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# COVID-19 Vaccines and the Skin



## The Landscape of Cutaneous Vaccine Reactions Worldwide

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### KEYWORDS

• COVID-19 • Vaccines • Cutaneous • Reactions • Urticaria • Side effects • Adverse • Moderna

### KEY POINTS

- The most common cutaneous reactions cited in the clinical trial data of COVID-19 vaccines are local injection site reactions.
- The most common cutaneous reactions cited in nontrial literature are delayed large local reactions.
- Dermatologic side effects of COVID-19 vaccines range from morbilliform rash and pernio to pityriasis rosea and erythema multiforme.
- As vaccine reactogenicity reports continue to surface, dermatologists and other health care providers should understand the landscape of the latest cutaneous reactions to guide and address patients' concerns.

### INTRODUCTION

As of April 22, 2021, the novel coronavirus disease 2019 (COVID-19) has sickened more than 142 million people and taken more than 3 million lives worldwide.<sup>1</sup> Although restrictions such as physical distancing are crucial to containment, these measures are only temporary solutions. One silver lining amid this crisis is that the tragedy has become a catalyst. Scientists around the globe have raced to develop a long-term solution to impede viral transmission. On March 13, 2020, just 63 days after the genetic sequence of severe acute respiratory syndrome novel coronavirus 2 (SARS-CoV-2) was published, researchers began testing the first doses of a human COVID-19 vaccine.<sup>2</sup> By December 2, 2020, the United Kingdom became the first country to approve of and

distribute the Pfizer-BioNTech BNT162b2 vaccine.<sup>3</sup> The United States followed suit days later, with the Food and Drug Administration (FDA) issuing Emergency Use Authorizations for both the Pfizer-BioNTech and Moderna vaccines.

Since then, several COVID-19 vaccines have been authorized and approved for distribution around the globe, with many more in the pipeline. Of significance to dermatologists are the increasing reports of cutaneous reactions associated with these vaccines. The American Academy of Dermatology and the International League of Dermatologic Societies COVID-19 Registry began collecting such cases in late December 2020. The cases submitted ranged from delayed large local reactions to pityriasis-rosea-like eruptions and reactivation of herpes simplex and varicella zoster.<sup>4</sup> Mass vaccination is key to achieving herd

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immunity and ending the pandemic. Therefore, it is critical that providers are aware of and understand the cutaneous side effects among the approved vaccines to better educate patients and provide proper counseling.

In this article, we evaluate the landscape of dermatologic side effects from COVID-19 vaccines worldwide. We first summarize the latest skin reactions reported in clinical trial data following the administration of 11 different approved COVID-19 vaccines, before describing additional skin findings in reports outside of clinical trials.

### CUTANEOUS MANIFESTATIONS OF COVID-19 VACCINATION IN CLINICAL TRIALS

As of April 15, 2021, 13 vaccines have achieved regulatory authorization and approval: Pfizer-BioNTech's BNT162b2, Moderna's mRNA-1273, Oxford-AstraZeneca's AZD1222, Gamaleya's Sputnik V, Johnson & Johnson's Janssen's Ad26.COV2.S, Sinovac's CoronaVac, Sinopharm's BBIBP-CorV, The Vector Institute's EpiVacCorona, CanSino's Convidecia, Bharat's Covaxin, Sinopharm's WIBP-CorV, Chumakov's CoviVac and Anhui Zhifei Longcom's ZF2001 (**Table 1**).<sup>5</sup> Of these vaccines, 11 have published trial data (**Table 2**).

The most common adverse cutaneous reactions noted were local injection site reactions such as erythema, swelling, tenderness, pain, induration, and pruritus within 7 days after injection. Mild to moderate injection site pain was the most prevalent event among all 11 COVID-19 vaccine trials, with up to 88% of participants experiencing pain that typically resolved within 24 to 48 hours after onset. Erythema, swelling, induration, and itch were less common, and reported in up to 20%, 15%, 25%, and 35% of participants, respectively (see **Table 2**). An emerging trend is the higher incidence of these local injection site reactions in the younger population compared with participants age 60 years and older.<sup>6-8</sup>

Delayed large local reactions, with a typical onset of 8 days or more after vaccination and consisting of erythema, induration, and tenderness, were specifically reported in Moderna's phase III trial.<sup>6</sup> After the first dose, 244 participants (0.8%) in the vaccinated cohort developed mild, delayed injection reactions that resolved over the course of 4 to 5 days.<sup>6</sup> After the second dose, 68 participants (0.2%) developed delayed large local reactions.<sup>6</sup> There was no mention, however, of whether those who had reactions after the first dose experienced a recurrence after the second dose.

Although infrequent, a series of other dermatologic manifestations with varying severity have been reported. Less than 0.2% of Moderna's

vaccinated cohort developed rashes, including allergic, atopic and contact dermatitis; eczema; exfoliative rash; hypersensitivity reactions; injection site urticaria; papular urticaria; and vesicular rash, among others (see **Table 2**).<sup>6</sup> Although specific characteristics such as timing and duration were not reported, none of these skin findings were labeled as severe.<sup>6</sup> Similarly, acneiform and allergic dermatitis, alopecia, petechial rash and eczema were seen in less than 0.1% of Sputnik V's vaccinated participants.<sup>9</sup> One participant developed an unspecified rash in the BBIBP-CorV vaccine trial and another developed a mild unspecified rash in the Covaxin trial.<sup>8,10</sup> Vaccine-related buccal ulceration and oral herpes were also noted in the Convidecia vaccine cohort.<sup>11</sup>

Three cases of serious cutaneous reactions were observed among these 11 vaccines. One participant in the CoronaVac trial developed a severe, acute hypersensitivity reaction with urticaria 48 hours after the first dose.<sup>12</sup> The rash resolved within 3 days after the administration of chlorphenamine and dexamethasone, and a similar reaction was not observed after the second dose.<sup>12</sup> Among the 11 recipients of the ZF2001 vaccine who developed unspecified rashes, 1 case was labeled as severe (grade 3 or higher).<sup>13</sup> The AZD1222 trial reported 1 case of severe cellulitis in addition to one case each of vaccine-induced psoriasis, rosacea, vitiligo, and Raynaud phenomenon.<sup>14</sup>

### CUTANEOUS MANIFESTATIONS OF COVID-19 VACCINATION IN REAL-WORLD SETTINGS

Dermatologic reactions to COVID-19 vaccines may be largely uncommon among clinical trial participants, but as we enter global mass vaccination, these adverse events will increase and new cutaneous reactions will emerge. In fact, numerous observational reports and case series of COVID-19 vaccine-related dermatoses have been published recently. An increased awareness of these manifestations can help dermatologists to identify potential risks, engage in anticipatory guidance, and initiate appropriate management. Here, we present an overview of the latest nontrial literature on reactive dermatoses to COVID-19 vaccines.

#### Delayed Large Local Reactions

A delayed large local reaction, defined as the onset of an erythematous and edematous patch at the injection site at least 4 days or more after vaccine administration, was the most commonly noted adverse cutaneous event in nontrial literature.<sup>4</sup> Across all 6 observational studies, 350 participants experienced at least one episode of delayed large local reaction (**Table 3**). Of these

**Table 1**  
**Characteristics of 13 authorized/approved COVID-19 vaccines as of April 21, 2021**

Vaccine Name(s)	Manufacturer(s)	Type	Country of Origin	Trial Phase with Published Data	Trial Time Frame	Age Group Tested
BNT162b2, Comirnaty	Pfizer-BioNTech, Fosun Pharma	mRNA	US, Germany	III	7/27/2020—11/14/2020	16+
mRNA-1273	Moderna, National Institute of Allergy and Infectious Diseases	mRNA	US	III	7/27/2020—10/23/2020	18+
AZD1222, ChAdOx1 nCoV-19	Oxford-AstraZeneca	Adenovirus	UK	I/II	4/23/2020—11/4/2020	18+
Sputnik V, Gam-COVID-Vac	Gamaleya Research Institute; Health Ministry of the Russian Federation	Recombinant adenovirus (rAd26, rAd5)	Russia	III	9/7/2020—11/24/2020	18+
Ad26.COV2.S, JNJ-78436735	Johnson & Johnson's Janssen Biotech	Nonreplicating viral vector	The Netherlands, US	I/IIa	7/22/2020—11/7/2020	18–55, 65+
CoronaVac	Sinovac Biotech	Inactivated (formalin with alum adjuvant)	China	I/II	Phase I: 4/16/2020—4/25/2020 Phase II: 5/3/2020—5/5/2020	18–59
BBIBP-CorV	China National Pharmaceutical Group (Sinopharm); Beijing Institute of Biological Products	Inactivated	China	I/IIa	5/18/2020—7/30/2020	18–59
EpiVacCorona	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	Peptide	Russia	I/III <sup>a</sup>	7/27/2020—Present	18–60
Convidicea, Ad5-nCoV	CanSino Biologics	Recombinant (adenovirus type 5 vector)	China	III	4/11/2020—4/16/2020	18+

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**Table 1**  
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Vaccine Name(s)	Manufacturer(s)	Type	Country of Origin	Trial Phase with Published Data	Trial Time Frame	Age Group Tested
Covaxin, BBV152	Bharat Biotech; Indian Council of Medical Research	Inactivated	India	I/II	9/5/2020—9/12/2020	12–65
WIBP-CorV	China National Pharmaceutical Group (Sinopharm); Wuhan Institute of Biological Products	Inactivated	China	I/II	4/12/2020—5/2/2020	18–59
CoviVac	Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products	Inactivated	Russia	I/II <sup>a</sup>	N/A	N/A
ZF2001	Anhui Zhifei Longcom Biopharmaceutical; Institute of Microbiology of the Chinese Academy of Sciences	Recombinant	China, Uzbekistan	I/II	Phase I: 6/22/2020—7/3/2020 Phase II: 7/12/2020—7/17/2020	18–59

<sup>a</sup> No data published yet as of April 22, 2021.

**Table 2**  
**Cutaneous side effects reported in the trial data of 11 authorized COVID-19 vaccines**

Vaccine name(s)	Erythema	Swelling	Tenderness	Pain	Induration	Pruritus	Other Skin Findings	Serious Cutaneous Reactions
BNT162b2, Comirnaty	Dose 1: 16–55 y: 5% >55 y 5% Dose 2: 16–55 y 6% >55 y 7%	Dose 1: 16–55 y 6% >55 y 7% Dose 2: 16–55 y 6% >55 y 7%	N/A	Dose 1: 16–55 y 83% >55 y 71% Dose 2: 16–55 y 78% >55 y 66%	N/A	N/A	N/A	None
mRNA-1273	Dose 1: 2.8% Dose 2: 8.6%	Dose 1: 6.1% Dose 2: 12.2%	Dose 1: 10.2% Dose 2: 14.2%	Dose 1: 83.7% Dose 2: 88.2%	N/A	N/A	Allergic, hand, atopic and contact dermatitis; eczema; exfoliative rash; hypersensitivity; injection site urticaria; erythematous rash; macular rash; maculopapular rash; pruritic rash; vesicular rash; urticaria; papular urticaria (<0.2%)	None
AZD1222, ChAdOx1 nCoV-19	Group 1a, 1b, 2a, 2b: Without paracetamol prophylaxis: 3% With paracetamol prophylaxis: 2%	Group 1a, 1b, 2a, 2b: Without paracetamol prophylaxis: 4% With paracetamol prophylaxis: 2%	Group 1a, 1b, 2a, 2b: Without paracetamol prophylaxis: 83% With paracetamol prophylaxis: 77%	Group 1a, 1b, 2a, 2b: Without paracetamol prophylaxis: 67% With paracetamol prophylaxis: 50%	Group 1a, 1b, 2a, 2b: Without paracetamol prophylaxis: 3% With paracetamol prophylaxis: 0%	Group 1a, 1b, 2a, 2b: Without paracetamol prophylaxis: 7% With paracetamol prophylaxis: 12%	One case each of psoriasis, rosacea, vitiligo and Raynaud phenomenon (<0.1%)	One case of severe cellulitis

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**Table 2**  
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Vaccine name(s)	Erythema	Swelling	Tenderness	Pain	Induration	Pruritus	Other Skin Findings	Serious Cutaneous Reactions	
	Group 3 None	Group 3 None	Group 3 Dose 1: 50% Dose 2: 50%	Group 3 Dose 1: 50% Dose 2: 20%	Group 3 None	Group 3 Dose 1: 10% Dose 2: 10%			
Sputnik V, Gam-COVID-Vac	N/A	N/A	N/A	N/A	N/A	N/A	Acneiform dermatitis, allergic rash, alopecia, indeterminate rash, petechial rash, and eczema ( $<0.1\%$ )	None	
Ad26.COV2.S, JNJ-78436735	7.3%	5.3%	N/A	48.6%	N/A	N/A	N/A	None	
CoronaVac	0/14 schedule: Dose 1: 3 $\mu$ g group: 0.8% 6 $\mu$ g group: None Dose 2: 3 $\mu$ g group: None 6 $\mu$ g group: 1.7% 0/28 schedule: Dose 1: 3 $\mu$ g group: None 6 $\mu$ g group: 0.8% Dose 2: None	0/14 schedule: Dose 1: 3 $\mu$ g group: 0.8% 6 $\mu$ g group: None Dose 2: 3 $\mu$ g group: 0.8% 6 $\mu$ g group: 2.5% 0/28 schedule: Dose 1: None Dose 2: 3 $\mu$ g group: None 6 $\mu$ g group: 0.9%	N/A	0/14 schedule: Dose 1: 3 $\mu$ g group: 9.2% 6 $\mu$ g group: 16.7% Dose 2: 3 $\mu$ g group: 13.3% 6 $\mu$ g group: 11.8% 0/28 schedule: Dose 1: 3 $\mu$ g group: 7.5% 6 $\mu$ g group: 10% Dose 2: 3 $\mu$ g group: 2.6% 6 $\mu$ g group: 5.9%	0/14 schedule: Dose 1: None Dose 2: 3 $\mu$ g group: 0.8% 0/28 schedule: None	0/14 schedule: Dose 1: None Dose 2: 3 $\mu$ g group: 0.8% 0/28 schedule: None	0/14 schedule: Dose 1: None Dose 2: 3 $\mu$ g group: 0.8% 0/28 schedule: None	N/A	One case of acute hyper- sensitivity with urticaria 48 h after dose 1 (6 $\mu$ g group)

BBIBP-CorV	1%	2%	N/A	16%	N/A	2%	Unspecified rash in 1 participant (<1%)	None
Convidicea, Ad5-nCoV	Low dose: 2% High dose: 1%	Low dose: 4% High dose: 4%	N/A	Low dose: 57% High dose: 56%	Low dose: 2% High dose: 2%	Low dose: 6% High dose: 2%	One case of buccal ulceration within 14 d One case of oral herpes	None
Covaxin, BBV152	Dose 1: 3µg group: 1% 6µg group: 1% Dose 2: None	N/A	N/A	Dose 1: 3µg group: 3% 6µg group: 3% Dose 2: 3µg group: 4% 6µg group: 2%	N/A	Dose 1: 3µg group: 1% 6µg group: 1% Dose 2: 3µg group: None 6µg group: 1%	One case of mild unspecified rash after dose 2 (3 µg group)	None
WIBP-CorV	Phase I (0, 28, 56-d group): Low dose: None Medium dose: None High dose: 4.2% Phase II 0 and 14-d group: Medium dose: None 0 and 21-d group: Medium dose: None	Phase I (0, 28, 56-d group): Low dose: 4.2% Medium dose: None High dose: 4.2% Phase II 0 and 14-d group: Medium dose: None 0 and 21-d group: Medium dose: 1.2%	N/A	Phase I (0, 28, 56-d group): Low dose: 20.8% Medium dose: 4.2% High dose: 25% Phase II 0 and 14-d group: Medium dose: 2.4% 0 and 21-d group: Medium dose: 14.3%	N/A	Phase I (0, 28, 56-d group): Low dose: None Medium dose: None High dose: None Phase II 0 and 14-d group: Medium dose: None 0 and 21-d group: Medium dose: 1.2%	N/A	None

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**Table 2**  
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Vaccine name(s)	Erythema	Swelling	Tenderness	Pain	Induration	Pruritus	Other Skin Findings	Serious Cutaneous Reactions
ZF2001	Phase I 25 µg group: 20% 50 µg group: 20% Phase II Two-dose group: 25 µg group: 8% 50 µg group: 8% Three-dose group: 25 µg group: 16% 50 µg group: 14%	Phase I 25 µg group: 5% 50 µg group: 15% Phase II Two-dose group: 25 µg group: 4% 50 µg group: 6% Three-dose group: 25 µg group: 14% 50 µg group: 13%	N/A	Phase I 25 µg group: 20% 50 µg group: 55% Phase II Two-dose group: 25 µg group: 3% 50 µg group: 5% Three-dose group: 25 µg group: 12% 50 µg group: 12%	Phase I 25 µg group: 10% 50 µg group: 25% Phase II Two-dose group: 25 µg group: 3% 50 µg group: 5% Three-dose group: 25 µg group: 9% 50 µg group: 7%	Phase I 25 µg group: 20% 50 µg group: 35% Phase II Two-dose group: 25 µg group: 6% 50 µg group: 9% Three-dose group: 25 µg group: 19% 50 µg group: 17%	One case of unspecified rash in the phase I trial (50 µg group) Three cases of unspecified rash in the phase II trial, 2-dose schedule, 25 µg group Four cases of unspecified rash in the phase II trial, 2-dose schedule, 50 µg group 2 cases of unspecified rash in phase II trial, three-dose schedule, 25 µg group One case of unspecified rash in phase II trial, three-dose schedule, 50 µg group	One case of unspecified grade ≥3 rash (50 µg group)

Abbreviation: N/A, not applicable.

**Table 3**  
**Reactive dermatoses to authorized COVID-19 vaccines reported in the nontrial literature<sup>a</sup>**

Article Reference	Study Design	Study Size	Study Period	Vaccine Name(s)	Cutaneous Reactions	Dose Number	Time to Onset after Vaccination	Time to Resolution	Intervention
<b>Delayed large local reactions</b>									
Fernandez-Nieto et al, <sup>24</sup> 2021	Retrospective study at a tertiary referral hospital in Spain	4775	1/11/2021–2/12/2021	BNT162b2/Comirnaty	103 participants with delayed large local reactions	Dose 1: 49/103 (47.6%) Dose 2: 54/103 (52.4%)	N/A	<8 h: 23/103 (22.3%) 8–24 h: 27/103 (26.2%) 48–72 h: 38/103 (36.9%) >72 h: 14/103 (13.6%)	N/A
Blumenthal et al, <sup>23</sup> 2021	Case series	12	N/A	mRNA-1273	12 participants with delayed large local reactions after dose 1 3 participants with similarly severe reactions, 3 participants with less severe reactions after dose 2	Dose 1: 12/12 (100%) Dose 2: 6/12 (50%)	Dose 1: 4–11 d (median 8 d) Dose 2: 1–3 d (median 2 d)	Dose 1: 2–11 d after onset (median, 6 d) Dose 2: N/A	Ice, antihistamines, glucocorticoids (topical, oral or both), antibiotics
McMahon et al, <sup>4</sup> 2021	Retrospective review of AAD/ILDS registry of vaccine-related cutaneous reactions	414	12/24/2020–2/14/2021	BNT162b2/Comirnaty mRNA-1273	BNT162b2/Comirnaty: 12 reports of delayed large local reactions mRNA-1273: 206 reports of delayed large local reactions	BNT162b2/Comirnaty: Dose 1: 5/34 (15%) Dose 2: 7/40 (18%) mRNA-1273: Dose 1: 175/267 (66%) Dose 2: 31/102 (30%)	BNT162b2/Comirnaty: N/A mRNA-1273: median 7 d after dose 1, median 3 d after dose 2	BNT162b2/Comirnaty: N/A mRNA-1273: median 4 d after dose 1; median 3 d after dose 2	Topical corticosteroids, oral antihistamines, pain relievers, antibiotics

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**Table 3**  
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Article Reference	Study Design	Study Size	Study Period	Vaccine Name(s)	Cutaneous Reactions	Dose Number	Time to Onset after Vaccination	Time to Resolution	Intervention
Wei et al, <sup>25</sup> 2021	Case series	4	N/A	mRNA-1273	Delayed large local reactions	Dose 1	Case 1: 8 d Case 2: 8 d Case 3: 7 d Case 4: 10 d	Case 1: N/A Case 2: 3 d Case 3: 4 d Case 4: 2 d	Case 1 and 2: topical corticosteroids, oral antihistamine Case 3 and 4: None
Ramos et al, <sup>27</sup> 2021	Case series	12	N/A	BNT162b2/Comirnaty mRNA-1273	BNT162b2/Comirnaty: 1 report of delayed large local reaction mRNA-1273 11 reports of delayed large local reactions	BNT162b2/Comirnaty: 1 case of delayed large local reaction after dose 2 only mRNA-1273 11 case of delayed large local reaction after dose 1 only	5–11 d (average 7 d)	3–8 d (average 5 d)	Topical corticosteroids, ice, oral antihistamines, pain relievers
Baek et al., 2021	Case report	1	N/A	BNT162b2/Comirnaty	Delayed large local reaction	Dose 1 only	6 d	5 d	N/A
Morbilloform rashes									
Jedlowski et al, <sup>30</sup> 2021	Case report	1	N/A	BNT162b2/Comirnaty	Morbilloform rash on lower back	Dose 1 and dose 2	Dose 1 and 2: 48 h	Dose 1 and 2: 24 h	None
CDC COVID-19 Response Team and FDA <sup>37</sup>	Case series	10	12/21/2020–1/10/2021	mRNA-1273	4 cases of morbilliform rash	Dose 1	5–45 min	N/A	Intramuscular epinephrine
CDC COVID-19 Response Team and FDA <sup>37</sup>	Case series	21	12/14/2020–12/23/2020	BNT162b2/Comirnaty	7 cases of morbilliform rash	Dose 1	2–25 min	N/A	Intramuscular epinephrine

Ackerman et al., <sup>29</sup> 2021	Case report	1	N/A	BNT162b2/ Comirnaty	Maculopapular exanthema (30% body surface area)	Dose 1 (dose 2 avoided)	3 h	>1 mo	Corticosteroids
Corbeddu et al., 2021	Case series	11	N/A	BNT162b2/ Comirnaty	3 cases of morbilliform rashes	Dose 2: 3/3 (100%)	Dose 2: 5 hours–3 days	2–3 d	None
McMahon et al., <sup>4</sup> 2021	Retrospective review of AAD/ILDS registry of vaccine-related cutaneous reactions	414	12/24/2020–2/14/2021	BNT162b2/ Comirnaty mRNA-1273	BNT162b2/ Comirnaty: 9 reports of morbilliform rash mRNA-1273 18 reports of morbilliform rash	BNT162b2/ Comirnaty: Dose 1: 6/9 (67%) Dose 2: 3/9 (33%) mRNA-1273 Dose 1: 11/18 (61%) Dose 2: 7/18 (39%)	Dose 1: Median of 3 d Dose 2: Median of 2 d	Dose 1: Median of 4.5 d Dose 2: Median of 2.5 d	Topical corticosteroids, oral antihistamines, pain relievers, antibiotics
Urticaria									
CDC COVID-19 Response Team and FDA <sup>37</sup>	Case series	10	12/21/2020–1/10/2021	mRNA-1273	1 case of urticaria	Dose 1	11 min	N/A	Intramuscular epinephrine
CDC COVID-19 Response Team and FDA <sup>37</sup>	Case series	21	12/14/2020–12/23/2020	BNT162b2/ Comirnaty	10 cases of urticaria	Dose 1	5–54 min	N/A	Intramuscular epinephrine
John M. Kelso, 2021	Case series	4	N/A	mRNA-1273	1 case of urticaria	Dose 1 (dose 2 refused)	1 min	N/A	Diphenhydramine, IV epinephrine, diazepam
Corbeddu et al., 2021	Case series	11	N/A	BNT162b2/ Comirnaty	2 cases of urticaria	Dose 1: 2/2 (100%)	Dose 1: 1 hour–2 days	2–3 d	None
Park et al., <sup>38</sup> 2021	Case report	1	N/A	BNT162b2/ Comirnaty	Urticaria with immediate anaphylaxis	Dose 1 only	3 min	2 d	Intramuscular epinephrine and diphenhydramine

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**Table 3**  
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Article Reference	Study Design	Study Size	Study Period	Vaccine Name(s)	Cutaneous Reactions	Dose Number	Time to Onset after Vaccination	Time to Resolution	Intervention
McMahon et al, <sup>4</sup> 2021	Retrospective review of AAD/ILDS registry of vaccine-related cutaneous reactions	414	12/24/2020–2/14/2021	BNT162b2/Comirnaty mRNA-1273	BNT162b2/Comirnaty: 17 reports of urticaria mRNA-1273 23 reports of urticaria	BNT162b2/Comirnaty: Dose 1: 9/17 (53%) Dose 2: 8/17 (47%) mRNA-1273 Dose 1: 16/23 (70%) Dose 2: 7/23 (30%)	BNT162b2/Comirnaty: Dose 1: 9 cases after 24 h Dose 2: 1 case within 24 h, 7 cases after 24 h mRNA-1273 Dose 1: 13 cases after 24 h 3 cases of unknown timing Dose 2: 2 cases within 24 h, 5 cases after 24 h	Dose 1: Median 5 d Dose 2: Median 3 d	Topical corticosteroids, oral antihistamines, pain relievers, antibiotics
<b>EM</b>									
Gambichler et al., 2021	Case report	1	N/A	BNT162b2/Comirnaty	Rowell's syndrome	Dose 1	1 d	N/A	Oral corticosteroids
McMahon et al, <sup>4</sup> 2021	Retrospective review of AAD/ILDS registry of vaccine-related cutaneous reactions	414	12/24/2020–2/14/2021	mRNA-1273	3 reports of EM	mRNA-1273 Dose 1: 3/3 (100%)	N/A	N/A	N/A

DIRs to hyaluronic acid dermal fillers

Munavalli et al, <sup>40</sup> 2021	Case series	2	N/A	BNT162b2/ Comirnaty mRNA-1273	BNT162b2/ Comirnaty 1 report of DIR to hyaluronic acid dermal fillers mRNA-1273 1 report of DIRs to hyaluronic acid dermal fillers	BNT162b2/ Comirnaty: Dose 2: 1/2 (50%) mRNA-1273 Dose 1: 1/2 (50%)	BNT162b2/ Comirnaty: Dose 2: 24 h mRNA-1273 Dose 1: 48 h	BNT162b2/ Comirnaty: Dose 2: 24 h mRNA-1273 Dose 1: Initiation of lisinopril at 48 h, resolved after 24 h	BNT162b2/ Comirnaty: Corticosteroids mRNA-1273: Antihistamines, acetaminophen, lisinopril
Munavalli et al, <sup>41</sup> 2021	Case series	4	N/A	BNT162b2/ Comirnaty mRNA-1273	BNT162b2/ Comirnaty 2 reports of DIRs to hyaluronic acid dermal fillers mRNA-1273 2 reports of DIRs to hyaluronic acid dermal fillers	BNT162b2/ Comirnaty: Dose 1: 1/2 (50%) Dose 2: 1/2 (50%) mRNA-1273 Dose 1: 16/23 (70%) Dose 2: 1/2 (50%)	BNT162b2/ Comirnaty: Dose 1: 10 d Dose 2: 2 d mRNA-1273 Dose 1: 18 h (recurred with dose 2) Dose 2: 24 h	BNT162b2/ Comirnaty: Dose 1: 7 d Dose 2: Initiation of lisinopril at 72 h, resolved after 24 h mRNA-1273 Dose 1: Initiation of lisinopril at 48 h, resolved after 24 h Dose 2: Initiation of lisinopril at 48 h, resolved after 72 h	Low-dose lisinopril
McMahon et al, <sup>4</sup> 2021	Retrospective review of AAD/ILDS registry of vaccine-related cutaneous reactions	414	12/24/2020–2/14/2021	BNT162b2/ Comirnaty mRNA-1273	BNT162b2/ Comirnaty: 1 report of DIR to hyaluronic acid dermal fillers mRNA-1273 8 reports of DIR to hyaluronic acid dermal fillers	BNT162b2/ Comirnaty: Dose 2: 1/1 (100%) mRNA-1273 Dose 1: 3/8 (38%) Dose 2: 5/8 (63%)	N/A	N/A	N/A

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**Table 3**  
(continued)

Article Reference	Study Design	Study Size	Study Period	Vaccine Name(s)	Cutaneous Reactions	Dose Number	Time to Onset after Vaccination	Time to Resolution	Intervention
<b>Local injection site reactions</b>									
McMahon et al, <sup>4</sup> 2021	Retrospective review of AAD/ILDS registry of vaccine-related cutaneous reactions	414	12/24/2020–2/14/2021	BNT162b2/Comirnaty mRNA-1273	BNT162b2/Comirnaty: 16 reports of local injection site reactions mRNA-1273 186 reports of local injection site reactions	BNT162b2/Comirnaty: Dose 1: 8/16 (50%) Dose 2: 8/16 (50%) mRNA-1273 Dose 1: 117/186 (63%) Dose 2: 69/186 (37%)	Dose 1: Median day 1 Dose 2: Median day 1	Dose 1: Median days 4 Dose 2: Median days 3	N/A
<b>Erythromelalgia</b>									
McMahon et al, <sup>4</sup> 2021	Retrospective review of AAD/ILDS registry of vaccine-related cutaneous reactions	414	12/24/2020–2/14/2021	BNT162b2/Comirnaty mRNA-1273	BNT162b2/Comirnaty: 3 reports of erythromelalgias mRNA-1273 11 reports of erythromelalgias	BNT162b2/Comirnaty: Dose 1: 1/3 (33%) Dose 2: 2/3 (67%) mRNA-1273 Dose 1: 5/11 (45%) Dose 2: 6/11 (55%)	Dose 1: Median day 7 Dose 2: Median day 1	Dose 1: Median days 5.5 Dose 2: Median days 3	N/A
<b>Lichen planus</b>									
Hiltun et al., 2021	Case report	1	N/A	BNT162b2/Comirnaty	Lichen planus flare	Dose 2	48 h	N/A	Topical corticosteroids
<b>Varicella zoster</b>									
Bostan et al., 2021	Case report	1	N/A	N/A	Varicella zoster flare	N/A	5 d	1 wk	Oral valacyclovir

McMahon et al, <sup>4</sup> 2021	Retrospective review of AAD/ILDS registry of vaccine-related cutaneous reactions	414	12/24/2020–2/14/2021	BNT162b2/Comirnaty mRNA-1273	BNT162b2/Comirnaty: 5 reports of varicella zoster mRNA-1273 5 reports of varicella zoster	BNT162b2/Comirnaty: Dose 1: 1/5 (20%) Dose 2: 4/5 (80%) mRNA-1273 Dose 1: 5/5 (100%)	N/A	N/A	N/A
<b>Herpes simplex</b>									
McMahon et al, <sup>4</sup> 2021	Retrospective review of AAD/ILDS registry of vaccine-related cutaneous reactions	414	12/24/2020–2/14/2021	N/A	4 reports of herpes simplex flares	N/A	N/A	N/A	N/A
<b>Pityriasis rosea</b>									
McMahon et al, <sup>4</sup> 2021	Retrospective review of AAD/ILDS registry of vaccine-related cutaneous reactions	414	12/24/2020–2/14/2021	BNT162b2/Comirnaty mRNA-1273	BNT162b2/Comirnaty: 3 reports of pityriasis rosea mRNA-1273 1 report of pityriasis rosea	BNT162b2/Comirnaty: Dose 1: 2/3 (67%) Dose 2: 1/3 (33%) mRNA-1273 Dose 1: 1/1 (100%)	N/A	N/A	N/A
Busto-Leis et al, <sup>47</sup> 2021	Case series	2	N/A	BNT162b2/Comirnaty	2 reports of pityriasis rosea	Dose 2	24 h, 7 d	N/A	N/A
<b>Pernio/chilblains</b>									
Kha et al, <sup>45</sup> 2021	Case report	1	N/A	mRNA-1273	1 report of pernio/chilblains	Dose 1 and 2	Dose 1: 2 d Dose 2: 3 d	Dose 1: 14 d Dose 2: 7 d	Topical corticosteroids

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**Table 3**  
(continued)

Article Reference	Study Design	Study Size	Study Period	Vaccine Name(s)	Cutaneous Reactions	Dose Number	Time to Onset after Vaccination	Time to Resolution	Intervention
McMahon et al, <sup>4</sup> 2021	Retrospective review of AAD/ILDS registry of vaccine-related cutaneous reactions	414	12/24/2020–2/14/2021	BNT162b2/Comirnaty mRNA-1273	BNT162b2/Comirnaty: 5 reports of pernio/chilblains mRNA-1273 3 reports of pernio/chilblains	BNT162b2/Comirnaty: Dose 1: 3/5 (60%) Dose 2: 2/5 (40%) mRNA-1273 Dose 1: 3/3 (100%)	N/A	N/A	N/A
Lopez et al, <sup>44</sup> 2021	Case report	1	1/2021	BNT162b2	Pernio/chilblains	Dose 2	3 d	>28 d	Clobetasol as needed, avoidance of cold exposure
<b>Petechiae</b>									
McMahon et al, <sup>4</sup> 2021	Retrospective review of AAD/ILDS registry of vaccine-related cutaneous reactions	414	12/24/2020–2/14/2021	BNT162b2/Comirnaty mRNA-1273	BNT162b2/Comirnaty: 1 report of petechiae mRNA-1273 3 reports of petechiae	BNT162b2/Comirnaty: Dose 1: 1/1 (100%) mRNA-1273 Dose 1: 1/3 (33%) Dose 2: 2/3 (67%)	N/A	N/A	N/A
<b>Purpura</b>									
Malayala et al, <sup>48</sup> 2021	Case report	1	3/2021	mRNA-1273	Brown to red purpuric, nonblanchable rash	Dose 1	1 d	N/A	Monitoring of platelet, liver, renal function panels; antihypertensives

**Abbreviations:** AAD, American Academy of Dermatology; CDC, Centers for Disease Control and Prevention; DIRs, delayed inflammatory reaction; EM, erythema multiforme; FDA, Food and Drug Administration; ILDS, International League of Dermatologic Societies; N/A, not applicable.

<sup>a</sup> Articles within each morphology group are organized in order of publication date.

350 individuals, 117 (33.4%) received the BNT162b2 vaccine and 233 (66.6%) received the mRNA-1273 vaccine (see **Table 3**).

Of note, female patients younger than 65 years of age consistently composed the majority of these delayed large local reactions, prompting the question of sex's role in vaccine response. Notably, women also comprise an overwhelming majority (>70%) of the national and international health care workforce.<sup>15–17</sup> Therefore, the observation may reflect a reporting bias, given that vaccination campaigns initially targeted health care professionals and that women may be more likely to visit their doctor. However, the cause is likely multifactorial, because biology is also at play. Women have stronger immune responses to foreign antigens than men, and decades of research have shown that although women exhibit a greater immune response to vaccines, they also experience more adverse events.<sup>18–22</sup>

Although studies varied in their reporting of characteristics, most of the delayed large local reactions were mild and transient, with few recurrences after the second dose. All delayed large local reactions reported in the nontrial literature resolved within 11 days. In the study by McMahon and associates,<sup>4</sup> only 11 participants developed reactions after both doses; all were mRNA-1273 vaccine recipients, and reactions after the second dose were frequently smaller in size with an earlier onset at a median of 2 days. Six of the 12 patients who received the mRNA-1273 vaccine in Blumenthal and colleagues<sup>23</sup> had recurrent reactions that were of lesser severity than those after the first dose and also occurred at a median of 2 days. Likewise, of the 11 patients who received the mRNA-1273 vaccine in Ramos and Kelso, 4 developed similar local reactions after the second dose with an onset of 2 to 3 days after injection. Although most delayed large local reaction reports in nontrial literature occurred with the mRNA-1273 vaccine, these findings have also been observed with the BNT162b2 vaccine. Of the 103 patients reported on by Fernandez-Nieto and colleagues<sup>24</sup> and who developed delayed large local reactions after the first dose of BNT162b2, one-half experienced similar recurrent reactions after the second dose (onset not reported).

The morphology of these delayed large local reactions ranged from erythematous targetoid patches to large plaques.<sup>4,24</sup> In 2 studies of mRNA-1273 vaccine recipients, lesion diameters ranged from 5.0 to 19.5 cm, with 7 of the 16 lesions labeled as grade 3 plaques ( $\geq 10$  cm in diameter).<sup>23,25</sup> Histology of these skin lesions revealed superficial and deep perivascular lymphocytic infiltrates with rare eosinophils and scattered mast

cells, confirming a delayed type, T-cell-mediated hypersensitivity reaction.<sup>23,24,26</sup> To date, no such findings have been reported with other non-mRNA COVID-19 vaccines and the exact etiology is still unknown. However, a delayed hypersensitivity reaction to polyethylene glycol, an allergen, may be one explanation because both BNT162b2 and mRNA-1273 vaccines contain this excipient.<sup>25</sup>

Treatment has not been necessary; most reactions are mild and resolve spontaneously. Although some patients were treated with ice, antihistamines, pain relievers, and glucocorticoids (topical, oral, or both), others received no intervention.<sup>4,23,24,26,27</sup> However, some patients received unnecessary antibiotics owing to concern for cellulitis or other infections, highlighting the need for more providers to recognize that these delayed large local reactions are benign and not a contraindication to the second dose.

### **Morbilloform Rashes**

Morbilloform and maculopapular exanthems have been described in 43 participants across 3 observational studies (see **Table 3**). Of these 43 individuals, 21 (49%) received the BNT162b2 vaccine and 22 (51%) received the mRNA-1273 vaccine (see **Table 3**). Of these cases, 11 (4 associated with mRNA-1273; 7 associated with BNT162b2) had been submitted to the Vaccine Adverse Event Reporting System (VAERS) and labeled by the Centers for Disease Control and Prevention (CDC) as part of an anaphylaxis reaction.<sup>28</sup>

Among the cases not characterized as anaphylaxis, most rashes occurred within 2 to 3 days after injection and resolved within 1 week. One recipient of the BNT162b2 vaccine developed a pruritic, maculopapular exanthem that persisted for more than 1 month. This patient, who had no significant past medical history or drug allergy, erupted in an erythematous rash over 30% of his body, including the face, trunk, upper extremities, and thighs, but sparing the oral and genital mucosa.<sup>29</sup> Histologic examination revealed lymphocytic perivascular infiltrates, consistent with maculopapular toxidermia.<sup>29</sup> Despite a lack of other systemic manifestations, the patient developed concomitant liver injury with slightly elevated aspartate transaminase and gamma-glutamyl transferase enzymes.<sup>29</sup> Given the persistence of this exanthem, the patient was advised to avoid the second dose, and gradually the rash and elevated liver enzymes improved with corticosteroids.<sup>29</sup> Another BNT162b2 vaccine recipient developed a pruritic morbilliform rash across his lower back 48 hours after injection; the rash self-resolved within

24 hours.<sup>30</sup> Upon receiving the second dose, he developed a recurrent and more robust morbilliform eruption involving not only the lower back, but also the flanks, proximal extremities, and upper back.<sup>30</sup> This rash also resolved within 24 hours without intervention.

Notably, morbilliform rashes have been reported in several cases of COVID-19 infection in both pediatric and adult populations.<sup>31–34</sup> Histologic examinations of such cases have revealed spongiosis and mild dermal perivascular lymphocytic infiltrates, suggesting an immune-mediated etiology rather than a direct viral effect.<sup>35</sup> Therefore, although the exact mechanism of COVID-19 vaccine-induced morbilliform rashes remains unknown, it is plausible that these cutaneous manifestations are also the result of an immune activation.

### **Urticaria**

Urticaria is defined as wheals (hives) that typically resolve within 24 hours.<sup>36</sup> It can either present as part of immediate hypersensitivity reactions, defined by the CDC as an onset within 4 hours after injection, or occur as similar reactions 4 hours after injection.<sup>37</sup> This delineation is important to recognize because the former are potential contraindications to the second dose.

There are 55 cases of urticaria among the 6 observational reports in nontrial literature (see **Table 3**). Of these 55 individuals, 30 (55%) received the BNT162b2 vaccine and 25 (45%) received the mRNA-1273 vaccine (see **Table 3**). Of these cases, 11 (1 associated with mRNA-1273 and 10 associated with BNT162b2) had been submitted to the Vaccine Adverse Event Reporting System (VAERS) and labeled by the CDC as part of an anaphylaxis reaction.<sup>28</sup> In contrast, in an analysis of 414 COVID-19 dermatology registry cases, none of the 40 urticaria reactions (17 associated with BNT162b2, 23 associated with mRNA-1273) were classified as an immediate hypersensitivity rash.<sup>4</sup>

One female patient in the report from Park and colleagues<sup>38</sup> developed pruritic urticaria on her extremities and face within 3 minutes after administration of the BNT162b2 vaccine. However, history and test results demonstrated a baseline proclivity to allergic reactions and revealed a previously undiagnosed, underlying cholinergic urticaria.<sup>38</sup> Given that she felt overheated while waiting in line for the dose, the anaphylaxis likely arose from heat-induced rather than vaccine-induced cholinergic urticaria. As such, she received the second dose in a cool, temperature-controlled room without incident.<sup>38</sup> This case illustrates that categorically denying patients a second dose based solely on an anaphylactic reaction

may erroneously prevent patients from reaping the benefits of immunization, because not all cases of anaphylaxis are directly vaccine related.

### **Delayed Inflammatory Reactions to Dermal Hyaluronic Acid Fillers**

Hyaluronic acid fillers are increasingly resistant to biodegradation, resulting in longevity and more delayed inflammatory reactions (DIRs) to these implants. Among the known triggers of DIRs to fillers include viral illness, low-quality products, dental procedures, influenza vaccines, and, most recently, COVID-19 vaccines.<sup>4,39,40</sup> To date, 15 cases have been reported across 3 observational studies. Of these reports, 11 (73%) are associated with the mRNA-1273 vaccine and 4 (27%) are associated with the BNT162b2 vaccine (see **Table 3**).

In many cases, DIRs occurred to fillers that had been injected more than 1 to 2 years before the COVID-19 vaccination.<sup>40</sup> These reactions developed rapidly, often within 24 to 48 hours, and presented as swelling and inflammation focused around areas previously treated with fillers.<sup>39,40</sup> Most cases were recalcitrant to antihistamines, hyaluronidase, and acetaminophen.<sup>39,40</sup>

However, a novel mechanism for these reactions has been proposed, generating a potential pathogenesis-based treatment. Previous research revealed high expression of angiotensin-converting enzyme (ACE) 2 receptors in adipose tissue, where most fillers are injected.<sup>40</sup> These receptors are targeted by the SARS-CoV-2 spike protein, and the resulting interaction in the skin releases a proinflammatory cascade, which may explain the DIRs to hyaluronic acid fillers seen in COVID-infection.<sup>41</sup> By blocking the production of angiotensin II and thus reducing the substrate for ACE2, ACE inhibitors (ACE-I) in effect promote an anti-inflammatory response.<sup>39,40</sup> Indeed, upon initiation with oral lisinopril, all DIRs resolved completely within 24 to 72 hours.<sup>39,40</sup> Despite the success of ACE-Is in treating DIRs, further research on the proposed mechanism of action is warranted.

Important factors to consider when treating these reactions with ACE-Is include laboratory tests to assess for metabolic disturbances, especially if a patient is on medications that could interact with ACE-Is.<sup>39,40</sup> Given that treatment of DIRs to hyaluronic acid fillers do not require a long course of ACE-Is, a brief discontinuation of concurrent drugs may suffice.

### **Pernio and Chilblains**

Pernio-like lesions have been observed in COVID-19 infected individuals since the beginning of the

pandemic.<sup>42,43</sup> Only recently have they also been associated with COVID-19 vaccines. Of the 10 cases described across 3 observation studies, 6 (60%) were associated with the BNT162b2 vaccine, and the rest were associated with the mRNA-1273 vaccine.

Pernio-like lesions tend to present as painless, erythematous, and violaceous papules and macules on the hands and feet, with some cases exacerbated by cold exposure.<sup>44,45</sup> Histopathologic examinations of these vaccine-associated lesions reveal dense, perivascular lymphocytic infiltrates in the superficial to deep dermis, confirming the pernio diagnosis.<sup>44,45</sup> With topical corticosteroids, these lesions can resolve in 1 week to 1 month.<sup>44,45</sup>

The appearance of pernio lesions not just during COVID-19 infection, but also after vaccination suggests that the vaccines and SARS-CoV-2 activate a similar immune pathway. Although the mechanism remains unclear, these findings suggest that the pernio lesions seen in COVID-19 infection and after vaccination may be less directly related to viral effects.

### Other Reactions

Reports of other cutaneous reactions include early-onset local injection site reactions, erythromelalgia, erythema multiforme, lichen planus, varicella zoster and herpes simplex reactivation, pityriasis rosea-like reactions, petechial rash, and purpuric rash (see **Table 3**). Local injection site reactions occurring within 3 days of vaccination were the second most common skin manifestations observed in the analysis of 414 COVID-19 dermatology registry cases.<sup>4</sup> Of the 202 cases of local injection site reactions, 186 (92%) were attributed to the mRNA-1273 vaccine.<sup>4</sup> These findings were also widely reported in clinical trial data, but less frequently discussed in the nontrial literature, likely because this pattern of reactogenicity is commonly observed in other vaccines.<sup>46</sup>

Some reactions, such as erythromelalgia, erythema multiforme, and pityriasis rosea, mimic known cutaneous manifestations of COVID-19 infection. Of the 14 reports of erythromelalgia, 11 (79%) were associated with the mRNA-1273 vaccine.<sup>4</sup> Of the 4 cases of erythema multiforme, 3 (75%) were associated with the mRNA-1273 vaccine, and among the 6 reports of pityriasis rosea, 5 (83%) were associated with the BNT162b2 vaccine.<sup>4,40,47</sup> Similarly, varicella zoster and herpes simplex reactivations have also been reported with COVID-19 infection cases and after COVID-19 vaccinations (see **Table 3**). Rarer reactions include a flare of previously well-controlled lichen

planus, as well as petechial and purpuric rash, the latter of which has been associated with thrombocytopenia after the mRNA-1273 vaccine.<sup>48</sup>

### SUMMARY

As of April 2021, more than 1 billion COVID-19 vaccine doses have been administered worldwide.<sup>49</sup> Although these vaccines are instrumental against the pandemic, important knowledge gaps remain, such as our understanding of the mechanistic relationship between these vaccines and their associated cutaneous side effects.

Currently, no reactive dermatoses have been recorded outside of trial data for vaccines other than BNT162b2 and mRNA-1273. However, the COVID-19 vaccine frontier is evolving rapidly. We have summarized the latest clinical trial data for authorized COVID-19 vaccines as of April 15, 2021, and described the associated cutaneous manifestations reported in nontrial literature. Recognition of these common and emerging reactions has key implications for vaccine strategy because concerns about reactogenicity can significantly influence an individual's willingness to return for a second dose. Because the benefits of immunization far outweigh the risks, it is crucial for health care providers, particularly dermatologists, to recognize our role in encouraging vaccine completion, educating our patients, and allaying their fears.

### CLINICS CARE POINTS

- The most common cutaneous manifestations of COVID-19 vaccination in clinical trials were local injection site reactions, of which there is a higher incidence in individuals younger than 60 years.
- The most common cutaneous manifestation of COVID-19 vaccination in real-world settings is delayed large local reactions, of which two-thirds were associated with the mRNA-1273 vaccine and one-third was associated with the BNT162b2 vaccine.
- Other reactive dermatoses to COVID-19 vaccines in real-world settings include morbilliform rashes, urticaria, erythema multiforme, delayed inflammatory reactions to dermal fillers, erythromelalgia, lichen planus, varicella zoster, herpes simplex, pityriasis rosea, petechiae, purpura. Most are self-limiting and resolve with topical steroids or oral medications.

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## DISCLOSURE

Dr. Freeman is the Principal Investigator of the AAD/ILDS COVID-19 Dermatology Registry. The authors have nothing to disclose.

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