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Clinical and pathologic correlation of cutaneous COVID-19 vaccine reactions including V-REPP: A registry-based study

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Background: Cutaneous reactions after COVID-19 vaccination have been commonly reported; however, histopathologic features and clinical correlations have not been well characterized.

Methods: We evaluated for a history of skin biopsy all reports of reactions associated with COVID-19 vaccination identified in an international registry. When histopathology reports were available, we categorized them by reaction patterns.

Results: Of 803 vaccine reactions reported, 58 (7%) cases had biopsy reports available for review. The most common histopathologic reaction pattern was spongiotic dermatitis, which clinically ranged from robust papules with overlying crust, to pityriasis rosea-like eruptions, to pink papules with fine scale. We propose the acronym "V-REPP" (vaccine-related eruption of papules and plaques) for this spectrum. Other clinical patterns included bullous pemphigoid-like (n = 12), dermal hypersensitivity (n = 4), herpes zoster (n = 4), lichen planus-like (n = 4), pernio (n = 3), urticarial (n = 2), neutrophilic dermatosis (n = 2), leukocytoclastic vasculitis (n = 2), morbilliform (n = 2), delayed large local reactions (n = 2), erythromelalgia (n = 1), and other (n = 5).

Limitations: Cases in which histopathology was available represented a minority of registry entries. Analysis of registry data cannot measure incidence.

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Conclusion: Clinical and histopathologic correlation allowed for categorization of cutaneous reactions to the COVID-19 vaccine. We propose defining a subset of vaccine-related eruption of papules and plaques, as well as 12 other patterns, following COVID-19 vaccination. (J Am Acad Dermatol 2022;86:113-21.)

Key words: Ad26.COV2.S; AZD1222; BNT162b2; bullous pemphigoid; chilblains; COVID-19; delayed large local; dermal hypersensitivity reaction; dermatology; dermatopathology; erythema multiforme; erythromelalgia; Johnson & Johnson Janssen; lichen planus; Moderna; morbilliform; mRNA-1273; Oxford-AstraZeneca; papular; papulosquamous; pathology; pernio; Pfizer-BioNTech; pityriasis rosea; psoriasis; registry; SARS-CoV-2; Stevens-Johnson syndrome; urticaria; vaccine; zoster.

INTRODUCTION

As of June 2021, a total of 1.84 billion doses of COVID-19 vaccines have been administered globally.[1] The Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2) vaccines, which use a novel mRNA technology, have been reported to cause various dermatologic side effects, such as delayed large local reactions, local injection site reactions, urticaria, morbilliform reactions, erythromelalgia, zoster, pernio, and cosmetic filler reactions.[2-4] The Johnson and Johnson (Ad26.COV2.S) vaccine, which uses a nonreplicating viral vector, appears to have relatively fewer dermatologic side effects, with the clinical trial reporting only local injection site reactions.[5] The Oxford-AstraZeneca (AZD1222) trial reported local injection site reactions and 1 case each of psoriasis, rosacea, vitiligo, and Raynaud's syndrome, although real-world studies are lacking.[4,6]

Although clinicopathologic correlation is key to understanding the pathophysiology, to our knowledge there have been no systematic studies examining the clinicopathologic correlations between the cutaneous reactions associated with COVID-19 vaccine across a broad spectrum of reaction patterns and their accompanying histopathology. Hence, the purpose of this study was to improve the characterization of dermatologic reactions to COVID-19 vaccination through an analysis of biopsy reports and corresponding clinical photographs from cases entered into an international COVID-19 dermatology registry. Given that a growing percentage of the world's population is being vaccinated, such data may aid with the diagnosis of cutaneous side effects of COVID-19 vaccination.

CAPSULE SUMMARY

- In this registry-based study, we observed diverse COVID-19 vaccine-associated cutaneous reactions, including papulovesicular, pityriasis rosea-like, and papulosquamous eruptions classified as vaccine-related eruption of papules and plaques.
- This detailed study using the clinical and histopathologic correlation of 13 reaction patterns may aid with the diagnosis of cutaneous side effects from the COVID-19 vaccine.

METHODS

In December 2020, our international COVID-19 dermatology registry, established in collaboration with the American Academy of Dermatology and the International League of Dermatological Societies, began collecting reports of patients with cutaneous reactions to COVID-19 vaccination (www.aad.org/covidregistry).[2,7] Entry of de-identified patient cases was restricted to only health care workers. The Massachusetts General Brigham Institutional Review Board exempted this study as not human subject research.

The registry collected data regarding COVID-19 vaccination and characteristics of the cutaneous reactions.[2] As in prior work, we defined a wheal on the vaccinated arm as a local injection site reaction if it occurred within 3 days of the first dose of vaccination and a delayed large local reaction if it occurred more than 4 days after vaccination.[2] Additionally, the registry queried whether a skin biopsy report was available and asked for full details of any biopsy reports. Physicians and other health care providers who entered pending or incomplete biopsy reports were contacted for updates and additional clarifying information. For records where full biopsy reports were available, health care providers were then contacted to request de-identified patient photos.

Biopsy reports, and clinical photographs when available, were reviewed by 4 board-certified dermatologists (Drs Kovarik, Damsky, Fox, and Freeman), 2 of whom are dermatopathologists (Drs Kovarik and Damsky); these were organized by group reaction patterns and histopathologic findings into

Abbreviations used:

IQR: interquartile range
V-REPP: vaccine-related eruption of papules and plaques

harmonized clinical and histopathologic entities. We used Stata (version 16, StataCorp LLC) to analyze data.

RESULTS

From December 24, 2020 to May 19, 2021, health care providers entered 803 cases of COVID-19 vaccine-related cutaneous reactions into the American Academy of Dermatology or International League of Dermatological Societies registry. A portion of these cases (n = 414) have been previously reported without pathology.[2] Of the 803 cases, vaccine manufacturers overall were Moderna (69%), Pfizer (25%), Johnson and Johnson (1.0%), Oxford-AstraZeneca (0.6%), and unspecified (4.4%). The most commonly reported morphologies were local injection site reactions, delayed large local reactions, urticaria, morbilliform, zoster, and papulosquamous eruptions (Supplemental Table I; available via Mendeley at https://data.mendeley.com/datasets/cyxcbmc5zc/1.) Cases were reported by dermatologists (46%), other physicians (22%), mid-level providers (9.2%), nurses (9.1%), and other health care providers (13%).

Of the 803 cases, 78 providers (9.7%) indicated that a skin biopsy was performed. Records listed as pending (n = 15) or incomplete (n = 5) were not included, leaving 58 (7%) complete biopsy reports for review (Table I). The median age of these 58 patients was 61 years (interquartile range [IQR], 44-77); 62% were women, 75% were White, and 95% were from the United States. The majority of cases for whom skin biopsy reports were available were reported by dermatologists (94%). Vaccine manufacturers were Moderna (46%), Pfizer (42%), Johnson and Johnson (1.7%), Oxford/AstraZeneca (1.7%), and unspecified (8.6%).

For patients receiving vaccines requiring 2 doses (ie, primarily Moderna/Pfizer), 55% of biopsy reports were taken following the first dose. Of note, 8 patients biopsied after the first dose were not planning to receive the second dose, given the severity of the cutaneous reaction. These included 2 cases of leukocytoclastic vasculitis, 2 cases of papulosquamous eruptions, 1 case of urticaria, 1 case of dermal hypersensitivity reaction, 1 case of bullous pemphigoid, and 1 case of Stevens-Johnson syndrome.

Clinicopathologic correlation revealed 13 different COVID-19 vaccine reaction patterns where biopsy reports were evaluable: vaccine-related eruption of papules and plaques (V-REPP) (n = 15), bullous pemphigoid-like (n = 12), dermal hypersensitivity reactions (n = 4), herpes zoster (n = 4), lichen planus-like (n = 4), pernio (n = 3), urticaria (n = 2), neutrophilic dermatosis (n = 2), leukocytoclastic vasculitis (n = 2), morbilliform (n = 2), delayed large local reactions (n = 2), erythromelalgia (n = 1), and other (n = 5), including Stevens-Johnson syndrome (n = 1) and erythema multiforme (n = 1). Clinical photographs correlated with histopathology are shown in Supplemental Fig 1 (available via Mendeley at https://data.mendeley.com/datasets/cyxcbmc5zc/1.)

The histologic reaction pattern most commonly biopsied was a spectrum of spongiotic dermatitis after Moderna (40%), Pfizer (47%), Oxford-AstraZeneca (6.7%), and unspecified (6.7%) vaccines. These vaccine-related eruptions of papules and plaques, which we call V-REPP (Fig 1), clinically had papules and/or plaques with surface changes. They ranged on a clinical spectrum from edematous and crusted papules (robust), to edematous and erythematous scaly papules and plaques resembling pityriasis rosea-like changes (moderate), to subtle scaly papules and plaques (mild). The findings were clinically diverse, but had similar histopathology, which existed on a spectrum related to the degree of spongiosis present on the biopsy compared to the degree of interface changes. Robust V-REPP on biopsy showed marked spongiosis with intraepidermal vesicles and minimal to no interface changes (biopsy reports, n = 3). Moderate V-REPP showed moderate spongiosis more often than interface changes (n = 8). Mild V-REPP demonstrated mild spongiosis and more-prominent interface changes (n = 4). Eosinophils were commonly present in the cases with marked spongiosis and were less likely to be present in the cases with minimal spongiosis.

The median time to V-REPP was 12 (IQR, 4-16) days after COVID-19 vaccination. Robust V-REPP occurred at a median of 5.5 (IQR, 4-7) days after vaccination and lasted up to 49 days at the time of reporting. However, because 100% of these eruptions were ongoing at the time of reporting, the natural history of the cutaneous reaction has yet to be determined. Moderate V-REPP occurred a median of 13 (IQR, 4-19) days after vaccination and lasted up to 90 days, with 88% ongoing at the time of reporting. For several of the cases that were pityriasis rosea-like, V-REPP started after the first dose of the mRNA vaccine and then flared with the second dose. Mild V-REPP occurred a median of 16 (IQR, 14-18) days after vaccination and lasted up to 18 days, with 50% ongoing at the time of reporting.

Table I. Categorization of clinical and histopathologic features of COVID-19 vaccine cutaneous reactions*

Clinical reaction pattern		Age (range), y	Vaccine brand (%)	Distribution	Morphology (based on clinical photograph review)	Histopathology
V-REPP (n = 15)						
Robust	Papulovesicular (n = 3)	29-81	Moderna (33%), Pfizer (67%)	Trunk, extremities > neck, face, head	Discrete edematous papules, some with central vesiculation and crusting	Spongiotic dermatitis as robust intercellular edema with intraepidermal vesicles, papillary dermal edema, and dermal eosinophils; interface changes may or may not be present
Moderate	Pityriasis rosea-like (n = 8)	41-82	Moderna (38%), Pfizer (50%), Oxford-AstraZeneca (12%)	Trunk, extremities > face	Oval, pityriasis rosea-like pink edematous papules and plaques, some with central crust and some with trailing scale	Spongiotic dermatitis >> interface changes and dermal eosinophils are often present
Mild	Papulosquamous with subtle scale (n = 4)	31-71	Moderna (50%), Pfizer (25%), Unspecified (25%)	Trunk, extremities	Oval or annular pink thin papules coalescing into plaques, with mild surface changes and subtle scale	Spongiosis as mild intercellular edema and vacuolar interface changes are present and may be focal; eosinophils may or may not be present
Bullous pemphigoid-like (n = 12)		42-97	Moderna (36%), Pfizer (64%)	Trunk, extremities > face, head, neck, oral mucosa, genital mucosa	Tense unilocular clear fluid-filled bullae on an erythematous base	Subepidermal blister formation and mixed inflammation with eosinophils • C3d: 0/1 positive • DIF: 5/8 positive for linear IgG and C3 BMZ, 1/8 positive for only IgG BMZ • ELISA: 1/1 positive BP180
Dermal hypersensitivity reaction (n = 4)		34-83	Moderna (25%), Pfizer (25%), Unspecified (25%)	Trunk, extremities > face, neck	Pink edematous papules coalescing into plaques without surface change; individual lesions last >24 h	Perivascular infiltrate with mixed inflammation, which may include lymphocytes, neutrophils, and eosinophils

Herpes zoster (n = 4)					
	39-78	Moderna (50%), Pfizer (12%), Johnson and Johnson (25%)	Trunk, extremities, face	Grouped vesicles on an erythematous base not crossing the midline	All with viral cytopathic changes present. Involvement of the hair follicle in 2 of 4 cases
Lichen planus-like (n = 4)					
	31-72	Moderna (25%), Pfizer (75%)	Trunk, extremities	No clinical images	Lichenoid interface dermatitis; dermal eosinophils may be present
Pernio (n = 3)					
	22-60	Moderna (33%), Pfizer (67%)	Fingers, toes	Pink to violaceous papules of the toes? fingers too? Maybe just say toes > fingers or digits?	Perivascular lymphocytic infiltrate with papillary dermal edema and interface changes
Urticaria (n = 2)					
	47-68	Moderna (50%), Pfizer (50%)	Trunk, extremities, face	Erythematous, well-circumscribed papules and plaques without surface change lasting < 24 h	Dermal edema with sparse perivascular lymphocytes, neutrophils and eosinophils
Neutrophilic dermatosis (n = 2)					
	68-93	Moderna (50%), Pfizer (50%)	Trunk, extremities, face	Bright red to violaceous dermal papules and plaques	Dense dermal neutrophilic infiltrate with papillary dermal edema; leukocytoclasis and secondary vasculitic changes may be present
Leukocytoclastic vasculitis (n = 2)					
	57-61	Moderna (50%), Pfizer (50%)	Lower extremities	Deep red to maroon palpable purpura	Epidermal infiltrate of neutrophils and extravasated erythrocytes with perivascular neutrophils and leukocytoclasis
Morbilliform (n = 2)					
	50-85	Moderna (100%)	Trunk, extremities	No clinical images	Perivascular mixed infiltrate; interface changes may be present

Continued

Table I. Cont'd

Clinical reaction pattern	Age (range), y	Vaccine brand (%)	Distribution	Morphology (based on clinical photograph review)	Histopathology
Delayed large local reactions (n = 2)					
	27-35	Moderna (100%)	Vaccinated arm	Indurated, erythematous plaque	Superficial perivascular and perifollicular lymphocytic infiltrate with rare eosinophils and scattered mast cells
Erythromelalgia (n = 1)					
	27	Moderna (100%)	Hands, feet	Erythematous, edematous hands and feet (with burning sensation)	Superficial and deep perivascular inflammation and edema
Other (n = 5)					
Stevens-Johnson Syndrome	46	Moderna (100%)	All skin surfaces, oral and genital mucosa	Atypical targetoid papules with duskiness, bullae, and epidermal necrosis in the center; hemorrhagic crusting on the vermillion lips; lesions involved palms and soles	Full-thickness epidermal necrosis
Erythema multiforme	42	Moderna (100%)	Arms, hands	Erythematous, targetoid papules and plaques	Spongiotic and vacuolar interface dermatitis
Granuloma annulare	85	Pfizer (100%)	Trunk	No clinical images	Interstitial granulomatous reaction
Tattoo sarcoidal reaction	38	Moderna (100%)	Leg	No clinical images	Tattoo with suppurativa granulomatous inflammation
New onset psoriasis	67	Moderna (100%)	Trunk, extremities, head, neck, face	Well demarcated erythematous papules and plaques with overlying silvery scale	Epidermal acanthosis, confluent parakeratosis with trapped clusters of neutrophils, and focal spongiform pustule formation. Diminished thickness of granular layer

BMZ, Basement membrane zone; *BP*, blood pressure; *DIF*, direct immunofluorescence; *ELISA*, enzyme-linked immunosorbent assay; *IgG*, immunoglobulin G; *V-Repp*, vaccine-related eruptions of papules and plaques.

*These data from 58 biopsy reports represent a subset of the overall 803 cases in the registry, where biopsy was performed and the report was available for review. For clinical photos of these reactions see Supplemental Fig 1.

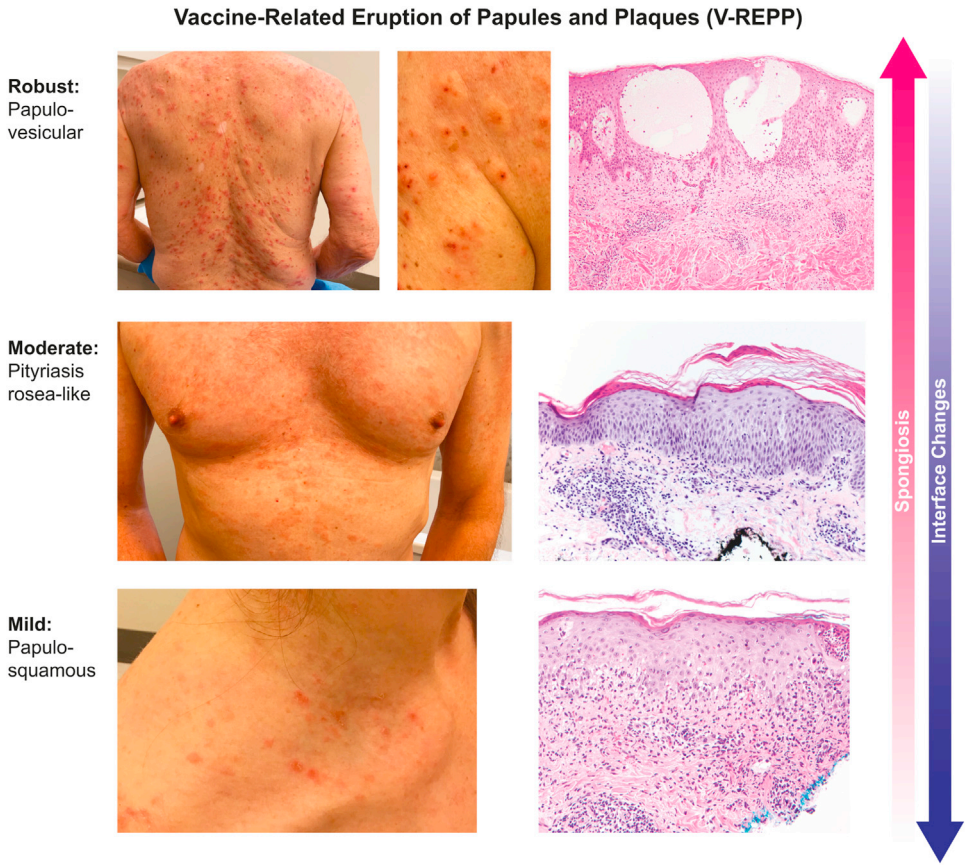

Fig 1. Spectrum of V-REPP following COVID-19 vaccination by degree of spongiosis and interface changes present on histopathology. *V-REPP*, Vaccine-related eruption of papules and plaques.

DISCUSSION

In this registry-based study, we grouped 58 biopsy reports and clinical photographs of COVID-19 vaccine reactions into 13 patterns, with the most common categories including V-REPP, bullous pemphigoid-like, dermal hypersensitivity reactions, herpes zoster, lichen planus-like, and pernio. The relative frequency of these biopsy-proven categories differs from the overall 803 dermatologic vaccine reactions in the registry, possibly because providers were less likely to biopsy common and well-described vaccine side effects, such as local injection site reactions, delayed large local reactions, morbilliform eruptions, and urticaria. For example, for delayed large local reactions occurring 4 days or more after vaccination, there were 301 total reports in the registry but just 2 were biopsied.

The most commonly biopsied reactions in the registry were what we describe here as V-REPP (Fig 1). The histopathologic spectrum of V-REPP all showed some degree of spongiosis, ranging from significant spongiosis with intraepidermal vesicle formation (robust V-REPP), to pityriasis rosea-like changes (moderate V-REPP), to minimal spongiosis (mild V-REPP). One previously reported case of pityriasis rosea-like eruption following a second dose of the Pfizer vaccine similarly showed spongiosis with interface changes.[8] Pityriasis rosea-like eruptions have previously been described after vaccination for smallpox, tuberculosis, polio, influenza, papillomaviruses, diphtheria, tetanus, hepatitis B, pneumococcus, and yellow fever.[9] Unlike classic pityriasis rosea, pityriasis rosea-like reactions following vaccination or medications may lack herald patches and may feature a more diffuse papulosquamous exanthem, similar to what we observed in the registry.[9] Although the more robust papulovesicular spectrum of V-REPP can clinically mimic an id reaction, there are several key distinctions. An id reaction or autoeczematization, is generally a dermatitis distant to an initial site of inflammation or infection; it is not usually seen after vaccination, and would not typically have the same spectrum of clinical and pathologic changes.[10]

The mechanism of V-REPP after COVID-19 vaccination is unknown, but the delayed occurrence of these reactions suggests 2 potential mechanisms: (1) delayed hypersensitivity response to vaccination; or (2) T-cell-mediated skin reaction due to molecular mimicry with a viral epitope. In fact, infection with SARS-CoV-2 itself has been associated with pityriasis rosea-like eruptions.[11] Histopathology of pityriasis rosea-like eruptions following SARS-CoV-2 infection have similarly been reported to demonstrate spongiosis and a superficial perivascular lymphocytic infiltrate.[12] However, robust V-REPP, in which papulovesicles may be observed due to exuberant spongiosis, appear to be different from other vesicular eruptions caused by true SARS-CoV-2 infection. Vesicular eruptions by SARS-CoV-2 infection show vacuolar degeneration on biopsy and have been proposed to relate to direct cytotoxic effects of the virus.[13,14] Lesional biopsy demonstrated interface changes, with parakeratosis and scattered dyskeratotic keratinocytes.

Histopathologic features of the more-common reaction patterns to Moderna and Pfizer vaccines have been previously described in the literature. Similar to our findings, histopathology of delayed large local reactions showed perivascular lymphocytic infiltrates with eosinophils and mast cells, consistent with a delayed T-cell-mediated hypersensitivity reaction.[15-17] Morbilliform eruptions after vaccination similarly demonstrated perivascular lymphocytic inflammation.[18] Additionally, some cutaneous vaccine reactions, such as pernio/chilblains, had similar morphology and histopathology to pernio described in association with SARS-CoV-2 infection.[11,19-21]

Biopsy reports of additional dermatologic morphologies were also reported in the registry, such as lichen planus, neutrophilic dermatoses, and psoriasis (Supplemental Fig 1). COVID-19 vaccines can elicit strong T- and B-cell responses against SARS-CoV-2. Their role and the mechanism by which they might elicit off-target immune-stimulatory effects, including provoking T-cell dependent disorders, requires further study.[22,23] We also observed other immune-mediated dermatologic disorders, such as bullous pemphigoid and leukocytoclastic vasculitis, potentially driven by off-target immune activation following COVID-19 vaccination.[24] These shifts in the immune response after vaccination may also be associated with reactivation of other viruses; eg, 4 cases of confirmed herpes zoster with viral cytopathic changes observed in the registry.[25,26]

Although these cutaneous reactions may lead to hesitation in receiving future vaccine doses, it is important for patients and providers alike to recognize that in the cases of 2-dose vaccines, most eruptions, across a broad range of different reaction patterns, did not lead to anaphylaxis or severe adverse events with the second dose. It is important to distinguish cutaneous reactions that can be managed after a second dose (the majority of cases) versus the rare reactions that represent absolute contraindications.[2,27] We did receive 1 report of biopsy confirmed Stevens-Johnson syndrome following vaccination, which represents an absolute contraindication to second-dose vaccination.[28]

Our observational registry-based study has multiple limitations. Our overall registry case numbers may not be representative of the true incidence or prevalence of vaccine-associated cutaneous reactions, as providers may be more likely to submit more-severe or uncommon cases to the registry. Additionally, biopsy reports may be less representative of cutaneous vaccine reactions overall, given provider predilection to reserve biopsies for unusual and/or previously undescribed conditions, rather than taking biopsies of more-common or easily recognized conditions. This study is also limited in generalizability, because patients in the registry were predominantly from the United States where vaccine roll out has been greatest for mRNA-based vaccines. Additionally, this study relied on the text entered from biopsy reports and clinical photographs, which may oversimplify the interpretation of histopathologic and in-person evaluations. Another limitation is that the V-REPP classification was not part of the original registry entry choices, because this classification was developed during data analysis. These cases were reclassified after review of photographs and pathology reports by the authors of the study.

In conclusion, this case series demonstrated the clinical and histopathologic characteristics of multiple dermatologic conditions after COVID-19 vaccination. We hope these data will aid physicians and other providers in the diagnosis of dermatologic conditions associated with the COVID-19 vaccine, which will likely be encountered more frequently as vaccine distribution expands globally.

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Conflicts of interest

Drs Freeman, Hruza, Rosenbach, Lipoff, Fox, and Thiers are members of the American Academy of

Dermatology COVID-19 Ad Hoc Task Force. Dr French is the President and Dr Lim a board member of the International League of Dermatological Societies. Dr Thiers is the Immediate Past President of the American Academy of Dermatology. Dr Freeman is an author of COVID-19 dermatology for UpToDate. Drs McMahon, Kovarik, Damsky, Nazarian, Desai, and Blumenthall and Authors Tyagi, Chamberlin, and Fathy have no conflicts to declare.

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