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Skin reactions to COVID-19 vaccines: An American Academy of Dermatology/International League of Dermatological Societies registry update on reaction location and COVID vaccine type

To the Editor: We thank the authors for their reply to our article and would like to clarify the concerns described.[1] The letter noted that the distribution of COVID-19 vaccine skin reactions was unclear and suggested we delineate each reaction pattern as local, distant, or generalized.[1] While we did not specify the body part affected by each reaction, we would also like to highlight the challenges with adopting the proposed local/distant/generalized approach. Patients often experienced multiple reactions simultaneously, including reactions both local and distant to the injection site. For instance, patients can exhibit concurrent, delayed large local reactions at the injection site and papulovesicles of the elbow/hand.[2] Others had local reactions combined with generalized morbilliform eruptions.[1] We do agree that at the level of the reaction pattern, certain eruptions were typically more generalized (such as morbilliform, urticaria, or vaccine-related eruption of papules and plaques[3]), while others usually occurred at/near the injection site (local injection site reactions and delayed large local reactions). Others are harder to classify with regard to location: erythema multiforme and vasculitis, for example, could be either distal, in one location (for example, hands/feet only) or generalized.

Our study also captured an extensive vaccine reactogenicity profile. Reactogenicity is defined as a subset of reactions occurring shortly after vaccination, including local signs and symptoms, such as pain, redness, swelling and induration, and systemic manifestations, such as fever, myalgia, headache, and rash.[4] We described reactogenicity for each dose of the Moderna/Pfizer vaccines, including fatigue, myalgia, headache, fever, arthralgia, nausea, chills, lymphadenopathy, diarrhea, vomiting, nasal congestion, and others.[1]

We would also like to highlight new data on skin reactions to other COVID-19 vaccines, including AZD1222, Johnson & Johnson's Ad26.COV2.S, Sputnik V, and Sinovac-Coronavac (Table I). As of August 16, 2021, the American Academy of Dermatology/International League of Dermatological Societies registry included 2063 cutaneous vaccine reactions from 870 patients. We identified 24 reactions after AZD1222 vaccination, most commonly local erythema and pain. Johnson & Johnson's Ad26.COV2.S, another adenovirus vector vaccine, generated 15 reactions, including pityriasis rosea and alopecia. One individual developed urticaria and pruritus to the Sputnik V vaccine. Our data on skin reactions to other vaccine classes, such as the inactivated virus-based vaccine, Sinovac's CoronaVac, are limited. Four cases of reactions have been reported to the registry, including pityriasis rosea and zoster. Clinical trials frequently lump skin reactions into a nonspecific "rash" category, but real-world data better characterizing these cutaneous manifestations can provide mechanistic clues.

Poulas and Farsalinos[3] hypothesized the spike glycoprotein from vaccination drives these skin phenomena, but the underlying mechanism is likely multifaceted and may vary by vaccine reaction. For instance, delayed large local reactions suggest a delayed hypersensitivity response to vaccination or a T-cell-mediated response resulting from molecular mimicry to viral epitopes. Other manifestations, such as viral reactivation, bullous pemphigoid, and leukocytoclastic vasculitis, may be explained by off-target immune activation postvaccination.[3] RNA-mediated activation of innate immunity via Toll- and RIG-like receptors could also result in type I interferon release. Analysis of the underlying mechanisms for each pattern of skin reaction and systematic characterization of these cutaneous manifestations are paramount to understanding how these side effects influence vaccine adoption, particularly as additional doses, boosters, and vaccine mixing become increasingly common.

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Table I. Characteristics of dermatologic vaccine reactions reported after COVID-19 vaccination to the AAD/ILDS COVID-19 Dermatology Registry*

	Moderna dose 1	Moderna dose 2	Pfizer dose 1	Pfizer dose 2	Astrazeneca dose 1	Astrazeneca dose 2	Johnson & Johnson	Sputnik V dose 1	Sputnik V dose 2	Sinovac-Coronavac dose 1	Sinovac-Coronavac dose 2	Unknown dose 1	Unknown dose 2	Total
Number of individuals	427	214	114	140	9	2	11	0	1	3	1	19	21	870
Patient age (Median, IQR)	49 (37-66)	47 (37-61)	46 (35-56)	51 (37-64)	49 (44.5-55.5)	39.5 (37-42)	51 (28-60)	-	38	42 (19-85)	42	61 (45-75)	60 (49-75)	-
Patient sex (F)	366 (85.7%)	181 (84.5%)	77 (67.5)	103 (73.6%)	5 (55.5%)	1 (50%)	10 (90.9%)	-	0 (0)	3 (100%)	1 (100%)	16 (84.2%)	13 (61.9%)	776 (89.2%)
Number of vaccine reactions	998	526	208	228	22	2	15	0	2	3	1	27	31	2063
Local reactions														
Local swelling	151	97	12	14	2	0	1	0	0	0	0	2	2	281
Local erythema	169	101	13	15	3	0	1	0	0	0	0	3	2	307
Local pain	116	81	14	14	3	0	0	0	0	0	0	1	2	231
Delayed local hypersensitivity reaction	230	50	12	17	2	0	0	0	0	0	0	1	2	314
Distal and/or generalized reactions														
Pruritus	138	64	23	25	2	0	2	0	1	0	0	5	3	263
Urticaria	28	22	24	21	1	0	2	0	1	0	0	0	2	101
Morbilliform	26	17	16	15	1	0	1	0	0	0	0	3	2	81
Zoster	19	5	11	13	0	1	1	0	0	1	0	4	4	59
Vesicular	14	8	11	14	0	0	0	0	0	0	0	0	0	47
Pityriasis rosea	10	6	3	5	2	0	1	0	0	1	1	2	0	31
Pernio/chilblains	7	3	5	7	0	0	0	0	0	0	0	4	0	26
Erythema multiforme	13	3	1	4	1	0	0	0	0	0	0	1	1	24
Bullous disease	7	1	5	9	0	0	1	0	0	0	0	0	0	23
Erythromelalgia	7	7	2	4	0	0	0	0	0	0	0	0	0	20
Filler reaction	7	7	1	2	0	0	0	0	0	0	0	0	0	17
Angioedema	6	5	3	0	2	0	0	0	0	0	0	0	0	16
Contact dermatitis	5	3	0	5	0	0	0	0	0	0	0	0	1	14
Vasculitis	3	1	5	1	0	0	0	0	0	0	0	0	1	11
Alopecia	1	2	1	1	0	0	2	0	0	0	0	0	2	9
Petechiae	1	3	3	1	0	0	0	0	0	0	0	0	0	8
Reaction in breast-fed infant	0	1	2	1	0	0	0	0	0	0	0	0	0	4
Livedo reticularis	0	0	3	0	0	0	0	0	0	0	0	0	1	4
New dermatologic condition	7†	3‡	1§	8‖	0	0	0	0	0	0	0	0	2¶	21
Flare of existing dermatologic condition	9	13	15	9	1	0	0	0	0	0	0	0	2	49
Other	24	23	20	23	2	1	3	0	0	1	0	1	2	100

F, Female; *IQR*, interquartile range.

*December 24, 2020—August 16, 2021.

†Moderna first dose: lichen planus (4); psoriasis (1); possible leukocytoclastic vasculitis (1); Acne vulgaris (1).

‡Moderna second dose: granuloma annulare (1); lichen planus (1); psoriasis (1).

§Pfizer first dose: herpes zoster (1).

‖Pfizer second dose: lichen planus (2), granuloma annulare (1), morphea (1), Raynaud (1), pityriasis lichenoides (1); "lichen striatus versus inflammatory linear verrucous epidermal nevus versus Wolf isotopic response" (1); unspecified toe rash (1).

¶Unknown second dose: granuloma annulare (1); sarcoidosis (1).

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Conflicts of interest

Drs Freeman, Hruza, and Fox are part of the American Academy of Dermatology (AAD) COVID-19 Ad Hoc Task Force. Dr French is the President of the ILDS. Dr Freeman is an author of COVID-19 dermatology for UpToDate. Drs Sun, McMahon, and Blumenthal have no conflicts of interest to declare. Authors Singh, Fathy, and Tyagi have no conflicts of interest to declare.

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