Title

Anaphylaxis and Related Events Post-COVID-19 Vaccination: A Systematic Review

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Abstract

The Coronavirus Disease 2019 (COVID-19), induced by the SARS CoV-2 virus, is responsible for a global pandemic following widespread transmission and death. Several vaccines have been developed to counter this public health crisis using both novel and conventional methods. Following approval based on promising efficacy and safety data, the AstraZeneca, Janssen, Moderna, Pfizer/BioNTech, and SinoVac vaccines have been administered globally among different populations with various reported side effects. Reports of life-threatening anaphylaxis following administration were of particular concern for both

healthcare providers and the public. A systematic literature search using PubMed, Embase, Scopus, Web of Science, Science Direct, MedRxiv, and Lens.org databases identified relevant studies reporting anaphylaxis following vaccine administration. This systematic review includes 41 studies reporting anaphylaxis out of 19908 studies that were retrieved for screening. A total of 7942 cases, including 43 deaths, were reported across 14 countries. Most cases occurred following the administration of the first dose. Importantly, the benefits of vaccination far outweigh the risks of anaphylaxis. Subsequently, as populations continue to get vaccinated, it is important for healthcare providers to be able to recognize individuals at risk of developing anaphylaxis. Furthermore, they must be familiar with both the clinical hallmarks and treatment of anaphylactic reactions to minimize long term sequalae and prevent death in vaccinated individuals.

Introduction

A local outbreak of atypical pneumonia of unexplained etiology was detected in late December 2019 in Wuhan, Hubei Province, China, and reported by the world health organization (WHO) in early January 2020 [1]. Over the course of the next few months, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induced coronavirus disease 2019 (COVID-19) rose to become a leading public health concern worldwide- a multivariant-fueled pandemic responsible for 540.6 million known infections and 6.3 million recorded deaths as of 22nd June 2022 [2]. The disease is characterized by a wide spectrum of clinical manifestations, ranging from acute asymptomatic to potentially life-threatening complications such as multi-organ system failure and septic shock [3]. Its symptoms present most commonly within a week of infection in the form of fever, dry cough, sore throat, fatigue, difficulty breathing, anosmia and dysgeusia. While the disease affects individuals of all age groups regardless of medical history, the increased risk of infection and severity of symptoms in those with chronic comorbidities and those aged above 60 years is medically established [4].

Following the publication of the genome of this β-coronavirus in early January 2020, the urgency for therapy and vaccine development to respond to the pandemic resulted in expedited research and collaboration between scientists and biopharmaceutical companies across the globe [5–7]. This period involved the inception of development of multiple anti-SARS-CoV-2 vaccines, most of which target the surface Spike (S) protein responsible for viral entry within the host cells. As of 17th July 2021, there are over 300 COVID-19 vaccine candidates, out of which 20 are currently being administered under either full or emergency use authorizations of respective national regulatory authorities. These include the adenovirus vector-based vaccines Oxford/AstraZeneca (or Covishield), Johnson and Johnson's Janssen,

Convidecia, Sputnik V and Sputnik Light; the mRNA-based vaccines Pfizer/BioNTech and Moderna; the inactivated vaccines CoronaVac (SinoVac), Sinopharm (BBIP and WIBP), Covaxin, CoviVac, QazCovid-in, Minhai, COVIran and Covidful; and lastly the subunit vaccines EpiVacCorona, Zifivax, Abdala and Soberna 02 [8–13]. Below we briefly review the composition, mechanism of action, mode of delivery, approval dates and number of doses administered for the various vaccines covered in this review.

The Pfizer/BioNTech (BNT162b2) SARS-CoV-2 vaccine, distributed commercially as Cominarty in Europe and Fosun Pharma in China, is composed of a nucleoside-modified mRNA (modRNA) coding for a mutated spike protein that is encapsulated and delivered in lipid nanoparticles (LNPs) through an intramuscular (IM) injection. The vaccine primarily induces CD4+ and CD8+ T-cell responses resulting in high neutralizing and antibody titers [14]. Early approval from the United Kingdom's (UK) Medicines and Healthcare products Regulatory Agency (MHRA) on 2nd December 2020 was followed by similar directions from the regulatory bodies of Canada and Bahrain, while the United States (US) Food and Drug Administration (FDA) approved it under emergency use authorization (EUA) on 11th December 2020 [15–17]. The European Medicines Agency (EMA) granted a conditional marketing authorization (CMA) on 21st December 2021, and the WHO authorized it for emergency use on 31st December 2020. Since then, the vaccine has been distributed in various regions under emergency and full approvals [18]. Outside clinical trials, the first dose of the vaccine was administered in the UK on 8th December 2020, the US on 14th December, and Israel soon followed on 20th December 2020 [19,20]. As of June 2022, over 350 million doses of the Pfizer/BioNTech vaccine have been administered across the United States [21].

The **Moderna** (mRNA-1273) vaccine, distributed under the trade name Spikevax in Europe, is similar with respect to its structural components to the Pfizer/BioNTech vaccine. It

constitutes of an S protein-coding modRNA delivered using LNPs and is also administered intramuscularly [22]. It was approved under EUA by the US FDA on 18th December 2020 and by Health Canada on 23rd December 2020; the WHO followed suit on 20th April 2020 [23–25]. Official recommendations of two doses at an interval of 28 days, compared to 21 days for the Pfizer/BioNTech regimen, were found to induce CD4+ and CD8+ T cell responses, leading to effective neutralizing antibody production [14]. While the first dose of the vaccine outside of clinical trials was administered in the US on 21st December 2020, over 223 million doses have been administered across the nation as of June 2022 [21,26].

The **Oxford/AstraZeneca** (AZD1222) vaccine, distributed under the trade names of Covishield in the Indian subcontinent and Vaxzevria in Europe, consists of a replication-deficient Chimpanzee adenovirus vector containing the coding sequence for the SARS-CoV-2 spike protein, in addition to a tissue plasminogen activator (tPA) leader sequence [27]. The UK MHRA first approved the vaccine for emergency use on 30th December 2020; India and the EU followed on 1st and 29th January 2021, respectively [28–30]. The vaccine has not yet been approved in the USA [31]. Since administration of the first dose of the Oxford/AstraZeneca vaccine in the UK on 4th January 2021, the country has since ordered about 100 million doses from the manufacturer [32,33], while AstraZeneca has reported orders of more than 2 billion as of November, 2021 [34]. The recommended dosage by the WHO is two doses delivered intramuscularly with an interval of 8 to 12 weeks [35].

Johnson and Johnson's "**Janssen**" (Ad26.COV2.S) vaccine consists of a replication-incompetent adenovirus type 26 (Ad26) vector encoding the gene for the SARS-CoV-2 spike protein in addition to other inactive stabilizers [31]. The US FDA and the EU approved the vaccine for emergency use on 27th February and 11th March 2020, respectively, followed by the WHO and the UK on 29th March and 28th May 2020, respectively [36–39]. It is recommended

as a one dose vaccine administered intramuscularly [40]. Since its roll-out in March 2021, over 18 million doses have been administered across the US alone [21].

CoronaVac, also known as **Sinovac** COVID-19 vaccine, involves a whole inactivated SARS-CoV-2 virus prepared by isolating a CN2 strain of virus from a patient's bronchoalveolar lavage fluid, which was then purified, adapted, and cultured *en masse* using Vero cells, inactivated using beta-propiolactone, and lastly mixed with an adjuvant of aluminum hydroxide [41]. China approved the vaccine for emergency use amongst its healthcare workers (HCWs) by late August 2020 [42], followed by a general use green-light in early February 2021 [43]. On 1st June 2021, the WHO validated the emergency use of the vaccine with high safety confidence amongst healthy adults [44]. As of October 2021, Sinovac accounted for the largest number of vaccines deliveries around the globe, with figures just shy of 2 billion doses [44].

With over 6.33 million doses of COVID-19 vaccines being administered daily, 12 billion doses have been administered as of June 2022, with about 66.3% of the world having received at least one dose of any vaccine [21]. Extensive clinical trials were held to test the efficacy and safety of the new COVID-19 vaccines. Across all age groups, the Pfizer/BioNTech and Moderna vaccines were initially shown to have efficacy rates of 95% and 94.1%., respectively, while the AstraZeneca vaccine was shown to be 70.4% effective following the administration of 2 doses [22,45,46]. Furthermore, the Sinovac vaccine was shown to be 83.5% effective against PCR-confirmed symptomatic cases, while the Janssen vaccine was reported to have an efficacy of 66% for the same [47,48].

A protocol regarding the "Background Rates of Adverse Events of Special Interest (AESIs) for COVID-19 Vaccine Safety Monitoring" was published by the US FDA Center for Biologics Evaluation and Research. Possible side effects listed included acute myocardial infarction, transverse myelitis, appendicitis, Bell's palsy, deep vein thrombosis, disseminated

intravascular coagulation, encephalomyelitis, Guillain-Barre syndrome, both hemorrhagic and non-hemorrhagic stroke, immune thrombocytopenia, myocarditis/pericarditis, narcolepsy, pulmonary embolism, and anaphylaxis [49].

Anaphylaxis refers to an acute, systemic type I hypersensitivity reaction mediated by release of mast cell and basophil contents in response to an allergen that is potentially fatal without rapid treatment. Anaphylactoid reactions on the other hand produce similar clinical manifestations as anaphylaxis without IgE mediation [50]. Anaphylaxis in response to vaccination remains to be a rare event, reported to have an incidence of 1.31 (95% CI: 0.90-1.84) per million doses, that usually occurs within an hour of exposure to allergens found in drugs, toxins, food, and vaccines [51]. According to Nokebly et al., anaphylactic reactions have been reported following administration of almost all vaccines, including the MMR, diphtheria, HPV, Hepatitis, and rabies vaccines [52]. Importantly, reports of anaphylaxis following administration of vaccines against COVID-19 have also emerged in months following vaccine roll-out [53].

This systematic review compiles and analyzes data concerning reports of anaphylaxis or anaphylactoid reactions following COVID-19 vaccination as published in literature. As most studies utilized the Brighton Collaboration criteria (BCC) [54] to classify an reaction as anaphylaxis, this was used as the primary sorting factor to warrant inclusion of cases; if not explicitly stated, clinical symptoms were graded using the BCC. Although first introduced in 2003, the BCC has been widely utilized by clinicians worldwide to report vaccine-associated adverse events; although we acknowledge the presence of World Allergy Organization (WAO) 2020 [55] guidelines and the recent move away from the use of the BCC [56], primary re-evaluation of these symptoms would likely lead to inaccuracies and inconsistencies that would render their reporting of little value. Future primary studies reporting vaccine-

associated anaphylaxis should utilize more recent guidelines (such as the WAO) while reporting cases; for this, compatible and updated reporting systems must be firstly put in place.

Methods

Information Sources and Search Strategy

A comprehensive search strategy has been summarized in **Table 1**.

Eligibility Criteria

We made no restrictions with regards country of vaccination, age, or sex. Duplicated articles and articles that did not have any primary data such as review articles, were excluded from the study.

Study Selection and Data Collection

During the screening phase, the studies that reported anaphylaxis or anaphylactoid reactions post-COVID-19 vaccination were selected regardless of country, age or sex. Studies that were not in English or those that did not have primary clinical data were also excluded. Title, abstract andfull-text screening were conducted by two different reviewers for each study using Covidence, disagreements were resolved by consensus. Demographic and clinical data of patients reported in each study (where available) were extracted independently by two different reviewers, disagreements were resolved by consensus.

Data Items

Extracted data included age, sex, comorbidities, treatment/interventions and clinical progress. Categorical variables were expressed as percentages while continuous variables were expressed as mean standard deviation or range of results.

Risk of Bias and Quality Assessment

The quality of the included studies was assessed using the different methods depending on the type of study. The Newcastle-Ottawa Quality Assessment Scale (NOS)[57] was used to assess the cohort studies. The Jadad scale [58,59] was used to assess the randomized clinical trials (RCT) and the scale developed by Murad et al.[60] was used to assess the case reports and case series. Quality assessment was conducted by two independent reviewers.

Results

The screening protocol involved multi-step inclusion criteria. Excluding duplicates, 19908 imported papers were screened, with 381 qualifying for full text screening. Of these, 186 lacked data of interest, 107 lacked primary data, and 3 lacked enough primary data. Another 8 were not in English, 6 were ongoing studies, 16 were duplicates, 1 study was performed in animal models, 3 studies were still unpublished, and 10 did not meet criteria for anaphylaxis, ultimately leaving 41 included studies (**Figure 1**).

Types of Studies

Only 41 studies met our inclusion criteria[22,61–100]; these consisted of 18 case series/reports, 18 cohort studies without control groups, and 4 cohort studies with control groups - one of which was a double blinded randomized clinical trial (RCT). The last study, Kaplan et al.[79], contained both a cohort analysis and a case series.

Of the 18 case series/reports, 7 were from the USA – 2 of which were from VAERS, 2 were from the UK, Canada, and Singapore each, while Lebanon, Nepal, Turkey, Sweden, and Thailand each had 1. Of the 22 cohort studies, 13 were from the USA - 3 of which utilized VAERS database - 3 were from The Republic of South Korea, 2 were from Japan, while Poland, Australia, Ecuador, and Singapore each had 1. The clinical trial was from the USA.

There were six[62,69,72,80,97,98] studies that utilized the United States' VAERS database and derived their data at different periods of time. One study[69] also had independent data from the European EudraVigilence database, which was included in the main analysis of this review. To avoid repetition of reporting cases of anaphylaxis from the same database and from other independent studies reporting cases across the US, the VAERS-based data from these six were analyzed in isolation. The specific demographics of each study and the quality assessment results can be found in Supplementary Table 1 (**Table S1**).

Demographic and Clinical Data

Table S1 summarizes the demographic and clinical data of the reported cases in the 41 included studies. A total of 7942 cases of anaphylaxis were reported among these studies, not including the data from the VAERS database. In total, 5288 cases of anaphylaxis occurred following administration of the Pfizer/BioNTech vaccine, 1073 after the Moderna vaccine, 3 after either the Pfizer/BioNTech or Moderna vaccines, 1435 after the AstraZeneca vaccine, 127 after the Janssen vaccine, and 16 after the Sinovac vaccine (**Table S2-S4**).

The numbers from McMurry et al. [100] were not compiled with the above results as that cohort has been presented in a person-days format which cannot be distinguished from the results of other studies compiled in this review. They are still available to view in **Table S1**.

Participants covered a wide age range, including data from participants below the age of 18, with various studies reporting ages as a range or a mean, with or without reporting the interquartile ranges (IQR) or standard deviations (SD). The eldest subjects were 95 and 68 among the cohort and case studies respectively. The reported cases of anaphylaxis included 501 females, 146 males, and 7295 cases where sex was not reported (**Figure 2**).

Some studies did not report whether anaphylaxis developed after the first or the second dose which included 7734 cases while 176 reactions were reported following the first dose, 30 after the second dose, and 2 after the third dose (**Figure 3a**). Furthermore, **Figures 3b** illustrates the time between vaccination and the onset of the symptoms.

Across the studies, there are 43 cases of known death. In all others, the subjects either recovered or their clinical outcome was unreported (**Figure 4**).

Among the 6 VAERS studies, a minimum of 195.5 million doses of the Pfizer/BioNTech vaccine, 139.97 million doses of the Moderna vaccine, and 13.6 million doses of the Janssen vaccine were administered from 14th December 2020 to 6th August 2021. Anaphylaxis was reported following a minimum of 965 Pfizer/BioNTech doses, 646 Moderna doses, and 101 Janssen doses. More details are presented in **Table 2**.

Discussion

Beyond being an acute, life-threatening condition, anaphylaxis is associated with a wide range of clinical presentations and triggering mechanisms. Subsequently, it is difficult to establish strict diagnostic criteria for anaphylaxis [101]. Furthermore, as corticosteroids and

antihistamines are generally insufficient to counter anaphylaxis due to their slow action onset time, it is important to identify it so that epinephrine can be administered, preventing serious complications and death [101].

In most of the studies with diagnostic methodologies available, anaphylaxis was diagnosed either according to symptoms and treatment or patient self-report, excluding Nava et al.[62] where the EVANS criteria was utilized. Several studies utilized the BCC Anaphylaxis criteria or a clinical panel to assess whether patients met the criteria for anaphylaxis.

Anaphylaxis Post-COVID-19 Vaccination

Clinical Trials

Anaphylaxis has not been noted to be a side effect for any of the vaccine trials excluding the mRNA-1273/Moderna trial [22], which reported 1 case amongst the vaccination cohort of 15166 participants; this was found to be insignificant compared to the placebo group as well as other vaccines. Drug trials for Pfizer/BioNTech and Moderna also suggested that while there would be a higher prevalence of side effects, they would be of lower severity, while severe side effects (like anaphylaxis) are expected to be rarer.

Cohort Studies

A total of 7858 (425M, 138F, 7295NR) cases of anaphylaxis were reported across the cohort studies.

Subjects throughout these studies generally depicted statistically equivalent anaphylactic rates among the vaccines. For example, Klein et al.[90] reported a rate of 5.1 per million doses and 4.8 per million doses for the Pfizer/BioNTech and Moderna vaccines respectively, noting that they were comparable. However, Arroliga et al.[91] noted an increased risk of anaphylaxis

following administration of the Pfizer/BioNTech vaccine compared to Moderna, citing rates of 11.1 per million and 2.5 per million respectively. The rates for the AstraZeneca vaccine Most cases developed within the first 30 minutes after administration. No patient deaths were reported among these data. Song et al. [63] reported 23 cases following the AstraZeneca vaccine (out of 2,426) and 1 following the Pfizer/BioNTech (out of 52) vaccines in a cohort of HCWs from three institutions in South Korea, i.e., incidences of 0.9% and 1.9%, respectively, that was found to be insignificant between the two ($p=0.447$); however these adverse events are self-reported and hence may not be fully accurate. Furthermore, only the single Pfizer/BioNTech case fit the Brighton criteria for anaphylaxis. In addition, the incidence may be overstated as those who experienced adverse events were more likely to respond to the survey in the study than those who did not.

Interestingly, Wentrys et al. [82], a cohort study with controls reported 2 cases of severe anaphylactic reaction and 1 case of anaphylactic shock among its Pfizer control group (subjects with no allergic history) and 1 case of severe anaphylactic reaction among its AstraZeneca control group (subjects with no allergic history) but not its test groups (subjects with an allergic history). Among other cohorts with controls, there was no significant difference in anaphylaxis rates between groups.

Case Reports and Case Series

The case reports/series reported a total of 84 (76F, 8M) cases of patients who experienced anaphylaxis.

Several case reports detailed presentations that are representative of the array of symptoms possibly fitting an anaphylactoid or anaphylaxis like reaction and the demographic of patients generally shown to have anaphylaxis following vaccination. Park et al. [94] reported

anaphylaxis in a 34-year-old woman with a history of childhood asthma and eczema after the Pfizer/BioNTech vaccine. Following diagnosis of moderate cholinergic urticaria, they concluded that the anaphylaxis was likely due to a severe episode of cholinergic urticaria and that with prior vaccine reactions and a history of cholinergic urticaria, the patient was predisposed to developing allergic reactions. Two days after the event, CRP (1.27 mg/dL) and normal IgE levels (74.98 IU/mL) were noted. She later received the second dose without premedication. Similarly, Csuth et al. [87] reported anaphylaxis in 7 female patients, 3 without any allergic history and 4 with allergies (most of them anaphylactic) to substances including food, wasp stings, latex, and drugs, and 1 male patient with a history of obesity, diabetes, cardiovascular disease, and anaphylactic allergy to multiple vaccines. These patients all had similar symptoms including respiratory symptoms (dyspnea, throat closure and swelling, and hoarseness), cardiovascular symptoms (tachycardia, hypotension), gastrointestinal symptoms (nausea, vomiting, generalized discomfort), and inflammatory symptoms (angioedema, pruritis, erythema). Therefore, while most reported cases involved patients with extensive or severe allergic histories, several also reported cases in patients with otherwise no allergic history. Furthermore, most cases of anaphylaxis occurred within the first 30 minutes, with no deaths reported. Patients were typically administered steroids (methylprednisolone), antihistamines (diphenhydramine), epinephrine, and other medication like salbutamol, plus other necessary supportive treatment.

VAERS Studies:

From 14th December to 6th August, the VAERS database has recorded 195.9 million and 139.97 million doses for the Pfizer/BioNTech and Moderna vaccines respectively, with 965 and 646 cases of anaphylaxis each [69]. From 1st January to 6th August, 13.6 million doses of

the Janssen vaccine with 101 cases of anaphylaxis have been reported. However, throughout these periods the anaphylaxis rates reported have fluctuated greatly. Shimabakuro et al. [7297] initially reported rates of 11.1 and 4.7 cases of anaphylaxis per millions of doses while Singh et al. [80] most recently reported a rate of 2.34 for the Pfizer/BioNTech vaccine. Within the same timeframe, Shimabakuro et al. and the CDC[97] reported a rate of 2.5 cases of anaphylaxis per millions of doses, however Singh et al. [80] now reports a rate of 8.23. For the Janssen vaccine, a rate of 7.05 anaphylactic cases per millions of doses has been reported. Importantly, Maltezou et al. [69] did not present rates, but rates of 4.93, 4.62, 7.43 anaphylactic cases per millions of doses can be calculated for the three vaccines respectively using the presented data. It is difficult to ascertain the cause of these fluctuations. It could be attributed to increased reporting of adverse events leading to inflation of rates, administration of doses to a larger population, increased administration of doses to younger populations with healthy immune systems capable of triggering anaphylactic reactions, or just increased administration among patients who would be at risk for allergic reactions as more data about the vaccine and its reactions became available.

Which Vaccine Ingredients May Induce Anaphylaxis?

Anaphylaxis following vaccination is frequently thought to be linked to stabilizers, preservatives, antibiotics, or other vaccine components not including the vaccine antigen, such as gelatin, formaldehyde, and egg protein [52]. For example, in the AstraZeneca vaccine, the suspected allergen is polysorbate 80, which is meant to function as an excipient, while the mRNA vaccines use PEG to stabilize the lipid nanoparticles. Three different potential allergens in the COVID-19 vaccines are described below.

Polyethylene Glycol

Polyethylene glycols, also known as macrogols or PEGs, are a group of polymers of ethylene oxide of various molecular weights (MWs) that are extensively used as stabilizing agents in the cosmetic, food, and medicinal industries [53]. Depending on the polymer length, the molecular weight of the PEG may vary, and hence different PEGs are classified according to their MWs, with the PEGs used in both the Moderna and Pfizer BioNTech vaccines being 2000 PEG. PEGs is used as an inactive ingredient in some drugs such as penicillins, IV corticosteroids, antacids, laxatives and PEGylated liposomal doxorubicin. However, PEGs have been shown to cause potential allergic reactions in the past, with three PEG containing drugs being withdrawn from the market due to severe side effects: pegnivacogin, pegloticase, and peginesatide [102]. The mRNA vaccines are the first vaccines to contain PEGs as excipients with 2000 molecular weight. As such, the PEGs have been suspected as the main culprit behind the anaphylaxis reactions observed in certain recipients of the Moderna and Pfizer-BioNTech vaccines, with both classical and non-classical mechanisms being suggested. Of note, the allergic reactions caused by PEGs are more commonly attributed to higher molecular weight PEGs.

Polysorbates

Polysorbates, like PEGs, are polymers of ethylene oxide, but are lower in molecular weight, and thus less commonly trigger allergic reactions. Furthermore, they are also commonly used as excipients in vaccines, such as DtaP, HepB, HPV, pneumococcal conjugate vaccine, herpes zoster, and influenza vaccines [53]. In addition, polysorbates are used in drugs such as amiodarone and anti-neoplastic agents [73]. Due to the similarity in structure between polysorbate 80 and PEGs used in other products, there is potential of cross-reactivity, and which was clinically observed ([103]). Reported cases of anaphylaxis due to polysorbate 80 are

very rare, despite its widespread use [53]. One such example has been seen in response to Gardasil, the HPV vaccine, in one patient, which may potentially be due to polysorbate 80. Furthermore, other cases of anaphylaxis due to polysorbate 80 were reported in Korea [104]. Furthermore, the reported cases of anaphylaxis following Jansen COVID-19 vaccine could be attributed to the presence of polysorbate 80 as an excipient.

Spike Protein

Another hypothesis is the involvement of the spike protein as a causative agent of anaphylaxis post-vaccination. Upon vaccination, the mRNA vaccine penetrates human cells and is translated into various protein fragments. These are then displayed on the surface of antigen-presenting cells which exhibits fragments of spike protein on MHC-II molecules. The MHC-II-antigen complex is then recognized by T helper cells, thereby initiating an adaptive cell-mediated immune response. This immune cascade includes the production of interleukins involved in the activation of allergen-specific B cells. These then stimulate the release of IgE antibodies which initiate an allergic immune response [105]. It is postulated that fragments of water-soluble glycoprotein confined within the spike protein of SARS-CoV-2 is the major element that triggers anaphylactic events post-vaccination. This hypothesis could be supported by the computationally predicted allergenicity of the spike protein using AllerTOP v.2.0 and AllergenFP v.1.0. which are used for subunit vaccine design [106,107]. The findings indicate that the receptor-binding domain of the SARS-COV-2 spike protein that binds to ACE2 receptor is likely to be an allergen [105].

Vaccine Induced Anaphylactic Reactions and Associated Risk Factors

Out of 84 case report subjects, 69 individuals had a history of prior allergy or asthma, with a history of anaphylaxis in 19 of them. Furthermore, a large proportion of anaphylactic subjects amongst the cohorts also had an allergic or anaphylactic history, such as Iguichi et al. [93] reporting 78% (35/47) of patients. Anaphylaxis was also more common in women, with 76 of the cases series being female. Cohort studies, such as Arroliga et al. [91] and Klein et al. [90] also reported that the vast majority of anaphylactic cases occurred in females. Moreover, they suggested that this difference in adverse events could be due to genetic differences, hormonal influences, environmental or immunological variance between men and women. This is supported by data from other studies that suggests that anaphylaxis may occur more frequently in individuals with pre-existing allergic conditions and (in the case of adults) women, possibly due to increased estrogen levels [108]. In other cases, such as that of Sellaturay et al. [61] and Wentrys et al. [82], an allergy to a vaccine component such as PEG or Polysorbate 80 can be assumed to be causative. Furthermore, Hashimoto et al. [95] suggested that the Pfizer BNT162b2 mRNA vaccine may have an ethnic bias in Japanese populations, citing a rate of 204.2 cases per million doses or 38.6 cases per million doses when considering studies that met the Brighton Collaboration criteria for anaphylaxis. In contrast, Lee et al. [92] found there to be no significant difference in adverse events among Western populations (UK, USA) and the South Korean population, although most of their subjects were over 75, an age group with a lower incidence of anaphylaxis. No study reported a link with any other known medical condition when other medical comorbidities were reported.

Potential mechanisms of anaphylaxis post-COVID-19 vaccination

Possible mechanisms of vaccine-induced anaphylaxis have been summarized in Figure 5. The classical model of anaphylaxis is defined as a Type I hypersensitivity reaction in which previous exposure to an allergen leads to production of IgE by plasma cells. These IgE molecules then travel throughout the body and bind to fragment crystallizable region receptors, FcεR1, on mast cells and basophils. Upon subsequent exposure to the same allergen, IgE molecules bind to the epitopes of the antigen and cross-link, leading to rapid degranulation of these cells and release of inflammatory and pro-inflammatory molecules and cytokines such as histamine, leukotrienes, prostaglandins, and proteases, all of which contribute to the acute state of anaphylactic shock [109]. PEGs and polysorbate 80 have both been shown to induce IgE production, with patients that have history of PEG-related anaphylaxis displaying anti-PEG IgE antibodies in serum [53,102,110]. Additionally, IgE sensitization towards polysorbate 80 has also been detected, although without clinical reactivity [53]. In other reports of anaphylaxis in patients after receiving bowel preparations or products containing PEGs, skin prick tests (SPTs) performed afterwards demonstrated positive tests to high molecular weight PEGs as well as systemic allergic responses, typical of IgE-mediated allergy [111]. Usage of omalizumab, an anti-IgE monoclonal antibody, has also been shown to suppress histamine release, which supplements the IgE-mediated hypothesis of PEG sensitivity [102].

Complement-activation related pseudo-allergy (CARPA) is an alternative mechanism proposed for anaphylaxis that does not involve IgE. Rather, it involves the activation of the complement system, resulting in the production of the anaphylatoxins C3a and C5a. These molecules can then bind to mast cells and result in degranulation, leading to the identical

anaphylactic presentation displayed in the classical IgE-mediated model. However, the mechanism by which the complement system is activated can differ from one case to another. For example, the infusion of Doxil, the liposomal formulation of doxorubicin, resulted in the detection of sC5b-9 in serum approximately 10 minutes after infusion in the absence of any anti-PEG antibodies [111]. which may suggest direct activation of the alternative pathway. Such a mechanism may explain the phenomenon observed in which vaccine recipients who have no known prior exposures to PEGylated products may develop anaphylaxis, as no sensitization is required.

Another way in which CARPA may occur is via the classical pathway of complement activation, where either IgM or IgG antibodies may bind to PEGs, activate the complement, and produce the anaphylatoxins. To this effect, in-vitro experiments have shown that PEG and lipid nanoparticles are capable of activating the complement [110].This mechanism is supported by the presence of anti-PEG antibodies in individuals that exhibit adverse side effects when given PEG-containing chemotherapies [111]. However, IgG itself may potentially bind directly to platelets, mast cells and other granulocytes via Fcγ receptors and trigger release of pro-inflammatory molecules such as serotonin, cytokines, and leukotrienes, similar to the IgE-mediated mechanism proposed earlier [111] Another fact that may implicate CARPA as the major mechanism is the finding that binding avidity of IgG increases with increasing MW of PEGs, which is consistent with the increasing risk of hypersensitivity with higher MW PEGs. Additionally, Turk et al. [102], reported that individuals that had high levels of anti-PEG IgE also showed high IgG titers. In fact, two of the three PEGylated drugs mentioned earlier that were removed due to dangerous side effects, pegnivacogin and pegloticase, both

show a strong association between anti-PEG IgG antibodies and severe (pseudo) allergic reaction.

Time until Onset of the Symptoms

Importantly, most symptoms appeared rapidly after the first dose. The case reports and case series reported more clinical details for the reported anaphylaxis cases following vaccination. Shimabukuro et al. [72] reported 21 of 23 cases following administration of the Pfizer/BioNTech vaccine and 10 of 11 cases following administration of the Moderna vaccine occurred within the first hour. Similarly, Laisuan et al. [86] reported 8 of 10 cases following Sinovac administration also occurred within the first hour, with all 10 within three hours. Several repeat episodes were also reported. Frank et al. [83] reported a repeat episode in a patient 6 hours after her initial symptoms (which had developed 10 minutes after the first Pfizer/BioNTech dose) and Lim et al. [74] reported recurrence of anaphylactic symptoms within 8 and 27 hours after initial symptoms developed within 30 minutes in another female patient.

In general, the included studies reported 176 anaphylactic reactions occurred after the first dose, 30 after the second dose, and 2 after the third dose while the dosage was not reported for most of the cases. For those with a known time interval following vaccination to onset of symptoms, 552 presented within half an hour, and 122 presented within 24 hours of vaccination. Those individuals could be either previously sensitized or the anaphylactic reaction may have developed through an antibody-independent mechanism such as the alternative pathway of the complement activation.

Although less common than following the first dose, a total of 19 cases following second doses of Pfizer,/BioNTech, 3 following Moderna, and 3 following Sinovac vaccines were

reported; signaling towards the high probability of these individuals not being sensitized to the allergic material before their first dose. PEG is present in skin creams, lotions, soaps, hair products and shower gels, that also is found in both mRNA vaccines, but not Sinovac. Hence the 19 individuals experiencing anaphylactic reactions following second dose are most likely those who were not sensitized to the reactant, or at least not to those with similar molecular weights, until the first dose, followed by strong reactions following the second dose.

The Outcome of Anaphylaxis Post-COVID-19 Vaccination

Despite the severity of anaphylaxis, the clinical outcome is generally positive. Out of the 7942 individuals with known outcomes, 7420 recovered. Excluding Maltezou et al. [69] who reported 43 deaths in the non-VAERS groups and 9 deaths among the VAERS groups, none of the studies reported any anaphylaxis associated deaths. In general, outcomes appear to be favorable with most patients recovering within 21 days. This is a positive sign, suggesting that adequate treatment via corticosteroids, antihistamines, supportive treatment, and other medication, most anaphylactic cases do not result in death, especially given that deaths would likely be reported if occurred. This is an important reminder of the highly treatable nature of anaphylaxis, which supports continued administration of vaccines to fight the pandemic, rather than their discontinuation due to a small chance of anaphylaxis.

Anaphylaxis post-COVID-19 Vaccination Is A Rare Event

While anaphylaxis is a rare event with an incidence of 1.31 cases per million doses [51], Klein et al. reported a rate of 5.1 per million for Pfizer/BioNTech, 4.8 per million for Moderna, while Hwang et al. [77] reported a rate of 4.1 per million for AstraZeneca. These numbers could suggest a higher risk of anaphylaxis following administration of the mRNA vaccines

compared to the traditional dead or live attenuated vaccines. However, most data such as that of Blumenthal et al. [99] disagrees, arguing that the risk is comparable to that of traditional vaccines. Additionally, reactions compared amongst the vaccines are also unclear, as demonstrated by Blumenthal et al. [99] and Song et al. [63] who found rates of anaphylaxis following vaccination among recipients of Pfizer and Moderna and Pfizer and AstraZeneca to be insignificant. Since there has never been such an accelerated or widespread global collaboration to counter a public health issue prior to COVID-19, it is important to understand the frequency of anaphylaxis while continuing to arm ourselves against the pandemic. Considering that the incidence of allergies and conditions like asthma has been increasing in Western countries [112], the incidence of anaphylaxis may also see a concurrent increase. Therefore, it is possible that a larger number of cases may be seen due to either stricter reporting protocols due to rushed approvals, increasing allergy rates, or simply due to more widespread administration of the COVID-19 vaccines compared to their traditional counterparts. Additionally, while the VAERS database also depicts higher rates of anaphylaxis, Maltezou et al. [69], the authors of the most updated VAERS dataset, unified the VAERS and EudraVigilence data and concluded that the estimated mean rate of vaccine-associated anaphylaxis (10.67 cases per million doses) was still lower than the risk of other routine vaccination such as the MMR, HPV, Varicella, and rabies vaccines.

Limitations of the Study

The main limitation in this study was the possible overlap between the reported cases among some studies especially those that obtained their data from the same databases. In order to overcome this problem, we did not compile the data extracted from 6 studies which all used

VAERS as the source for their data. Furthermore, only 1 study reported data from the European EudraVigilence database, which was included in the main analysis of this review.

Conclusion and Recommendations

While the exact statistics for anaphylactic rates differ among the included studies, there is a consensus that the risk of anaphylaxis is not significant when compared to the risks posed by COVID-19 infection. A graphical summary of the findings of this review has been provided in **figure 6**. Much of the risk can be averted with careful screening and patient observation. In the case of the minority, educating patients on the signs and symptoms of anaphylaxis or similar severe reactions may minimize the negative outcomes. Due to the accelerated development and approval of these vaccines, as well as the relatively small cohort sizes compared to the rarity of anaphylaxis, it is possible that these side effects did not have enough subjects to manifest in the clinical trials. Furthermore, these studies usually exclude participants with severe allergic histories, who are the usual at-risk group for anaphylaxis. Subsequently, it is important to meticulously report serious adverse events and remain alert following vaccination for serious side effects. To do so, the 41 included studies share 4 main recommendations. Primarily, taking note of allergic histories before vaccination will allow an efficient and speedy intervention in case of anaphylaxis. Therefore, the guidelines recommend a 30-minute watch period for those with a history rather than 15-minute. This is generally consistent with our findings as most cases occurred within the first hour after vaccination. It is also recommended to screen the high risk individuals (defined as those with

a history of multiple or severe allergic reactions) for PEG reactions prior to vaccination, to avoid anaphylaxis. Some authors argue against receiving a second dose of the vaccine following the incidence of anaphylaxis after the first dose. However, Csuth et al. [87], Park et al. [94] and others recommend that such patients can undergo the skin prick tests and seek a professional advice. Desensitization protocols such as that detailed by AlMuhizi et al. [88] might also hold merit in allowing for more thorough vaccination in those with known allergies to the COVID-19 vaccines. Finally, the data strongly supports that the preparedness of the medical staff and the correct administration of the vaccine, may facilitate the management of anaphylaxis as a rare side effect.

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Table Legends:

Table 1. Summary of search strategy, inclusion and exclusion criteria, and quality assessment methodology.

Table 1. Summary of search strategy, inclusion and exclusion criteria, and quality assessment methodology.

First search	April 2021	
Last search	April 2022	
Databases searched	PubMed, Medline (Ovid, 1946 – April 2021), Embase (Ovid, 1974 -2021), Scopus, Web of Science, Science Direct, MedRxiv, and Lens.org. The search has been updated in April 2022 using PubMed	
Search strategy	("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR severe-acute-respiratory-syndrome-coronavirus-2[Title/Abstract] OR 2019-ncov[Title/Abstract] OR 2019ncov[Title/Abstract] OR covid-19[Title/Abstract] OR covid19[Title/Abstract] OR covid2019[Title/Abstract] OR ncov2019[Title/Abstract] OR ncov-2019[Title/Abstract] OR hcov19[Title/Abstract] OR sars-cov-2[Title/Abstract] OR coronavirus[Title/Abstract] OR coronaviruses[Title/Abstract] OR corona-virus[Title/Abstract] OR corona-viruses[Title/Abstract] OR covid[Title/Abstract] OR hcov[Title/Abstract] or "Wuhan Coronavirus"[Title/Abstract] or "coronavirus"[MeSH Terms] or "COVID-19"[MeSH] or "SARS-CoV-2"[MeSH]) AND (Vaccin*[Title/Abstract] or "Vaccination"[MeSH] or "COVID-19 Vaccines"[MeSH])	
Inclusion Criteria	Studies that reported anaphylaxis or anaphylactoid reactionspost-COVID-19 vaccination were selected regardless of country, age, or sex. Only studies that followed the Brighton Collaboration Criteria (BCC) for reporting anaphylaxis were included.	
Exclusion Criteria	Duplicated articles and articles that did not have any primary data such as review articles, and studies that were not in English or those that did not have primary clinical data were also excluded.	
Quality Assessment scales for corresponding type of studies	Newcastle-Ottawa Quality Assessment Scale (NOS)[57]	Cohort Studies
	Jadad scale[58,59]	Randomized Controlled Trial
	Murad Scale[60]	Case reports/series

Table 2. Summary of studies reporting cases of anaphylaxis following COVID-19 vaccine administration in the US based on data from the VAERS database.

Table 2. Summary of studies reporting cases of anaphylaxis following COVID-19 vaccine administration in the US based on data from the VAERS database.

Reference	Initial Date	Final Date	Vaccine Manufacturer	Reported cases	Doses administered (in millions)	Rate of cases per million doses
[72]**Shimabukuro et al, 2021**	14 December, 2020	23 December, 2020	Pfizer/BioNTech	21	1.89	11.1
[97]**CDC, 2021**	21 December, 2020	10 January, 2021	Moderna	10	4.04	2.5
[98]**Shimabukuro et al, 2021**	14 December, 2020	18 January, 2021	Pfizer/BioNTech	47	9.94	4.7
			Moderna	19	7.58	2.5
[62] **Nava et al, 2021**	1 December, 2020	5 March, 2021	mRNA vaccines (Pfizer/BioNTech AND Moderna)	185	-	-
[80]**Singh et al, 2022**	1 January, 2021	30 April, 2021	Pfizer/BioNTech	297	127.13	2.34
			Moderna	392	104.61	8.23
			Janssen	58	8.23	7.05
[69]**Maltezou et al, 2021**	21 December, 2020	6 August, 2021	Pfizer/BioNTech	965	195.90	4.93*
			Moderna	646	139.97	4.62*
			Janssen	101	13.60	7.43*

*Calculated based on number of cases (of anaphylaxis) and total doses (of each vaccine type) administered reported in paper.

Figure Legends:

Figure. 1: Flowchart of screening and study selection protocol

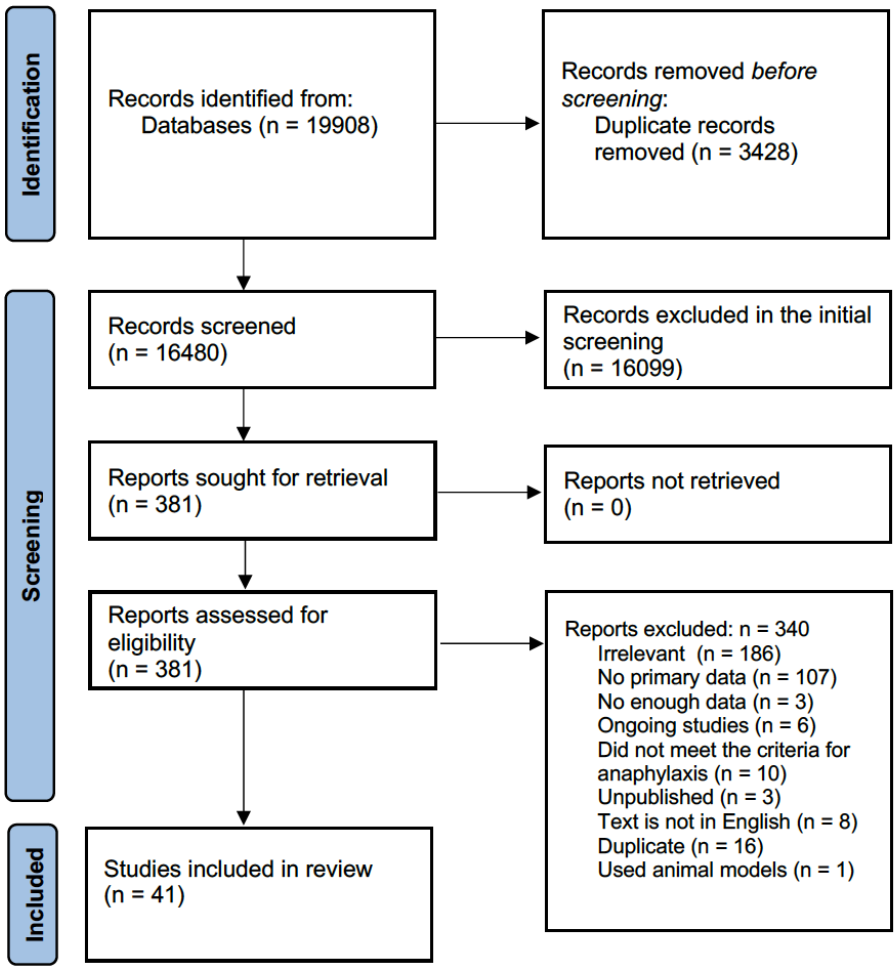


Figure 2: Total number of cases of anaphylaxis or related events following COVID-19 vaccination segregated according to vaccine manufacturer and sex of recipients. From 7942 total reported events, a total of 5288 (295F, 99M, 4894NR) individuals received the Pfizer/BioNTech vaccine; 1073 (74F, 23M, 976NR) received the Moderna vaccine; 3 (3NR) received either the Moderna or Pfizer/BioNTech vaccines*; 1435 (102F, 17M, 1316NR) received the AstraZeneca vaccine; 16 (15F, 1M) received the SinoVac vaccine; and 127 (15M, 6F, 106NR) received the Janssen vaccine. *The studies did not clarify the number of recipients of each vaccine. **F:** Female, **M**: Male, **NR:** Not Reported

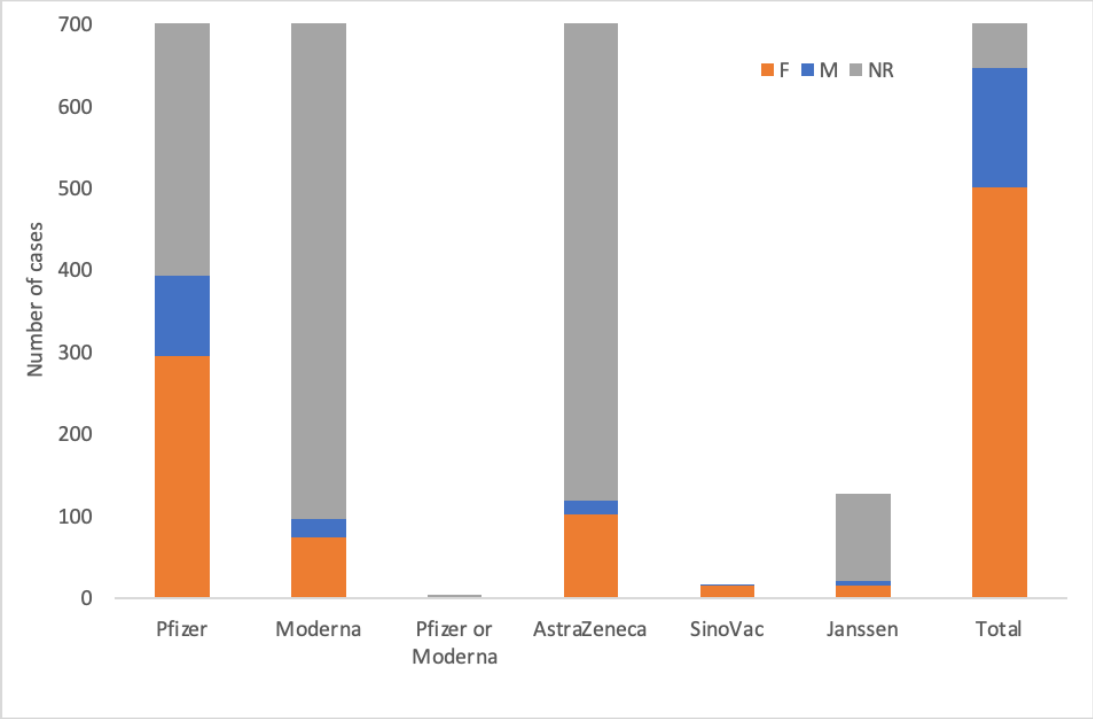
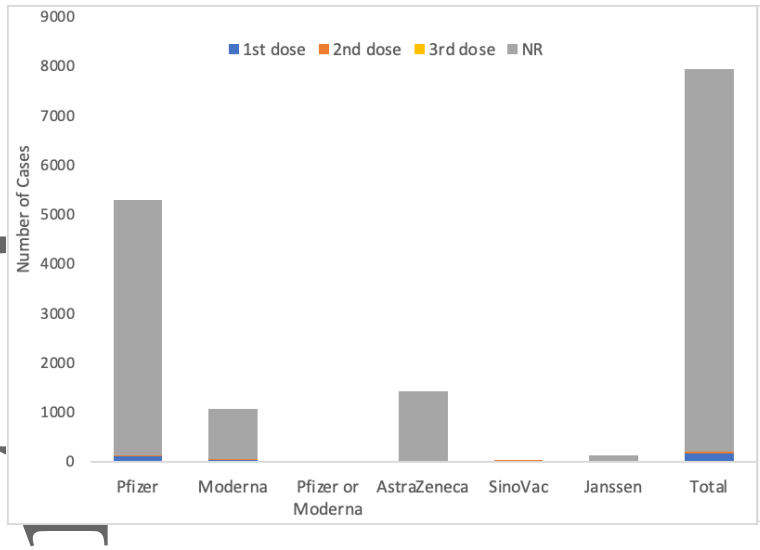


Figure 3: Total number of cases of anaphylaxis or related events following COVID-19 vaccination segregated according to vaccine manufacturer and the timing of anaphylaxis: **A)** Total number of cases of anaphylaxis following COVID-19 vaccination segregated according to dose number prior to episode. A total of 5288 (116 1st, 19 2nd, 2 3rd, 5151 NR) individuals received the Pfizer/BioNTech vaccine; 1073 (42 1st, 8 2nd, 1023 NR) received the Moderna vaccine, 3 (3 1st) received either the Moderna or Pfizer vaccines*, 1435 (2 1st, 1433 NR) received the AstraZeneca vaccine, 16 (13 1st, 3 2nd) received the SinoVac vaccine, and 127 (127 NR) participants received the Janssen vaccine. **B)** Total number of cases of anaphylaxis following COVID-19 vaccination segregated according to vaccine manufacturer and time interval until the display of symptoms among all studies. A total of 5288 (353 ≤30m, 71 >30m, 4864NR) individuals received the Pfizer/BioNTech vaccine; 1073 (78 ≤30m, 16 >30m, 979NR) received the Moderna vaccine; 3 (3 NR) received either the Moderna or Pfizer/BioNTech vaccines*; 1435 (91 ≤30m, 28 >30m, 1316NR) received the AstraZeneca vaccine; 16 (10 ≤30m, 6 >30m) received the SinoVac vaccine; and 127 (20 ≤30m, 1 >30m, 106 NR) received the Janssen vaccine. *The studies did not clarify the number of recipients of each vaccine. **≤30m**: Onset of symptoms within 30 minutes, **>30m:** Onset of symptoms after 30 minutes, **NR:** Not Reported.



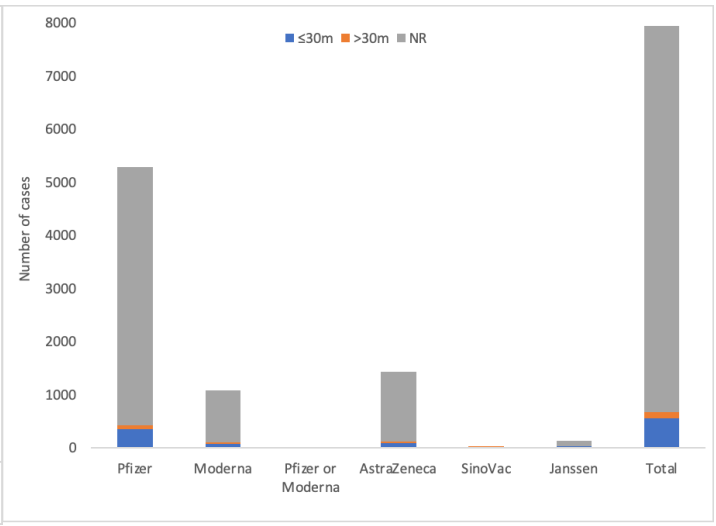


Figure 4: The total number of cases of anaphylaxis following COVID-19 vaccination segregated according to vaccine manufacturer and clinical outcome. A total of 5288 (4952R, 28D, 308NR/NS) individuals received the Pfizer/BioNTech vaccine; 1073 (1014R, 3D, 56NR/NS) received the Moderna vaccine; 3 (3R) received either the Moderna or Pfizer/BioNTech vaccines*; 1435 (1331R, 10D, 94NR/NS) received the AstraZeneca vaccine; 16 (16R) received the SinoVac vaccine; and 127 (104R, 2D, 21NR/NS) received the Janssen vaccine. *The studies did not clarify which vaccine each participant received. **R:** Recovered, **D:** Died, **NR/NS:** Not Reported/Not Specified. Additionally, Shimabakuro et al. [98] did not provide enough data to distinguish between which vaccine led to recovery and which were not reported (61R, 5NR) so all are included in the not recovered group.

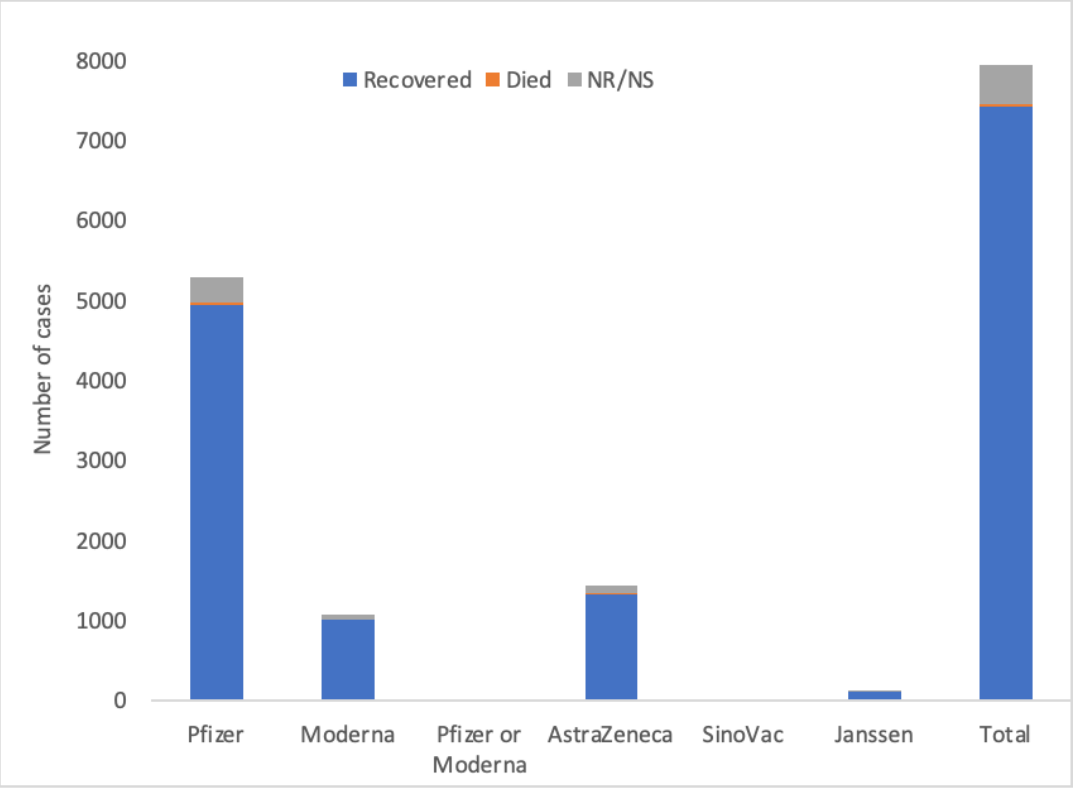


Figure 5: Possible mechanisms of anaphylaxis or related events following COVID-19 vaccination. In individuals who were previously exposed to the allergen, the IgE mediated mast cell degranulation is a possible mechanism. It was also found that the IgG antibodies may directly bind to the platelets and granulocytes leading to degranulation and the release of various inflammatory mediators. Furthermore, the complement activation-related pseudo-allergy (CARPA) is a potential mechanism when the IgM/IgG mediate the allergic reaction by activating the classical pathway of the complement leading to mast cell degranulation due to the production of anaphylatoxins. Anaphylaxis post-vaccination could be also triggered by CARPA in unsensitized individuals through the activation of the alternative pathway of the complement system.

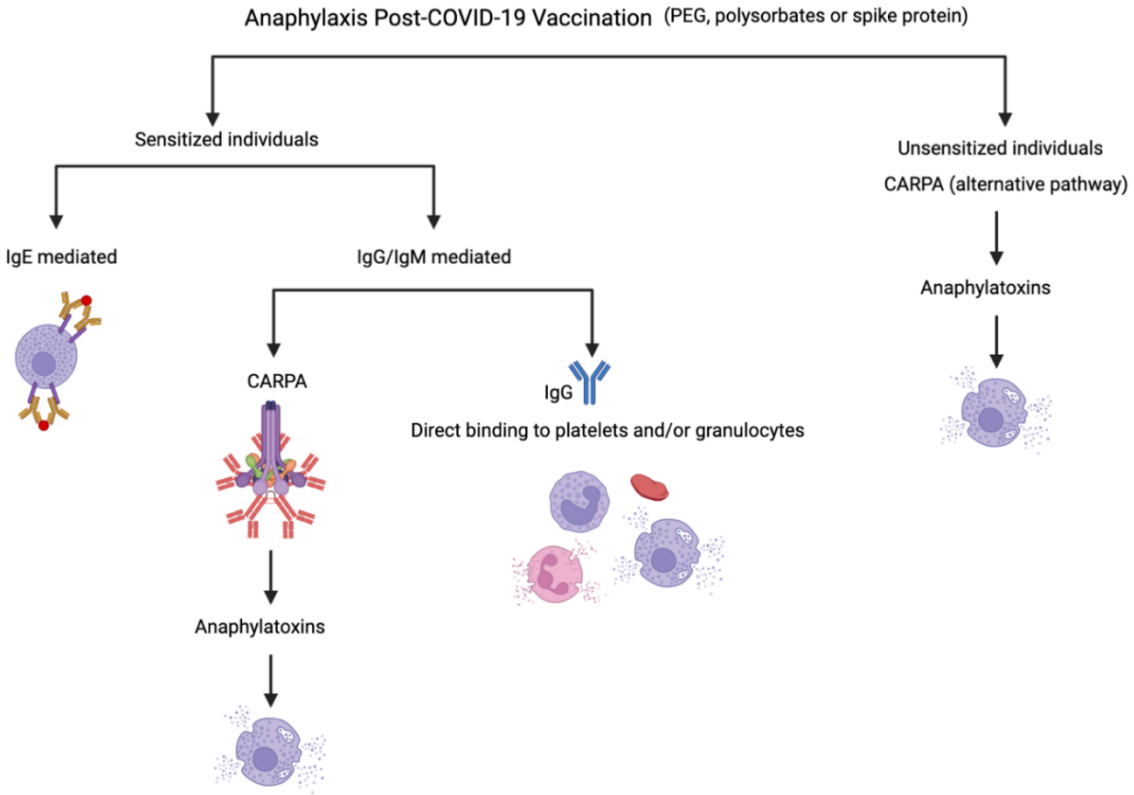


Figure 6: Graphical summary of the results detailing sex, time until onset of symptoms, most recent vaccine dose number, and clinical outcomes of subjects in a pooled analysis of 7942 reported anaphylaxis or related events following administration of either the Pfizer/BioNTech, Moderna, Janssen, AstraZeneca, or SinoVac vaccines.