZ et al. 2020 reported the following symptoms: Full body and face diffuse maculopapular rash, Pruritus, shortness of breath, diaphoresis, urticaria, diaphoresis, severe chills, and dysphagia in one subject after the receiving BNT162b2 vaccine. Samarakoon U et al. 2021 reported Delayed large local cutaneous reactions in 7% and 90% of Pfizer and Moderna COVID-19 mRNA vaccine recipients respectively. This data was extracted after reviewing 1422 reports. Ramos CL et al. 2021 reported “COVID Arm” symptoms in 1 vaccine recipients Pfizer vs 11 Moderna COVID-19 mRNA vaccine recipients. Jedlowski PM et al. 2021 reported a case of Morbilliform rash, fevers, headache, and injection site soreness in the deltoid region where as Pérez-Codesido S et al. 2021 reported one patient developing Pruritic edematous skin lesions on the trunk, shortness of breath, and dizziness after receiving Pfizer vaccine. Bousque Jet al 2021 reported Anaphylaxis reactions (manifested by skin involvement (Urticaria and Angioedema), GI symptoms, respiratory symptoms (dyspnea) and dizziness, cyanosis, and syncope in 0.0011% Pfizer vaccine recipients and 0.0028% of Moderna vaccines recipients. This data was compiled after reviewing more than one million reports. Magro C et al. 2021 also reported Eczematous dermatitis, interface dermatitis, granulomatous inflammation symptoms without specifying types of vaccines.

CONCLUSION

The Global effect of COVID-19 vaccines is dependent upon multiple factors such as developing protection against COVID-19 infection, the hesitancy of the public to receive these vaccines, healthcare professionals’ overall efforts in explaining and promoting the vaccination, the accessibility of a vaccine, and the side effect profile of said vaccines.⁶²

People should be cautious about allergies and need to understand their allergic sensitivities. If they do, they may be able to avoid some hypersensitivity reactions. Commonly occurring side effects are usually self-resolving, and sometimes it may just be a placebo effect. The benefits of COVID-19 vaccinations outweigh the risks significantly, and whenever possible, the administration of COVID-19 vaccines should be encouraged under proper medical oversight.

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