

Cutaneous reactions to COVID-19 vaccines: A review



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Background: The increasing number of reports on cutaneous reactions following COVID-19 vaccination has led to growing concerns among certain groups.

Objective: We reviewed the published reports of cutaneous lesions after COVID-19 vaccination.

Methods: We conducted a literature search for original and review articles published between January 1, 2020, and September 27, 2021.

Results: Eleven cutaneous reactions associated with COVID-19 vaccines were determined; the most prevalent reactions were local injection site reactions, delayed local reactions, urticaria, angioedema, and morbilliform eruptions. There were more reports on skin reactions following the administration of messenger RNA-based vaccines than on those following the administration of adenoviral vector or inactivated whole-virus vaccines, in part, due to their higher administration rate. Most reported skin reactions occurred after the first vaccine dose.

Limitations: A reporting bias could not be excluded, and skin biopsy results were not available for most included individuals. Moreover, given that the included trials focused on vaccine efficacy, there was a lack of details concerning cutaneous reactions and participant information.

Conclusion: Not all cutaneous reactions observed after COVID-19 vaccination are hypersensitivity reactions. Different cutaneous reactions may reflect underlying immune responses to the vaccines. A large majority of COVID-19 vaccination reactions were mild and self-limiting, and people should be encouraged to complete their vaccination regimen. (JAAD Int 2022;7:178-86.)

Key words: anaphylaxis; angioedema; chilblains; COVID-19; cutaneous reaction; herpes zoster; immunity; injection site reaction; pityriasis rosea; urticaria; vaccination.

INTRODUCTION

As COVID-19 mass vaccination is underway, increasing reports of adverse reactions associated with the vaccines are emerging. Anecdotal reports regarding novel formulations of messenger RNA (mRNA)-based vaccines are being inflated by social media, generating alarming misconceptions about vaccination.^{1,2} Therefore, understanding the spectrum of adverse reactions to COVID-19 vaccines is

crucial in creating awareness of the importance of vaccination in the general population.

Although systemic adverse effects are important, cutaneous effects are the immediate reason for dissuading vaccine administration. We reviewed the published reports of cutaneous reactions to COVID-19 vaccines and described these reactions in relation to clinical practice. We reported the prevalence of cutaneous reactions to different types

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of COVID-19 vaccines and the clinical severity of the reactions.

MATERIALS AND METHODS

For this review, we searched PubMed, OVID, EMBASE, MEDLINE, and Google Scholar for original and review articles written in English and published from January 1, 2020, to September 27, 2021. We used the key words “cutaneous,” “skin,” “rash,” “morbilliform,” “sweet syndrome,” “pityriasis rosea,” “pityriasis-rosea-like,” “pemphigus,” and “bullous pemphigoid” in combination with “COVID-19 vaccination,” “2019-nCoV,” “novel coronavirus,” “human coronavirus 2019,” “hCoV-19,” and “SARS-CoV-2.” We reviewed the published reports of cutaneous reactions to all

COVID-19 vaccines approved by the World Health Organization; we included Gam-COVID-Vac (Sputnik V; Gamaleya National Research Center of Epidemiology, Health Ministry of the Russian Federation) and BBV152 (Covaxin; Bharat Biotech International Ltd), given their global availability. We eliminated articles that were not relevant to cutaneous manifestations (Table I). We extracted the following data from the included studies: skin reactions, type of vaccine, administration dose (first or second dose), median duration between vaccine administration and the eruption of lesions, clinical outcomes, and skin biopsy results (Table I).

RESULTS

We summarized the findings of 75 articles: 7 randomized controlled trials, 1 registry-based study, 1 prospective cohort study, 4 retrospective studies, 21 case series, and 41 case reports. In total, 125,713 patients were included, and 48,740 cutaneous reactions were described (Supplementary Table I, available via Mendeley at <https://data.mendeley.com/datasets/vbjbr7ynh/1>).

The median age of individuals in whom cutaneous reactions developed after COVID-19 vaccination was 49.3 years; however, in 99% (48,387/48,740) of the cases, the age was not reported. Among the 48,740 reported cutaneous reactions, 45 (0.1%) occurred in men, 310 (0.6%) occurred in women, and 48,385 (99.3%) did not report their sex. Table I

presents these findings. Skin reactions occurred in 28,655 (58.8%) cases after the first dose, 19,987 (41%) cases after the second dose, and 98 (0.2%) cases in which the dose was undocumented.

A total of 213,198 COVID-19 vaccine doses were administered in the included articles; 91,111 doses

CAPSULE SUMMARY

- Most common cutaneous reactions were transient local reactions. No serious sequelae were reported.
- Different cutaneous reactions may reflect underlying immune responses to vaccines. Most reactions were minor and should not discourage vaccination. The majority of cutaneous reactions occurred after mRNA-based vaccine administration, which could be due to its widespread use.

of mRNA-1273 (Moderna, Inc; National Institute of Allergy and Infectious Diseases), 63,030 of BN-T162b2 (Comirnaty; Pfizer/BioNTech Manufacturing GmbH and Fosun Pharma), 31,465 of Gam-COVID-Vac, 21,895 of Ad26.COVS.2.S (Janssen Pharmaceuticals Companies of Johnson & Johnson), 2362 of BBIBP-CorV (Sinopharm; China National Biotec Group Co, Ltd and Beijing Institute of Biological Products Co, Ltd), 1798 of Vero cell (CoronaVac; Sinovac

Research and Development Co, Ltd), 676 of AZD1222 (ChAdOx1-S; Covishield/Vaxzevria; AstraZeneca and University of Oxford), and 596 of BBV152. However, in 265 cases, the vaccine type was not documented (Table I).

Among the 48,740 reported cutaneous reactions, 38,472 (78.93%) occurred after the administration of mRNA vaccines, 8920 (18.3%) after the administration of adenoviral vector vaccines, and 1333 (2.74%) after the administration of inactivated whole-virus vaccines (Table II). The vaccine name was not recorded in 15 (0.03%) cases. However, taking into consideration the total doses of mRNA vaccines (154,141 doses) and inactivated whole-virus COVID-19 vaccines (4756 doses) administered in the included studies, the prevalence of cutaneous reactions reported with mRNA vaccines (38,472/154,141; 25%) was lower than that with inactivated whole-virus COVID-19 vaccines (1333/4756; 28.3%). Table III provides the details of these findings. Cutaneous reactions occurred more commonly after the first dose (28,655/48,740; 58.8%) than after the second dose (19,987/48,740; 41%).

We classified the most commonly reported cutaneous reactions associated with COVID-19 vaccines into the following 11 classes:

1. Local injection site reactions: Local injection site reactions included pain, redness, and swelling, which occur within 7 days after vaccination.³⁻⁶ On average, these reactions started on the first

Abbreviation used:

SCAR: severe cutaneous adverse reactions

- day after vaccination, regardless of the dose.^{3,4} The median duration of these reactions was 2 to 3 days. These were the most common skin reactions associated with the COVID-19 vaccines (96%). For the 8 vaccines that were studied, the most common local injection site reaction was pain (36,883/48,740; 75.7%), followed by redness (4497/48,740; 9.2%) and swelling (5563/48,740; 11.4%). Most (58.7%) reactions occurred after the first dose. Younger individuals tended to have a higher incidence than older individuals. However, the median age and sex of the individuals were not documented.^{3,4}
2. Delayed local reactions: Delayed local reactions are local reactions with onset at ≥ 7 days after vaccination.^{4,7,8} These reactions were characterized by erythema, pruritus, induration, tenderness near the injection site, and a presentation mimicking cellulitis,^{4,7,9,10} and these accounted for 1.7% of the reported skin reactions. Nearly all the reported delayed local reactions (889/898; 99%) occurred after mRNA vaccination. Most (74.9%) of the delayed local reactions occurred after the first dose. The median age of individuals who experienced these reactions was 51.5 years. The median duration of the onset of delayed local reactions following COVID-19 vaccination was 7 days.
 3. Urticaria: Urticaria is characterized by pruritic erythematous wheals or plaques.^{7,11,12} A total of 440 (0.9%) urticarial reactions were reported. Most (97.9%) of the urticarial reactions occurred after mRNA vaccination. Among 19 individuals for whom the age and sex were documented, the median age was 37.9 years (women: 17/19, 89.5%; men: 2/19, 10.5%). The median duration of the onset of urticarial eruptions after COVID-19 vaccination was 22 hours.
 4. Angioedema: Angioedema is characterized by submucosal or subcutaneous swelling.^{7,11,12} It accounted for 0.5% of the reported skin reactions following COVID-19 vaccination. All the reported cases of angioedema occurred after mRNA vaccination. A total of 50.2% and 49.8% of the angioedema cases occurred after the first and second doses, respectively. Among 3% of cases for which the age and sex were documented, the median age was 40.4 years (women, 6/8, 75%; men: 2/8, 25%). The median duration of the onset of angioedema eruptions following COVID-19 vaccination was 12 hours.
 5. Morbilliform eruption: Of the reported skin reactions after COVID-19 vaccination, morbilliform eruption represented 0.09%. All the reported cases occurred after mRNA vaccination. A total of 72% and 28% of the morbilliform eruptions occurred after the first and second doses, respectively. The median age of individuals who reported a morbilliform eruption was 55 years. The median duration of the onset of morbilliform eruptions following COVID-19 vaccination was 3 days.
 6. Herpes zoster: Herpes zoster accounted for 0.08% of the reported skin reactions. Most (69.2%) cases occurred after the first dose. The median age of individuals who experienced herpes zoster following COVID-19 vaccination was 60 years. The median duration of the onset of herpes zoster following COVID-19 vaccination was 4 days.
 7. Bullous eruptions: The reported bullous eruptions included bullous pemphigoid (18/20; 90%), pemphigus vulgaris (1/20; 5%), and bullous fixed drug eruption (1/20; 5%). Bullous eruptions accounted for 0.04% of the reported skin reactions following COVID-19 vaccination. All the reported bullous eruptions occurred after mRNA vaccination, and most (60%) occurred after the first dose. The median age of individuals in whom bullous eruptions developed after COVID-19 vaccination was 79 years (men: 50%; women: 50%). The median duration of the onset of bullous eruptions following COVID-19 vaccination was 7 days.
 8. Filler reactions: Filler reactions refer to delayed inflammatory reactions to hyaluronic acid-based fillers. They manifest as erythema, painful induration, tissue hardening, and edema.^{13,14} Filler reactions accounted for 0.04% of the reported skin reactions following COVID-19 vaccination. All the reported filler reactions occurred after mRNA vaccination. In total, 50% occurred after the first dose and 50% after the second dose. The median age of individuals who experienced filler reactions was 47 years; 50% of them were women, whereas 50% did not report their age or sex. The median duration of the onset of filler reactions following COVID-19 vaccination was 1 day.
 9. Chilblains: Chilblains accounted for 0.03% of the reported skin reactions. All the reported cases of chilblains occurred after mRNA vaccination, and most (64%) occurred after the first dose. The median age of individuals who experienced chilblains was 70 years. The

Table I. Summary of the types of COVID-19 vaccines and cutaneous reactions

	mRNA-based vaccines						Adenoviral vector vaccines					Inactivated whole-virus vaccine						
	BNT162b2			mRNA-1273			Sputnik V		Vaxzevria/Covishield		Ad26.COV2.S	CoronaVac		Covaxin		Sinopharm		
	First dose	Second dose	NR	First dose	Second dose	NR	First dose	Second dose	First dose	Second dose	Single dose	First dose	Second dose	First dose	Second dose	First dose	Second dose	NR
Pain	3194	2737	0	12,784	12,385	0	NR	NR	88	55	4379	64	43	10	3	540	548	53
Swelling	256	262	0	1051	1764	0	NR	NR	3	4	2189	1	3	0	0	12	12	6
Redness	195	251	0	563	1261	0	NR	NR	2	5	2189	5	0	0	0	8	15	3
Delayed local reaction	56	62	0	611	160	0	NR	NR	1	0	0	0	0	0	0	0	0	0
Urticaria	50	38	0	154	191	0	0	0	0	0	0	1	3	0	0	0	0	0
Angioedema	23	22	0	112	120	0	0	0	0	0	0	0	0	0	0	0	0	0
Morbilliform eruption	19	5	0	14	8	0	0	0	0	0	0	0	0	0	0	0	0	0
Herpes zoster	11	8	0	15	2	0	0	0	0	0	0	0	0	1	0	0	0	0
Bullous eruptions	6	4	0	6	4	0	0	0	0	0	0	0	0	0	0	0	0	0
Filler reactions	3	3	0	6	6	0	0	0	0	0	0	0	0	0	0	0	0	0
Chilblains	5	3	0	3	3	0	0	0	0	0	0	0	0	0	0	0	0	0
Sweet syndrome	3	0	1	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0
Pityriasis rosea	3	4	0	1	1	0	0	0	0	0	0	1	1	0	0	0	0	0
Erythema multiforme	7	2	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Dermal hypersensitivity reactions	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Lichen planus	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pityriasis rosea-like eruptions	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Papulovesicular eruptions	0	0	2	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Severe cutaneous adverse reactions	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0
Facial pustular neutrophilic eruptions	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Generalized annular eruptions	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0

NR, Not reported.

Table II. Prevalence of cutaneous reactions following COVID-19 vaccination

	mRNA-based COVID-19 vaccines	Adenoviral vector COVID-19 vaccines	Inactivated whole-virus COVID-19 vaccines
Reported cutaneous reactions	38,472	8920	1333
Total vaccine doses given	154,141	54,036	4756
Prevalence of cutaneous reactions	38,472/154,141 = 25%	8920/54,036 = 16.5%	1333/4756 = 28.3%

Fifteen reported cases of cutaneous reactions did not have their types of vaccines recorded.

median duration of the onset of chilblains following COVID-19 vaccination was 3 days.

- Pityriasis rosea: In total, 0.023% of the reported skin reactions following COVID-19 vaccination were attributed to pityriasis rosea. Most (90%) occurred after mRNA vaccination and after the second dose (60%). The median age of individuals who experienced pityriasis rosea was 39 years; among them, 40% were women, 20% were men, and 40% did not report their age or sex. The median duration of the onset of the eruptions of pityriasis rosea following COVID-19 vaccination was 5.5 days.
- Severe cutaneous adverse reactions (SCARs): SCARs following COVID-19 vaccination were very rare and accounted for 0.004% (2 cases) of the reported skin reactions.^{15,16} Nonetheless, they posed a significant risk of morbidity and mortality in affected patients. The reported SCARs included acute generalized exanthematous pustulosis and Stevens-Johnson syndrome. The 2 reported cases occurred after the administration of adenoviral vector vaccines. The median age of individuals who experienced SCARs was 67 years, and both were men. The median duration of the onset of SCARs following COVID-19 vaccination was 3 days. Both the patients recovered, with no serious sequelae.

Other less-common cutaneous reactions reported following COVID-19 vaccination included erythema multiforme (0.02%),¹⁷⁻²⁴ Sweet syndrome (0.012%),^{18,25-28} dermal hypersensitivity reactions (0.01%),¹⁷ lichen planus (0.006%),^{29,30} papulovesicular eruptions (0.006%),¹⁷ pityriasis rosea-like eruptions (0.004%),^{31,32} generalized annular lesions (0.002%),³³ facial pustular neutrophilic eruptions (0.004%),³⁴ and flares of underlying autoimmune skin conditions (0.002%).³⁵ All the cases resolved, without serious sequelae.

DISCUSSION

The increasing number of reports of cutaneous reactions following mRNA vaccination has led to

misinformation in the media.^{1,2} Misleading claims arise from relatively short clinical trials and the novel mechanisms of mRNA vaccines. We sought to explore the skin reactions occurring after COVID-19 vaccination.

Local injection site reactions were more commonly observed in younger individuals than in older individuals.^{3,4} To date, no serious sequelae have been reported in individuals with local injection site reactions. By providing proper vaccine guidance, recipients can be mentally prepared for the possible occurrence of cutaneous reactions and, therefore, more likely to complete their second dose.

In observational studies, delayed local reactions were the most commonly reported cutaneous reactions following COVID-19 vaccination. Nearly all of these reactions occurred after mRNA vaccination, with a few occurring after DNA vaccination.^{3,4,6,9,10,36-56} The mechanism of these reactions is not fully understood. The skin biopsy results of these individuals support the speculation of T-cell-mediated hypersensitivity as the mechanism of delayed injection site reactions.⁵⁷ Delayed hypersensitivity reactions are expected to occur sooner and more robustly after the second vaccine dose than after the first dose owing to prior sensitization. However, most delayed local reactions to the first dose did not recur with the second dose.^{4,7,58}

Another hypothesis is related to the delayed appearance of the spike protein; mRNA vaccines require the translation of their mRNA to generate endogenously produced viral spike proteins to which the immune response is generated. Similarly, antigen production in adenoviral vector-based vaccines is delayed because the vaccine is delivered within a viral envelope, and host cells start producing spike proteins in a manner similar to that after the administration of an mRNA vaccine.⁵⁹ The immune response generated after the first dose can moderate the subsequent reaction to the second dose. The timing of a delayed local reaction onset coincides with that of the immune system's detection of the spike protein generated by the vaccine's mRNA at the injection site.^{60,61} Delayed local reactions to COVID-19 vaccines may reflect the protective immune

Table III. Summary of the 10-most common cutaneous reactions to COVID-19 vaccines and survival data

Cutaneous reactions	Number of reported reactions	Vaccine name	Dose	Median age, y	Sex	Clinical outcome
Local injection site reactions	46,943	BNT162b2: 6895 mRNA-1273: 29,808 Covishield/Vaxzevria: 157 Ad 26.COV2.S: 8757 CoronaVac: 116 Covaxin: 13 Sinopharm: 1197	Dose 1: 27,533 Dose 2: 19,348 NR: 62	NR	NR	No serious sequelae reported
Delayed local reactions	898	BNT162b2: 118 mRNA-1273: 771 Covishield/Vaxzevria: 1 NR: 8	Dose 1: 669 Dose 2: 222 NR: 8	51.5	7 M: 128 F 763 NR	No serious sequelae reported
Urticaria	440	BNT162b2: 88 mRNA-1273: 345 CoronaVac: 7	Dose 1: 205 Dose 2: 232 NR: 3	34.5	3 M: 16 F 421 NR	No serious sequelae reported
Angioedema	277	BNT162b2: 45 mRNA-1273: 232	Dose 1: 135 Dose 2: 142	42.5	2 M: 6 F 269 NR	No serious sequelae reported
Morbilloform eruptions	46	BNT162b2: 24 mRNA-1273: 22	Dose 1: 33 Dose 2: 13	55	2 M: 1 F 43 NR	No serious sequelae reported
Herpes zoster	39	BNT162b2: 19 mRNA-1273: 17 Covaxin: 1 NR: 2	Dose 1: 27 Dose 2: 10 NR: 2	60	13 M: 15 F 11 NR	No serious sequelae reported
Bullous eruptions	20	BNT162b2: 10 mRNA-1273: 10	Dose 1: 12 Dose 2: 8	79	10 M: 10 F	No serious sequelae reported
Filler reactions	18	BNT162b2: 6 mRNA-1273: 12	Dose 1: 9 Dose 2: 9	47	0 M: 9 F 9 NR	No serious sequelae reported
Chilblains	14	BNT162b2: 8 mRNA-1273: 6	Dose 1: 8 Dose 2: 6	70	2 M: 2 F 10 NR	No serious sequelae reported
Pityriasis rosea	11	BNT162b2: 7 mRNA-1273: 2 CoronaVac: 2	Dose 1: 5 Dose 2: 6	39	2M: 4F 1 NR	No serious sequelae reported

NR, Not reported.

response stimulated by the vaccine. Given the similarities in the appearance and timing of onset, these delayed local reactions are misdiagnosed as cellulitis.^{10,62} It is important to recognize these reactions to avoid unnecessary antibiotic prescriptions for presumed cellulitis.

Morbilliform eruptions following COVID-19 vaccination were increasingly being reported. The biopsy results demonstrated spongiosis and dermal perivascular lymphocytic infiltrate and were similar to the histochemical results found in the cases of COVID-19-associated cutaneous reactions. They also tended to recur with the second vaccine dose. All these suggested that morbilliform eruptions following COVID-19 vaccination reflect the underlying immune responses generated by the vaccines. Ohsawa et al⁶³ suggested that immunity to SARS-CoV-2 would have been established if morbilliform eruptions had developed in patients after they received the initial dose of the vaccine and, therefore, suggested considering omitting the second dose of COVID-19 vaccines.

Following BNT162b2 vaccination, herpes zoster developed in few patients with autoimmune diseases.⁶⁴ In immunocompromized patients, herpes zoster following COVID-19 vaccination may be similar to immune reconstitution inflammatory syndrome. The virus's reactivation might have been due to the paradoxical worsening of a latent infection unmasked by the host's inflammatory response to the COVID-19 vaccine. Nonetheless, there are few reports of herpes zoster after COVID-19 vaccination in healthy individuals.⁶⁵⁻⁶⁷ Preclinical trials of COVID-19 vaccines demonstrated a transient duration of lymphopenia within the first few days after vaccination.^{37,68} The timing of herpes zoster onset corresponds with that of lymphopenia; therefore, it is conceivable that the transient duration of lymphopenia after COVID-19 vaccination can trigger herpes zoster.

To date, 15 cases of delayed filler reactions after COVID-19 vaccination have been reported across 3 observational studies. Adipose tissue, where most fillers are injected, has a high expression of angiotensin-converting enzyme 2 receptors. Coincidentally, these receptors are targeted by the SARS-CoV-2 spike protein, and the resulting interactions may instigate an inflammatory cascade. This may explain the delayed reaction to hyaluronic acid fillers observed after COVID-19 vaccination. Munavalli et al^{13,69} proposed the use of lisinopril to treat delayed filler reactions after COVID-19 vaccination, which was deemed beneficial. The authors theorized that blocking the production of angiotensin II reduces the angiotensin-converting enzyme 2

substrate; thus, angiotensin-converting enzyme inhibitors can promote an anti-inflammatory response.

There are reported cases of pityriasis rosea eruption following COVID-19 vaccination. One of the hypotheses regarding this association is that a high cytokine response to the vaccine distracts the T-cell-mediated control of latent infections, such as human herpes virus 6 and 7 and, hence, the reactivation of the latent viruses.⁷⁰⁻⁷² In contrast, pityriasis rosea-like eruptions following COVID-19 vaccination may have a different pathophysiology. These have been postulated to be a manifestation of a delayed hypersensitivity response to the vaccine.⁷³

This literature review had some limitations. First, the focus of the included clinical trials was predominantly on vaccine efficacy; therefore, there was a lack of details regarding cutaneous reactions and participant information. Second, most of the included individuals did not undergo skin biopsy; it was challenging to differentiate causality from causation for some of the cutaneous manifestations without histologic results. Third, a reporting bias could not be excluded.

In conclusion, this review presents a spectrum of cutaneous reactions following COVID-19 vaccination. Most reactions were self-limiting and should not discourage vaccination. We observed that cutaneous reactions following mRNA-based vaccination were more commonly reported than those after inactivated whole-virus vaccination. This might have been due to the widespread use of mRNA-based vaccines. However, the safety of COVID-19 vaccines should continue to be monitored. Accurate and transparent communication with the communities about the adverse events associated with COVID-19 vaccines and their possible causes is important in increasing vaccine acceptance. Further studies with histopathological findings are needed to establish the causality of the skin reactions following vaccinations.

Conflicts of interest

None disclosed.

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