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Cutaneous Reactions after COVID-19 Vaccines

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ABSTRACT

This article provides an overview of cutaneous reactions after administration of COVID-19 vaccines. Cutaneous reactions post COVID-19 trials range from acute and immediate reactions to delayed reactions. The suspected triggers for the hypersensitivity reactions are the inactive ingredients, such as polyethylene glycol in mRNA vaccines and polysorbate 80 in AstraZeneca. Localized or injection-site reactions are generally self-limiting and occur within seven days. Younger, female patients were more likely to report injection-site reactions. Cutaneous reactions after the second dose occurred earlier than after the first dose. Delayed large local reactions or 'COVID arms' have been reported at least seven days post-vaccination and generally resolve within two weeks. However, this was reported as early as four days post-AstraZeneca vaccination. Other dermatological reactions, such as pityriasis rosea-like eruptions and flares of existing cutaneous conditions occurred in mRNA and AstraZeneca recipients but not with Sinopharm. Screening questions may be used to risk stratifying vaccine recipients into low, medium or high risk of developing severe allergic reactions. Skin testing may be considered for high-risk category patients. However, negative skin testing does not rule out a subsequent allergic response. Delayed cutaneous reactions may be misdiagnosed as cellulitis, resulting in unnecessary treatment with antibiotics.

Citation:

INTRODUCTION

At the end of 2019, China reported cases of respiratory illnesses in Wuhan City, Hubei Province, to the World Health Organization (WHO). These cases were the start of the Coronavirus disease 2019 (COVID-19) outbreak, which was declared a pandemic in March 2020 [1]. During the ongoing COVID-19 pandemic, global mass vaccination is consistently advocated. There are several main COVID-19 vaccine platforms, namely, messenger ribonucleic acid (mRNA) vaccines, such as BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna); adenoviral vector vaccines, such as ChAdOx1 nCoV-19 (Oxford-AstraZeneca) and inactivated whole-virus vaccines, such as BBIBP-CorV (Sinopharm) [2].

As of September 2021, seven COVID-19 vaccines (i.e., Pfizer/BioNTech (BNT162b2), Moderna (mRNA-1273), Oxford/AstraZeneca (ChAdOx1 nCoV-19), Janssen (Johnson & Johnson) (Ad26.COV2.S), Covshield (Oxford/AstraZeneca formulation), Sinopharm (Beijing) [BBIBP-CorV (Vero Cells)] and Sinovac (CoronaVac)), were authorized for use by the WHO [3]. It is crucial that health providers be aware of the potential side effects of each vaccine. Local cutaneous side effects, such as localized erythema and swelling, have been reported in clinical trials and clinical practice [4-8]. There were also observed varying types of dermatological reactions, ranging in terms of distribution (localized or generalised skin lesions), as well as time frame for developing symptoms such as acute, immediate reactions or delayed cutaneous reactions [2,9]. Delayed cutaneous reactions are a curious observation, occurring predominantly with the mRNA vaccines which have also been noted with other COVID-19 vaccine platforms. This paper provides an overview of cutaneous reactions after the administration of COVID-19 vaccines, based on a collection of pertaining published papers.

Hypersensitivity Reactions after COVID-19 Vaccines

Drug hypersensitivity reactions can be immediate (occurring within 1-6 h after administration), or non-immediate/delayed (occurring at least 12-24 h after the administration). Immediate reactions are usually immunoglobulin E (IgE)-mediated, whereas delayed reactions have non-IgE-mediated mechanisms, involving mast cell and basophil degranulation [10]. Factors that increase the risk of drug hypersensitivity reactions include patient, social, disease and drug-related factors. For example, older adults, pediatrics,

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female, pregnancy, heavy alcohol intake and concomitant diseases (such as diabetes, hypertension, renal impairment and human immunodeficiency (HIV) infections) are associated with a greater risk of hypersensitivity reactions [11].

While the active vaccine product itself has the potential to cause hypersensitivity reactions, the other components including inactive excipients are also potential causes for these reactions [12-13]. For COVID-19 vaccines, hypersensitivity reactions are mainly due to the excipients causing Ig-E mediated reactions. Excipients are a necessary component of vaccines as the medium for drugs and are used to increase the water solubility of vaccines. They also enhance the immune response in vaccine recipients, hinder bacterial contamination, and stabilize vaccine potency during transportation and storage.

Generally, vaccines may alter the levels of inflammatory mediators, which may trigger different immune responses. These responses range from Th1, Th2, Th17, Th22 responses, or imbalances of regulatory T-cells. The Th1 response or classical antiviral and anti-tumour response mainly involves interferon-γ, and tumor necrosis factor-α. The Th2 response involving mainly interleukins (IL)-4, IL-5 and IL-13, lead to delayed- type hypersensitivity reactions. The components of vaccines may also trigger an imbalance of regulatory T-cells, which may activate granulomatous reactions [14].

Both Pfizer-BioNTech and Moderna COVID-19 mRNA vaccines contain the excipient polyethylene glycol (PEG), which is postulated to be the major contributor to hypersensitivity reactions. The AstraZeneca vaccine does not contain PEG but contains polysorbate 80. Both PEG and polysorbate 80 may trigger Th-2 mediated immune responses [14]. While polysorbate and its degradation products are also known to predispose to anaphylaxis, the benefits of enhanced efficacy are believed to outweigh the risk of allergic reactions. Polysorbate is also commonly found in other medical products such as vitamins, other vaccines, anti-arrhythmics, anti-diabetics, thrombolytics, anti-cancer agents, contraceptives, creams, ointments [2,12].

Sinopharm does not contain PEG or polysorbate. It uses beta-propiolactone to inactivate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Beta-propiolactone has been shown to potentially cause immune complex-like reactions [15-16]. In addition, Sinopharm is adjuvanted with aluminium hydroxide, which may induce delayed hypersensitivity reactions such as localized eczema and granulomas at injection sites [15]. However, there are currently no available reports of such reactions after the Sinopharm vaccine.

I- Cutaneous Symptoms from COVID-19 Vaccinations in Phase 3 Trials

Pfizer/BioNTech (BNT162b2)

In the Phase 3 BNT162b2 trial, among the 21,720 out of 43,448 participants who received BNT162b2 vaccination, mild-to moderate localized pain was the most commonly reported localized reaction compared to redness (5-7%) or swelling (6-7%). Participants aged 55 years and below reported pain after their first and second doses more frequently (78-83%) than older participants aged above 55 years (66-71%). These reactions occurred within 7 days after the injection and resolved within a day or two. Localized reactions were more commonly reported after the first dose than the second dose. No participants reported severe grade 4 reactions that required emergency treatment or hospitalization [4].

Moderna (mRNA-1273)

In the phase 3 mRNA-1273 trial of 30,520 participants, 92% reported pain at the injection site, 14.7% had localized swelling and 10% had erythema. The median onset of these symptoms was between one and three days after vaccination [17]. The duration of injection-site events was shorter after the first dose (mean of 2.6 days) compared to after second dose (mean of 3.2 days). Delayed injection-site reactions (red, induration, tenderness) after the first and second dose occurred in 0.8% (n = 224) and 0.2% (n = 68) of the participants respectively. Delayed reactions are reactions which occur on or after day 8 of the vaccination, and generally resolves after four to five days. The delayed cutaneous reactions were more common in younger (between 18 and 65 years of age) compared to older participants [5].

Other dermatological reactions (<0.2%) include allergic, contact or irritant dermatitis, eczema, exfoliative rashes, injection site urticaria, papular urticaria and vesicular rashes. Three subjects with a history of dermatological fillers developed serious cutaneous reactions of facial swelling after vaccination [17-18].

Oxford/AstraZeneca (AZD1222)

In the Phase 2/3 AZD1222 trial with 560 participants aged 18 to 83 years, injection- site pain and tenderness were the most common local symptoms reported within the seven days after the first and second dose. The majority of these symptoms occurred within the first two days after vaccination [6]. Mild to moderate pain was more commonly reported in the younger compared to older people. In participants aged 18 to 55 years, 61% (30 out of 49 participants) and 49% (24 out of 49 participants) reported mild to moderate pain after first dose and second dose respectively. In those aged 56 to 69 years, 43% (13 out of 30 participants) and 34% (10 out of 30 participants) reported mild to moderate pain after first dose and second dose respectively. In participants aged 70 years and above, 20% (10 out of 49 participants) and 10% (5 out of 49 participants) reported mild to moderate pain after first dose and second dose respectively.

Similarly, more participants in the younger age group reported tenderness; with 70% experiencing mild to moderate tenderness after the first dose for ages 18-55years, 66% for ages 56 - 69 years and 49% in those aged 70 years and above. Only mild tenderness was reported in participants aged 70 years and above. None of the participants aged 18 to 69 years reported redness, swelling or induration after the first or second dose, except for one participant who experienced moderated redness after the second dose. Participants aged 70 years and older only reported mild to moderate redness (2% after first, 2% after second dose) and swelling (4% after first, 4% after second dose) as well as mild induration (2% after first, 2% after second dose).

Mild warmth (4-14%) and mild to moderate itch (2-12%) were also reported across both age groups after the first and second dose. No participants reported severe cutaneous reactions or required hospitalization from cutaneous reactions. Generally, there were more cutaneous reactions reported after the initial dose, while reactions after the second dose were less severe [18]. Other cutaneous reactions reported (< 0.1%) include psoriasis, rosacea, Raynaud's phenomenon and one case of severe cellulitis [19].

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Sinopharm (Beijing) [BBIBP-CorV (Vero Cells)]

According to WHO data, the most commonly reported localized reactions was injection site pain, followed by swelling, induration, erythema and itching. These were all mild to moderate severity and were self-limiting [7]. Among the 5.9 million Sinopharm recipients in China as of December 2020, 108 reported localized reactions; of which two had severe induration and six had severe redness and swelling. Other reported reactions included allergic or urticarial rashes. In terms of the older age group aged 60 years and older, 79 recipients out of 1.1 million reported adverse events following immunization, the most common being systemic symptoms followed by six cases of allergic dermatitis. The onset or duration of side effects were not reported [7].

II- Cutaneous Symptoms Post-COVID-19 Vaccinations

mRNA vaccines: Pfizer/BioNTech (BNT162b2)/ Moderna (mRNA-1273)

In a retrospective study of 84 patients who received the Moderna vaccine, 82 and 37 patients had delayed large injection- site reactions after the first and second dose respectively. These reactions are also known as the 'COVID arm' or the 'Moderna arm' [2]. More than 90% of these cases developed nine days after the first dose with a range of seven to 13 days. These reactions resolved within two to six days after oral antihistamines, anti-inflammatory agents and topical corticosteroids. Reactions after the second dose occurred sooner, between one to six days. There were seven patients who experienced more severe reactions after the second dose [20].

Another study reported 12 cases of delayed large local reactions eight days (range four to 11 days) after the first dose of the Moderna vaccine. The sizes of these lesions ranged from 3.0cm to 19.5cm and subsided within 11 to 19 days. Among these cases, three had a recurrence of similar reactions, three had milder symptoms, while six had no recurrence of delayed large local reactions with the second dose. The delayed cutaneous reactions occurred sooner after the second dose [21]. These reactions are not limited to specific ethnicities as reported by Blumenthal, in a published case series of vaccine recipients who were Black, Indigenous, or People of Color (BIPOC) [22].

Despite both the Moderna and Pfizer vaccines being the same vaccine platform, the COVID arms reactions were significantly less reported after the Pfizer vaccine [9]. The most commonly reported cutaneous reactions in Pfizer recipients were urticaria (without anaphylactic reactions), localized injection site reactions and morbilliform rashes. These were also seen after vaccination with mRNA-1273. Cutaneous reactions that were observed in COVID-19 patients, such as pernio/chilblains, erythromelalgia, pityriasis rosea- like eruptions, were also seen in Moderna and Pfizer vaccine recipients [2,9,23].

Flare-ups of existing dermatological conditions (herpes simplex, atopic dermatitis, psoriasis, urticarial vasculitis, eczema), herpes zoster and rashes in infants of vaccinated breastfeeding mothers have also been reported after mRNA vaccination [9]. Other cutaneous reactions post vaccination include hypopigmentation, Sweet's-like fixed urticarial plaque, pseudo-vesiculated patches, spongiotic dermatitis, canker sore on tongue, aphthous ulcer on labium and eczematous pigmented purpura.

In addition to the 3 reported cases from the Moderna phase 3 studies [17-18], swelling at the site of dermal fillers was also seen in a registry-based study. Although localized swelling in patients with a history of dermal fillers was not reported in the Pfizer trial, this has been reported subsequently [9]. A possible explanation of the delayed inflammatory reaction to hyaluronic acid dermal fillers is an immune response triggered by the Covid-19 spike protein. Treatment includes oral corticosteroids, hyaluronidase injection, Angiotensin Converting Enzyme (ACE) Inhibitors or Angiotensin-receptor blockers (ARBs). Pre-treatment with these medications may prevent recurrence [2]. Of note, all these cutaneous reactions were experienced or reported by females [8].

Oxford/AstraZeneca (AZD1222)

The 'COVID arm' problem is not limited to mRNA vaccines, as it has also been reported in AstraZeneca vaccine recipients [24-26]. The lesions occurring after AZD1222 range in measurement between 7.5cm to 18cm. The onset of these symptoms varies between four to 17 days after vaccination. The time to complete resolution ranges from four to 17 days. There was a reported case of purpuric patches observed a day after the AZD1222 vaccine, and a case of pityriasis- rosea like eruption three days after AZD1222 [26]. An unusual presentation of intense pruritic erythematous papules within a localized scleroderma, later extending to different body parts occurred three days after AZD1222 [2]. All these lesions cleared within 14 days after treatment with antihistamines and topical corticosteroids [2,26].

Sinopharm (Beijing) [BBIBP-CorV (Vero Cells)]

In a cross-sectional survey, 26 of 1080 participants reported cutaneous side effects; mainly typical localized pain at the injection site and to a lesser extent, localized severe pain, tenderness, redness, induration and pruritus. About a quarter of the recipients had these minor side effects after the first dose, while only 14% of the participants experienced these symptoms after the second dose. Females reported side effects more frequently than males, at incidence rates similar to the trials and were generally mild. Side effects were also more frequently reported by younger compared to the older participants (above 49 years old) [27]. The different cutaneous reactions reported after these four main COVID-19 vaccines are listed in the Table 1.

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Table 1. Summary of common and uncommon cutaneous reactions post COVID-19 vaccination.

Name of Vaccine	Clinical Trials		Clinical Practice	
	More Common	**Less Common**	**More Common**	**Less Common**
Pfizer/ BioNTech (BNT162b2)	- Localized injection site reactions		- Localized injection site reactions - Urticaria - Flares of existing dermatological conditions - "COVID" arm	- Pruritic Morbilliform rash - Pernio/chilblains - Erythromelalgia - Pityriasis rosea- like eruptions - Flares of herpes zoster, herpes simplex - Rashes in infants of vaccinated breastfeeding mothers - Swelling at site of dermal filler
Moderna (mRNA-1273)	- Localized injection site reactions	- Delayed injection site reactions (erythema, induration, tenderness) - Allergic/ contact/irritant dermatitis - Eczema - Exfoliative rash - Injection site urticaria - Papular urticaria - Vesicular rash - Facial swelling in patients with history of dermatological filler	- Localized injection site reactions - "COVID" arm - Morbilliform rash	- Pernio/chilblains - Erythromelalgia - Pityriasis rosea- like eruptions - Flares of herpes zoster, herpes simplex - Rashes in infants of vaccinated breastfeeding mothers - Swelling at site of dermal filler - Flares of existing dermatological conditions
Oxford/ Astra Zeneca (AZD1222)	- Localized injection site reactions	- Psoriasis - Rosacea - Raynaud's phenomenon - Cellulitis	- Localized injection site reactions - "COVID" arm	- Pityriasis- rosea like eruption - Intense pruritic erythematous papules within a localized scleroderma that later extended to different body parts
Sinopharm (Beijing) [BBIBP-CorV (Vero Cells)]	- Localized injection site reactions		- Pain at injection site	- Localized injection site reactions (severe pain, tenderness, erythema, induration, pruritus)

III- Approach to Vaccine Recipients with Previous Allergies

There were many concerns regarding the safety of COVID-19 vaccines due to possible adverse reactions. As mentioned previously, cutaneous drug reactions after vaccination are more likely due to the excipients in the vaccines. Based on Mass General Brigham and Vanderbilt allergy expert consensus, a suggested approach is to risk stratify vaccine recipients into high, medium or low risk using 4 screening questions:

1. Do you have a history of a severe allergic reaction to an injectable medication (intravenous, intramuscular, or subcutaneous)?
2. Do you have a history of a severe allergic reaction to a previous vaccine?
3. Do you have a history of a severe allergic reaction to another allergen (e.g. food, venom, or latex)?
4. Do you have a history of an immediate or severe allergic reaction to PEG-, a polysorbate, or polyoxyl 35 castor oil (e.g., paclitaxel)-containing injectable or vaccine?

Vaccine recipients from the low and medium risk groups will need an observation period of 15 to 30 minutes after vaccination. People in the high-risk category should be considered for evaluation by an allergist for clinical phenotyping and skin testing. If skin testing is positive, the individual should avoid mRNA vaccines and opt for a different COVID-19 vaccine platform. For those reported to have non-

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allergic type reactions after the first dose, they may proceed to the second dose with a similar 15-to-30-minute observation period post-vaccination. However, those with potential allergic reactions, such as urticarial and angioedema after the first dose, but do not fulfill the criteria for anaphylaxis should be considered for further evaluation by an allergist, who will review the clinical history and consider PEG skin testing.

Premedication with antihistamines prior to the second dose may be considered for those with a history of mild allergic symptoms. However, shared decision making is needed for recipients who developed potential anaphylaxis to the first dose, as antihistamines may mask cutaneous symptoms of anaphylaxis and delay seeking medical attention and treatment. Currently, there is no available data regarding the safety of the second dose for those who developed anaphylaxis after the first dose. There is also limited data on the efficacy of mRNA vaccines with split- dose challenges. In addition, as anaphylaxis is a life-threatening reaction, it is important to educate the vaccination staff and recipients regarding symptoms to look out for and ensure the access and availability of prompt treatment [12].

However, another study concluded that excipient skin testing has little use in stratifying the risk of allergic reactions towards mRNA COVID-19 vaccines. More than 80% of those who reported immediate reaction (≤ 4 h) after the first dose of mRNA COVID-19 vaccine had a negative skin test; while 75% of those who received the second dose did not develop symptoms. Furthermore, 25% of those who had negative skin testing developed reactions after the second dose [28]. This shows that negative skin testing does not rule out the development of a subsequent allergic response. Moreover, the reactions which developed after mRNA COVID-19 vaccines are only hypothesized to be attributed by IgE mediated reactions to PEG/polysorbate 12.

IV- Delayed Cutaneous Reactions vs. Cellulitis

An important differential diagnosis for delayed cutaneous reactions is cellulitis. This was reported in a case series where patients with delayed cutaneous reactions were treated as cellulitis, with subsequent recognition of this entity and treatment with topical steroids [29]. As mentioned previously, delayed cutaneous reactions are due to mast cell and basophil degranulation (as opposed to immediate reactions, which are IgE mediated) [10]. These delayed cutaneous reactions can be distinguished from cellulitis by the lack of progression of symptoms, the time to onset of symptoms (eight to 10 days vs. 5 days post-vaccination for cellulitis) and resolution of symptoms over four to five days. Nevertheless, there were also cases of "COVID-arms" which resolved beyond five days. A more definite diagnosis of cellulitis can be made with the laboratory-confirmed presence of bacteria, such as Staphylococcus aureus or group A beta-hemolytic streptococcus from the affected site [30].

In a local review of patients with reported delayed cutaneous reactions (unpublished data), 9 out of 10 cases were reported as severe cellulitis to the national pharmacovigilance center and treated with oral antibiotics. Among these 9 patients, most common presenting complaint was swelling (8 cases) followed by itchiness (4 cases), pain (3 cases) and redness (2 cases). The time of symptom onset ranged between four to ten days. Four patients reported localized reactions eight days after vaccination, two after seven days, one patient after nine days, and one patient at 10 days post vaccination, while only one patient reported the onset of symptoms four days after vaccination. Five patients received antihistamines, while only one patient received topical corticosteroids. Only one patient attended their follow-up appointment three days after treatment, with reduction in pain, redness, tenderness and swelling. Overall, the majority (except for one case) reported an onset of localized reactions beyond seven days, which makes them to be less likely due to cellulitis. This showed that delayed cutaneous reactions are under-recognized and are often treated inappropriately with antibiotics.

CONCLUSION

The majority of reported cutaneous reactions post COVID-19 vaccination were mild to moderate severity and self-limiting. Healthcare providers should be aware of these cutaneous reactions, which should not deter people from receiving COVID-19 vaccines. Delayed-type hypersensitivity reactions should be recognized as a possible adverse event and differentiated from cellulitis, which should be treated with topical corticosteroids rather than antibiotics.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interests.

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