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REVIEW ARTICLE

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A systematic review on mucocutaneous presentations after COVID-19 vaccination and expert recommendations about vaccination of important immune-mediated dermatologic disorders

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Abstract

With dermatologic side effects being fairly prevalent following vaccination against COVID-19, and the multitude of studies aiming to report and analyze these adverse events, the need for an extensive investigation on previous studies seemed urgent, in order to provide a thorough body of information about these post-COVID-19 immunization mucocutaneous reactions. To achieve this goal, a comprehensive electronic search was performed through the international databases including Medline (PubMed), Scopus, Cochrane, Web of science, and Google scholar on July 12, 2021, and all articles regarding mucocutaneous manifestations and considerations after COVID-19 vaccine administration were retrieved using the following keywords: COVID-19 vaccine, dermatology considerations and mucocutaneous manifestations. A total of 917 records were retrieved and a final number of 180 articles were included in data extraction. Mild, moderate, severe and potentially life-threatening adverse events have been reported following immunization with COVID vaccines, through case reports, case series, observational studies, randomized clinical trials, and further recommendations and consensus position papers regarding vaccination. In this systematic review, we categorized these results in detail into five elaborate tables, making what we believe to be an extensively informative, unprecedented set of data on this topic. Based on our findings, in the viewpoint of the pros and cons of vaccination, mucocutaneous adverse events were mostly non-significant, self-limiting reactions, and for the more uncommon moderate to severe reactions, guidelines and consensus position papers could be of great importance to provide those at higher risks and those with specific worries of flare-ups or inefficient immunization, with

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sufficient recommendations to safely schedule their vaccine doses, or avoid vaccination if they have the discussed contra-indications.

KEYWORDS
acute, adverse effect, adverse event, adverse event following immunization, allergy, angioedema, AstraZeneca, AstraZeneca/Oxford, atopic dermatitis, Bharat, collagen vascular disease, Comirnaty, COVID-19 vaccine, cutaneous, cyanosis, delayed, delayed-type hypersensitivity, dermatology, ecchymosis, edema, erythema multiforme, exanthematous rash, herpes, hidradenitis suppurativa, inflammatory bowel disease, injection site reaction, Janssen, Johnson & Johnson, late, local site reaction, maculopapular rash, mastocytosis, Moderna, morbilliform rash, mucocutaneous, mucosal, pemphigoid, pemphigus, Pernio, Petechia, Pfizer, Pfizer-BioNTech, pityriasis rosea, pruritus, psoriasis, purpura, remote site reaction, rheumatic disorders, SARS-Cov-2, side effect, Sinopharm, Sinovac, Sputnik, urticaria, vaccine, Vaccine Adverse Event Reporting System, zoster

1 | INTRODUCTION

1.1 | Rationale

The global impact of the Coronavirus Disease 2019 (COVID-19) pandemic does not need to be underscored. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly throughout the world and left tragic consequences, and vaccination appears to be a mainstay for overcoming this contagious calamity. Many candidate vaccines have been developed against SARS-COV-2, using different vectors and methods of production, which fall into different vaccine types. To name a few:

1. mRNA vaccines

   Pfizer-BioNTech "Comirnaty" (BNT162b2, tozinameran)[1–4]
   Moderna (mRNA-1273)[5–8]

2. Adenovirus viral vector vaccines

   Oxford–AstraZeneca (Covishield, Vaxzevria,ChAdOx1SnCoV-19, AZD1222)[9–14]
   Sputnik V (Gam-COVID-Vac)[15,16]
   Convidecia (Ad5-nCoV)[17,18]
   Janssen (Ad26.COV2.S, JNJ-78436735)(Johnson & Johnson)[19,20]

3. Protein subunit vaccines

   Novavax (NVX-CoV2373)[21,22]
   MF59-adjuvanted spike glycoprotein-clamp vaccine[23]
   SCB-2019[24]
   CoV2 preS dTM-AS03[25]
   ZF2001 (ZIFIVAX or ZF-UZ-VAC-2001)[26]
   V-01[27]
   EpiVacCorona (Aurora-CoV)[28]

4. Inactivated virus vaccines

   Sinovac (CoronaVac)[29–31]
   Sinopharm BIBP (BBIBP-CorV)[32,33]
   Sinopharm WIBP (WIBP-CorV)[34]
   Covaxin (BBV152, Bharat Biotech)[35]
   KCONVAC (Minhai)[36]
   IBMCAMS vaccine (Institute of Medical Biology)[37]

5. Virus-like particle vaccines

   CoVLP[38] From these many candidates, seven COVID-19 vaccines have been approved by WHO,[39] namely:

1. Pfizer-BioNTech "Comirnaty" (BNT162b2, tozinameran),
2. Moderna (mRNA-1273),
3. Janssen (Ad26.COV2.S, JNJ-78436735)(Johnson & Johnson),
4. Oxford–AstraZeneca (AZD1222),
5. Covishield (Serum Institute of India, Oxford–AstraZeneca formulation),
6. Sinopharm BIBP (BBIBP-CorV)(Vero Cells),
7. and Sinovac CoronaVac.[39]

Although studies have showed overall acceptable efficacy, safety, and tolerability of all available COVID-19 vaccines,[3,8,13,14,30,40,41] with the accelerated pace of vaccine production, distribution, and administration, several steps of vaccine development were condensed and got fast-tracked which increased the probability of unsolicited adverse reactions, warranting further attention to the potential side effects of these vaccines,[42,43] and an international effort to report the observed reactions, through the Vaccine Adverse Event Reporting System (VAERS),[44] or other registries. Previous studies have revealed the main side effects to include localized pain, swelling or redness at the injection site, along with constitutional or COVID-like symptoms, mostly comprised of generalized weakness, myalgia, headache, fever and chills, joint pain, nausea, and diarrhea.[45] Of note, mucocutaneous adverse events encompass a large number of post-vaccination reactions: local injection site reactions as previously mentioned, delayed large local reactions, morbilliform rashes, urticaria, erythema

multiforme, delayed inflammatory reactions to dermal fillers, erythromelalgia, lichen planus, varicella-zoster, herpes simplex, pityriasis rosea, petechiae, purpura, and mimickers of COVID-19 infection cutaneous manifestations (e.g., pernio or chilblains), which have predominantly been insignificant and self-limited.[46,47]

1.2 | Objective

With dermatologic side effects being fairly prevalent after COVID vaccination, and the multitude of studies aiming to report and analyze these events, the need for an extensive investigation on previous studies seemed urgent, in order to provide a comprehensive body of information about these post-COVID-19 immunization mucocutaneous reactions.

Therefore, the main objective of this qualitative systematic review is to recapitulate and categorize the clinical characteristics of mucocutaneous reactions following COVID vaccination, provide an update on the state of underlying mucocutaneous diseases after vaccination, their diagnoses and biopsies, therapeutic strategies, patients' outcomes, and further integrated guidance for approach to patients who have previously experienced these side effects or flares of underlying diseases with other vaccines.

We have also tried to classify experts' recommendations and consensus guidelines on COVID-19 vaccination in those with immune-mediated dermatologic disorders, allergic disorders, along with systemic disorders with probable mucocutaneous presentations, for example, autoimmune inflammatory rheumatic diseases (AIIRD); as these disorders could be underlying factors that may affect vaccine immunogenicity, either by themselves, or indirectly, with the use of immunosuppressive and immunomodulatory treatment for their control. Being knowledgeable and updated on the non-critical, critical or potentially life threatening mucocutaneous adverse effects of COVID-19 vaccine and the mutual effects of vaccination and dermatologic disorders on each other is a must for dermatologic, as well as general medical practice today, and we hope the present article provides a stepping stone to that aim.

This study is the first systematic review that thoroughly assesses all aspects of the various dermatological concerns regarding COVID-19 vaccination, condensing the results of all study types with a detailed categorization of the results.

2 | METHODS

2.1 | Protocol and registration

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to conduct and report this review.[48]

2.2 | Search strategy

A comprehensive electronic search was performed through the international databases including Medline (PubMed), Scopus, Cochrane, Web of science, and Google scholar from the beginning to July 12, 2021, and all articles regarding mucocutaneous manifestations and considerations after COVID-19 vaccine administration were initially retrieved using the following major keywords and their MeSH terms: COVID-19 vaccine, dermatology considerations and mucocutaneous manifestations. The search strategy is illustrated in Appendix S1 of supplement file. In addition, a manual search through the references of included reviews was conducted to identify any missing related studies. Two researchers separately performed the search and screening, and the details of each step in the search and screening process is provided in our PRISMA flow diagram,[49] depicted in Figure 1.

2.3 | Eligibility criteria

Our inclusion criteria were studies or reports on any dermatology-related adverse events following the administration of COVID-19 vaccines and vaccine related concerns and consideration for those with dermatologic disorders. Inclusion was not limited by the type of COVID-19 vaccine. Exclusion criteria were in vitro studies, animal studies, basic science studies, studies on non-dermatologic adverse events (AEs) of vaccines, COVID-19 disease manifestations, and any non-COVID-19 vaccine study.

2.4 | Screening and data extraction

After duplication removal of the primary search results, two reviewers independently screened the title and abstract of retrieved articles based on the above eligibility criteria. They then separately studied the full-text of the selected studies in detail, for evaluation of eligibility and data extraction. In case of disagreement, they discussed the subject and if they did not reach a consensus, another researcher expert in the field joined the discussion. The data extraction sheet contained the following information: first author name, patient characteristics in case reports, or number of patients, gender distribution and mean age in other studies, vaccine type, dose of vaccine, history of previous mucocutaneous conditions, constitutional symptoms after vaccine, characteristics and location of mucocutaneous reactions, mean time of onset, diagnosis, management of reactions, duration of reactions, and final outcomes. Studies regarding COVID-19 vaccination considerations and recommendations among dermatologic patients were assessed separately. The study design, data reporting, and validity of included RCTs were assessed in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement.

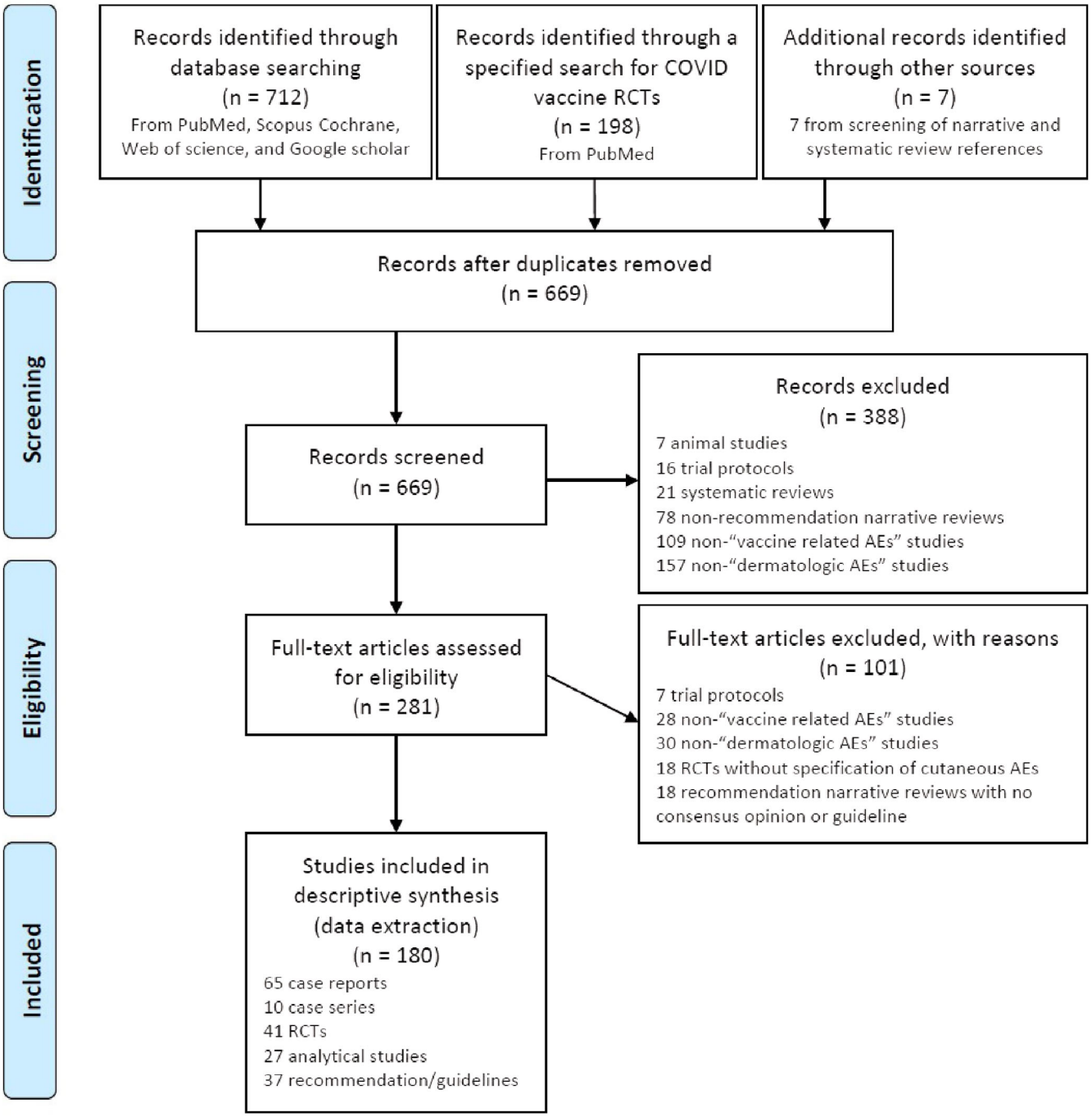

FIGURE 1 PRISMA flow diagram of the study

3 | RESULTS

3.1 | Overview of the studies

A total of 917 articles were retrieved from all databases and 248 duplicates were identified and removed. A total of 669 articles went through title and abstract screening. From those, 388 articles were excluded, including 7 animal studies, 16 trial protocols, 21 systematic reviews, 78 non-recommendation narrative reviews, 109 non-"vaccine related AEs" studies, and 157 non-"dermatologic AEs" studies. The remaining281 articles were selected for full text screening. From those, 101 studies were excluded, including 7 trial protocols, 28 non-"vaccine related AEs" studies, 30 non-"dermatologic AEs" studies, 18 RCTs without specification of cutaneous AEs, and 18 recommendation narrative reviews with no consensus opinion or guideline. Also, references of 20 retrieved narrative and systematic reviews, comprised of 152 articles, were manually screened for any missing articles and 7 related articles from those were also added to our included papers.

Finally, a total of 180 studies were included in our data extraction and descriptive synthesis, including 65 case reports, 10 case series, 41 RCTs, 27 analytical studies, and 37 recommendations or guidelines.

3.2 | Case reports

In total, 116 cases were included in the case reports table from a total of 65 articles, as depicted in Table 1. The mean age of participants was 47.37 years, with a female-dominant gender distribution (F/M: 1.7, F = 73[62.9%] M = 43[37.1%]). The vaccines studied in order of number of participants having received them were BNT162b2 ($n = 76$, 65.5%), mRNA-1273 ($n = 19$, 16.4%), ChAdOx1S nCoV-19 ($n = 9$, 7.8%), CoronaVac ($n = 7$, 6%), Ad26.COV2.S ($n = 3$, 2.6%), and BBV152 ($n = 2$, 1.7%).

A total of 73 cases (62.9%) developed mucocutaneous reactions after receiving the 1st dose of the vaccines, 19 cases (16.4%) after the 2nd dose, and 15 cases (13%) after both doses. Nine reports (7.7%) had not specified the administered dose.

Cases were further categorized into sections based on their clinical and pathological diagnosis:

3.2.1 | Injection site reactions, "Covid arm" ($n = 12$)

Injection site skin reaction (Covid arm) consisted of 12 cases (mean age: 47.9 years, 100% female). Three of them (25%) had atopic background (either themselves or their family). They developed symptoms including painful or pruritic erythematous swelling, urticarial oval patch, patch, vesicle, nodule, or induration at the vaccine injection site after 6.27 days (50% BNT162b2 and 50% mRNA-1273; 50% after 1st dose, 25% after 2nd dose and 25% after both doses). Resolution of symptoms was achieved in an average of 4.15 days, mainly with the use of topical corticosteroid cream (58.3%).

3.2.2 | Non-injection site reactions ($n = 104$)

Hypersensitivity reaction type 1 (n = 14)

A total of 14 patients were incorporated in the section of type 1 hypersensitivity reaction.

- Urticaria ($n = 5$)

Isolated urticaria occurred in 5 patients (mean age: 30.8 years, F/M: 4) in a range of 5 min to 8 h after inoculation (100% BNT162b2; 100% 1st dose), 80% had an allergic background and they were mainly treated by antihistamines and then oral corticosteroids.

- Flushing ($n = 3$)

Three patients experienced Flushing of the face (mean age: 48 years, all female) in a range of 5–30 min after inoculation (100% BNT162b2; 100% 1st dose). Two had an allergic background and 1 was treated with antihistamines.

- Angioedema ($n = 3$)

Three patients (mean age: 35 years, F/M:2) presented with angioedema within 10 min to 24 h of immunization (66.7% BNT162b2 and 33.3% mRNA-1273; 100% 1st dose). For two patients, no treatment was conducted and for the other one antihistamines and corticosteroids were prescribed and symptom relief was achieved in 24 h.

- Anaphylaxis ($n = 3$)

Three patients encountered anaphylaxis (mean age: 27.3 years, F/M:2) all of whom had an allergic background and developed symptoms pertaining to anaphylaxis, with systemic reactions such as tachycardia, tachypnea, dysphagia, dyspnea, severe chills, dysphagia, the feeling of a slurred mouth and hoarseness, wheezing and throat pruritus, along with mucocutaneous reactions such as diffuse maculopapular rash, urticaria, diaphoresis, palate pruritis, generalized rash and pruritus, sudden onset of rash followed by urticaria and angioedema in a span of a few minutes to 5 h after vaccination (66.7% BNT162b2 and 33.3% mRNA-1273; 100% after 1st dose). They were diagnosed as Biphasic anaphylaxis, Severe allergic reaction and Level 1 Anaphylaxis. Resolution was achieved 6 h to 1 day after the onset of symptoms using steroids, antihistamines, one patient was treated with an Epinephrine injection and Sodium Succinate, and one was given oxygen.

Generalized Eruptions (n = 21)

In the generalized eruptions section, we considered patients with miscellaneous presentations and diagnoses who could not be further categorized in other groups. A total of 21 patients were included (mean age: 55.14 years, F/M:1.63)(57.1% BNT162b2, 19% mRNA-1273, 14.3% ChAdOx1 nCoV-19, 9.6% Ad26.COV2.S; 66.7% after 1st dose, 14.3% after 2nd dose, 14.3% after both doses and 4.7% dose not mentioned).

Among the more distinguished presentations were:

- Steven-Johnson syndrome was a diagnosis of a patient (male, 60-year-old) who presented with fever, oral ulceration, eye congestion, erosions over the glans, and multiple purpuric macules all over the body with perilesional erythema which progressed to necrosis after 3 days of immunization (ChAdOx1 nCoV-19, 1st dose); resolution of his symptoms was achieved in 7 days on oral cyclosporine.
- Rowell's syndrome was diagnosed in a 74-year-old man with erythematous and partly violaceous coalescing macules and papules with slightly indicated cocarde formation on the trunk and extremities along with positive antinuclear autoantibodies (ANA) with

TABLE 1 Mucocutaneous reaction after COVID-19 vaccination reported in "Case reports" studies

Supplemental references[a]	First author	Case age	Case gender	Patients' mucocutaneous disease history	Patients' other comorbidity	Drug history at the time of vaccination	Vaccine dose	Any sign after vaccine	Description of mucocutaneous reactions	reactions onset	Skin or mucosal biopsy	Diagnosis	Resolution after (time)	Management of reactions
1. Injection site reactions, "Covid arm" ($n = 12$)														
With BNT162b2														
1	Gyldenløve, M.	33	F	NM	DM, obesity	NM	1	Neg	Asymptomatic rash at the injection site	12d	Perivascular, lymphocyte infiltration in the dermis	Reactions after incorrect subcutaneous administration	NM	Neg
2	Tammaro, Antonella	64	F	Neg	Neg	Neg	2	Neg	A nodule surrounded by an erythematous halo, extremely painful and pruritic	1d	NM	Localized reaction	4d	Topical Corticosteroid cream
2	Tammaro, Antonella	56	F	Neg	Neg	Neg	2	Neg	Small vesicular lesions surrounded by erythema	1d	NM	Localized reaction	7d	Topical Corticosteroid cream
2	Tammaro, Antonella	60	F	Neg	Neg	Neg	2	Neg	Severe xerosis and pruritus in the area injected, extensive erythematous pruritic and painful rash, on the shoulder and chest	7d	NM	Localized reaction	7d	Topical Corticosteroid cream
3	López-Valle, A.	27	F	Neg	NM	NM	1 & 2	1st: fever, 2nd: fatigue after 24 h of injection	1st: pain at the injection site, erythematous–edematous firm plaque over the deltoid area, 2nd: pain and an erythematous–edematous plaque on the injection site	1st:7d / 2nd:6 h	NM	NM	1st: 2d	Paracetamol for 2nd dose symptoms (resolved after 2d)
4	Baeck, M.	38	F	BNT	NM	NM	1	Pain at the injection site had completely resolved within 2 days, numbness of the fingers	Only after 1st dose: erythema of the upper arm	6d	sparse, superficial, deep lymphohistiocytic infiltrates with CD3+ (including CD8+ and CD4+) T cells and some eosinophils and very rare CD20+ B cells	Delayed local reaction	5d	Spontaneous resolution
With mRNA-1273														
5	Sidlow, J. S.	67	F	NM	mild atopy	NM	1	NM	Only after 1st[1]: itchy 7-cm erythematous red patch at the vaccine injection site of the upper portion of patient's left arm	7d	Spongiosis perivascular, interstitial infiltrate, mixed cell type with rare eosinophils, occasional neutrophils within the reticular dermis	Localized reaction	7d	Topical Corticosteroid use
5	Sidlow, J. S.	40	F	NM	atopic family history	NM	1 & 2	NM	1[st]: sharply demarcated warm urticarial oval patch, swelling and progressive erythema on the arm, 2nd: mild swelling at the injection site	8d	Spongiosis perivascular, interstitial infiltrate, mixed cell type with rare eosinophils, occasional neutrophils within the reticular dermis	Localized reaction	NM	Erythromycin for presumed erysipelas
5	Sidlow, J. S.	53	F	NM	mild atopic background	NM	1 & 2	2nd: weakness, diarrhea, patient could not raise her arm above 90° angle	1st: some mild sensitivity at the injection site and tenderness, 2nd: tender erythematous urticarial red ring on the injected arm	NM	Spongiosis perivascular, interstitial infiltrate, mixed cell type with rare eosinophils, occasional neutrophils	Localized reaction	3d	Neg

TABLE 1 (Continued)

Supplemental references[a]	First author	Case age	Case gender	Patients' mucocutaneous disease history	Patients' other comorbidity	Drug history at the time of vaccination	Vaccine dose	Any sign after vaccine	Description of mucocutaneous reactions	reactions onset	Skin or mucosal biopsy	Diagnosis	Resolution after (time)	Management of reactions
6	Lindgren, A. L.	60	F	NM	Neg	NM	1	Neg	Swollen, painful, extremely pruritic, erythematous plaque with minute papules in vaccination site	6d	NM	Hypersensitivity reaction	14 h	Clobetasol 0.05% cream twice
6	Lindgren, A. L.	44	F	NM	Neg	NM	1	fever, chills, headache, and myalgias	Erythema, pain, pruritus, induration and swelling at the vaccination site on patient's left arm	7d	NM	Hypersensitivity reaction	2d	Triamcinolone 0.1% cream
6	Lindgren, A. L.	33	F	NM	NM	NM	1	Neg	Redness, pain, itching, and swelling at the injection site	7d	NM	Hypersensitivity reaction	4d	1% Hydrocortisone cream
2. Non-injection site reactions ($n = 104$)														
2.1. Hypersensitivity reaction type 1 ($n = 14$)														
2.1.1. Urticaria ($n = 5$)														
With BNT162b2														
7	Bianchi, L.	24	F	NM	Allergic rhinitis	NM	1	NM	Generalized acute urticaria	5 min	NM	urticaria	NM	Betamethasone Sodium Phosphate IV
7	Bianchi, L.	28	M	NM	Allergic rhinitis	NM	1	NM	Generalized acute urticaria	5 min	NM	urticaria	NM	Neg
8	Pitlick M.	24	F	NM	NM	NM	1	NM	Urticaria	3 h	NM	NM	4d	antihistamines
8	Pitlick M.	45	F	NM	Food allergy	NM	1	Throat tightness	Urticaria	8 h	NM	NM	NM	Neg
8	Pitlick M.	33	F	NM	Asthma, venom anaphylaxis	NM	1	Tachycardia	Urticaria	15 min	NM	NM	12 h	antihistamines
2.1.2. Flushing ($n = 3$)														
With BNT162b2														
7	Bianchi, L.	58	F	NM	Allergic rhinitis and asthma	NM	1	NM	Flushing of the face	30 min	NM	Flushing	NM	Neg
7	Bianchi, L.	44	F	NM	Allergic rhinitis	NM	1	NM	Flushing of the face	20 min	NM	Flushing	NM	Neg
8	Pitlick M.	36	F	NM	NM	NM	1	NM	Facial flushing	5 min	NM	NM	1 h	antihistamines
2.1.3. Angioedema($n = 3$)														
With BNT162b2														
7	Bianchi, L.	31	F	NM	Allergic rhinitis	NM	1	NM	Angioedema (tongue, gums)	24 h	NM	Angioedema	NM	Neg
7	Bianchi, L.	54	F	atopic dermatitis, contact allergy	Allergic rhinitis	NM	1	NM	Angioedema (tongue, lips)	10 min	NM	Angioedema	NM	Neg
With mRNA-1273														
8	Pitlick M.	20	M	NM	Vaccine allergy	NM	1	NM	Angioedema	3 h	NM	NM	1d	Steroids, Antihistamines
2.1.4. Anaphylaxis($n = 3$)														
With BNT162b2														
9	Daou, Christophe Abi Zeid	30	M	Allergies to Meperidine, Amocixillin-Clavulonate Acid, pollen, and dust mites	NM	NM	1	Tachycardia, tachypnea, dysphagia, dyspnea, severe chills, dysphagia	Diffuse maculopapular rash + urticaria, diaphoresis, palate pruritis, rash, pruritus,diaphoresis, sudden onset of rash followed by urticaria, diaphoresis	a few minutes	NM	Biphasic anaphylaxis	1d	Diphenhydramine, Prednisone, Dexamethasone, Hydrocortisone Sodium Succinate, Epinephrine

(Continues)

TABLE 1 (Continued)

Supplemental references[a]	First author	Case age	Case gender	Patients' mucocutaneous disease history	Patients' other comorbidity	Drug history at the time of vaccination	Vaccine dose	Any sign after vaccine	Description of mucocutaneous reactions	reactions onset	Skin or mucosal biopsy	Diagnosis	Resolution after (time)	Management of reactions
10	Restivo, V.	30	F	Poly-allergic subject, urticaria-angioedema, immediate cutaneous reaction	NM	Prednisone, Chlorphenamine Maleate before vaccination	1	the feeling of a slurred mouth and hoarseness	erythematous spots on the face and neck	5 h	NM	Severe allergic reaction	NM	Dexamethasone, Chlorphenamine Maleate, 0.9% NaCl, Oxygen
With mRNA-1273														
8	Pitlick M.	22	F	NM	Allergic rhinitis	NM	1	wheezing, throat pruritus	Angioedema	20 min	NM	Level 1 Anaphylaxis	6 h	Antihistamines, Steroids
2.2. Generalized eruptions (n = 21)														
With BNT162b2														
11	Edriss, Manar	54	M	NM	NM	NM	1	Neg	Clustered erythematous papules and nodules on posterior upper left arm that extended to left elbow and forearm	5d	NM	erythematous papules and nodules	NM	Clobetasol BD
12	Ackerman, M.	55	M	NM	Neg	NM	1	injection-site soreness, slight hepatic cytolysis (ASAT and GGT 2 N)	Localized pruritic erythematous eruption, later spread on the face, trunk, upper extremities and thighs, 30% of body surface area involved	3 h	slight lymphocytic perivascular infiltrate, compatible with non-severe maculopapular toxidermia late biopsied	Persistent maculopapular exanthem	NM	one dose of Dermocorticoid Treatment, withholding of 2nd dose
13	Akinosoglou, K.	32	F	Neg	NM	NM	1 & 2	Neg	Itchy annular granulomatous rash over both elbows	2d	Cutaneous small cell vasculitis, possibly of leukocytoclastic origin	Annular rash	3d	Neg
14	Zafar, M.	84	M	NM	BPH	NM	2	Rise in D-dimers and eosinophils	Widespread disseminated mildly itchy rash	11d	NM	Rash with eosinophilia	NM	Oral Antihistamines, Topical Steroids
15	Patruno, C.	42	F	Neg	NM	Neg	1	NM	Wheals (acute urticaria) on the trunk and limbs	7d	NM	Acute urticaria	7d	Antihistamine, Prednisone 25 mg
15	Patruno, C.	55	M	NM	Neg	Neg	1	NM	Multiple itchy erythematous papules, vesicles, and blisters	10d	spongiosis, epidermal exocytosis of lymphocytes, apoptotic keratinocytes, dermal edema	Erythema Multiforme-like eruption	10d	Systemic Prednisone 25 mg/day
16	Lavery, M. J.	58	F	Erythema Multiforme (quiescent), recurrent episodes of herpes labialis	RA, Endometriosis, HTN, thyroid goiter	Abatacept, famciclovir	1 & 2	NM	A painful cutaneous eruption, erythematous concentric targetoid plaques on the palms of her hands and soles of the feet bilaterally	1st: 12 h,2nd:1d	NM	Erythema Multiforme-like eruption	NM	Topical Clobetasol
17	Gambichler, T.	74	F	NM	Severe dementia syndrome	Pantoprazole	1	NM	Erythematous partly violaceous coalescing macules and papules with slightly indicated cocarde formation on the trunk and extremities	1d	epidermal atrophy, vacuolar interface dermatitis, lymphocytic infiltrates, dyskeratoses of basal keratinocytes	Rowell's syndrome	NM	NM

TABLE 1 (Continued)

Supplemental references[a]	First author	Case age	Case gender	Patients' mucocutaneous disease history	Patients' other comorbidity	Drug history at the time of vaccination	Vaccine dose	Any sign after vaccine	Description of mucocutaneous reactions	reactions onset	Skin or mucosal biopsy	Diagnosis	Resolution after (time)	Management of reactions
18	Ohsawa, R.	55	F	NM	Neg	NM	1	pain at the injection	d2: pruritic papules and erythematous lesions developed over the entire body except for the face d6: mild pruritic vesicopapular, erythematous macular and morbilliform eruption on the bilateral flanks and extremities	2d	perivascular lymphocytic infiltrates, basal cell vacuolization and intraepidermal vesicle with mild spongiotic change containing collections of Langerhans cells and degenerated acantholysis-like keratinocytes, microthrombi in small vessels in the mid- and deep dermis,perivascular and intraepidermal lymphocytic infiltrates with CD8+ > CD4+ cells	Morbilliform rash	7d	2d: topical betamethasone dipropionate and oral antihistamine: ineffective, 6d: 15 mg of oral predonisolone, withholding 2nd dose of vaccine
19	Farinazzo, E.	37	F	NM	NM	NM	NM	NM	Morbilliform eruption	NM	NM	Morbilliform eruption	NM	NM
20	Weinstock-Guttman, B.	31	F	history of allergic reaction to cefixime	history of MOGSD and biopsy-confirmed smoldering myeloma with monoclonal gammopathy	IV RTX for the last 2 years, monthly doses of IVIG (1st vaccination 12 weeks after the RTX infusion)	1	local warmth	1st: multiple urticarial papules and plaques located on both lower extremities and gluteal area, primarily left side (unilateral side of the vaccination), local 2nd: lesions increased in size and became more evident Resolution: minimal hyperpigmentation residue	1st:7d, 2nd: 2d	NM	Late onset erythema	NM	oral corticosteroids tapered within 3 weeks (15 mg/ 10 mg/5 mg prednisone)
19	Farinazzo, E.	44	F	NM	NM	NM	2	NM	Purplish macule on the third finger of one hand	10d	NM	Fixed Drug Eruption	NM	NM
With mRNA-1273														
5	Sidlow, J. S.	45	M	NM	atopy and seasonal allergies	NM	1	Neg	Only after 1st: pruritic morbilliform rash with spread to the arms and abdomen	8d	spongiosis and a superficial and deep, perivascular and interstitial infiltrate, mixed cell type with numerously abundant eosinophils and occasional neutrophils within the reticular dermis	Generalized reaction	7d	Neg
5	Sidlow, J. S.	31	F	History of guttate psoriasis	NM	NM	1 & 2	2nd: low-grade fever, generalized achiness, and malaise	Both doses: urticarial papular eruption on the contralateral aspect of the right arm	3d	spongiosis and a superficial and deep, perivascular and interstitial infiltrate, mixed cell type with eosinophils and occasional neutrophils within the reticular dermis	Generalized reaction	7d	Neg
5	Sidlow, J. S.	88	F	NM	multiple drug allergies	NM	1	1st: pins and needles sensation on the limbs and dysesthesia on the tongue	Only after 1st: generalized and progressing pruritus	3d	spongiosis and a superficial and deep, perivascular and interstitial infiltrate, mixed cell type with eosinophils and occasional neutrophils within the reticular dermis	Generalized reaction	NM	Benadryl (Johnson and Johnson) and Sarna (Stiefel) lotion

(Continues)

TABLE 1 (Continued)

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21	Kong, Joyce	66	M	NM	HTN, hyperlipidemia, DM, CKD, CAD, idiopathic hypothyroidism	Amlodipine, Aspirin, Brimonidine, Clopidogrel, Furosemide, Gabapentin, Insulin, Levothyroxine	2	fever, myalgias, malaise; After 5d: lower extremity muscle tenderness, stiffness with preserved strength	Painful blistering rash on torso, arms, legs, violaceous, poorly demarcated patches on trunk, arms, thighs, large flaccid bullae, erosion on buttocks, posterior shoulder, and scrotum	1d	epidermal necrosis, with detachment from the underlying dermis forming a subepidermal blister, a very sparse lymphocytic inflammatory infiltrate and a sparse perivascular dermatitis	Extensive Bullous Fixed Drug Eruption	5d	Ibuprofen, High-dose Oral Prednisone, drainage of patient's bullae, Mupirocin Ointment with Vaseline
With Ad26.COV2.S														
22	Lospinoso, K.	74	M	Known allergy to sulfa drugs and amoxicillin-clavulanic acid, no prior vaccination-related reactions	Panhypopituitarism, adrenal insufficiency, neurogenic bladder, obstructive sleep apnea	Prednisone (20 mg, daily)	1	ipsilateral arm discomfort, including the axilla, within 24 h of administration	Generalized distribution (50% of body) of erythematous plaques, numerous small, non-follicular pustules, with sparing of the face, genitals, and mucosae; Significant acral swelling	3d	epidermal spongiosis with focal, dermal neutrophilic inflammation and occasional eosinophils, scattered subcorneal neutrophilic pustules	Spongiotic and pustular eruption	20d	Oral Prednisone (20 mg, daily), Topical Steroids
23	Song, E. J.	83	F	Neg	HTN, hypothyroidism, breast cancer	Palbociclib, Letrozole, Vitamin D	1	Neg	pruritic erythematous annular patches with central clearing on the breast, abdomen, and axilla; scattered petechiae on previous sites of involvement	2d	a mixed spongiotic and interface dermatitis with rare eosinophils and extravasated erythrocytes	Widespread annular eruption	14d	Fexofenadine 360 mg daily, Cetirizine 20 mg daily, Triamcinolone 0.1% cream BD
With ChAdOx1 nCoV- 19														
24	Dash, S.	60	M	NM	DM, HTN	Teneligliptin, Metformin and Amlodipine	1	Fever, oral ulceration and skin rash	Multiple purpuric macules present all over the body with peri-lesional erythema; lesions coalesced to form large sheets of necrosed skin over front and back of trunk, with bullae on few areas; Mucosal involvement: oral erosions, hemorrhagic crusting over the lips, eye congestion, erosions over the glans	3d	Orthokeratosis, epidermal atrophy, infiltration of lymphocytes, neutrophils spongiosis, scattered degenerated apoptotic keratinocytes, basal cell degeneration, interface dermatitis, perivascular and peri-adnexal inflammatory cell infiltrate, extravasation of erythrocytes in dermis	Steven-Johnson syndrome	7d	Oral Cyclosporine 300 mg
14	Zafar, M.	55	F	stable psoriasis and scleroderma	NM	NM	1	NM	new-onset non-itchy rashes, with progressive worsening over the past month on hands and back	2d	NM	Rash without eosinophilia	NM	oral antihistamines and topical steroid creams
25	Tammaro, A.	35	F	NM	Prior COVID-19 +	NM	1	fever, nausea, and pain on the site of injection for 2d	extended erythematous rash on the legs with pruritus and warmth 2d later: vesicular lesions on top of that rash Resolution: vesicular lesions were substituted by white discolorations	6d	NM	Local nonspecific inflammatory reaction to vaccination	NM	ebastine 10 mg and 2 tablets of betamethasone 1 mg (tapered for 4d)

TABLE 1 (Continued)

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2.3. Chilblain-like lesions (CBLL) ($n = 9$)														
With BNT162b2														
26	Lesort, C	82	F	psoriasis	NM	Methotrexate for more than 10 years	1	Neg	slightly painful macular violaceous and erythematous lesions of the fingers and toes, suggestive of CBLL	24 h	A partly necrotic epidermis, overlying a dense dermal lymphocytic infiltrate forming rather well-circumscribed aggregates around blood vessels, eccrine sweat glands and occasionally nerves	CBLL	NM	NM
27	Piccolo, V.	41	F	Neg	Neg	Neg	2	NM	CBLL on the volar aspects of, the second and the third fingertip of right hand along with an acrocyanosis of the hands	Soon after	NM	CBLL	NM	NM
28	Pileri, A.	42	M	NM	NM	NM	1	NM	Nonpainful erythematous, purplish patches located on his distal phalanges and nail beds	12d	NM	CBLL	NM	NM
29	Davido, Benjamin	41	F	NM	Bipolar disorder	Valproate for more than 10 years	1	Sudden toe pain with walking impairment, otherwise asymptomatic	chilblain-like skin changes on toes, itching at night; 10d after vaccination: non-tender violaceous toes of the left foot, with no other dermatological lesion	4d	NM	CBLL	28d	NM
19	Farinazzo, E.	27	F	NM	NM	NM	1&2	NM	1st: Chilblain-like rash on the first and third finger of one foot + urticarial rash 2nd: urticarial rash	1st: 4d,2nd:1d	NM	Chilblain-like rash	NM	NM
With mRNA-1273														
30	Watad A.	48	F	NM	Neg	NM	1	NM	Painful chilblains like lesions on fingers; itchy urticarial-type lesions (resembling urticarial multiforme)over volar aspect of both wrists and feet; evolving over thighs (asymptomatic) and extensor surfaces of both elbows; painful macular/nodular lesions over palmar surface of both hands	10d	NM	CBLL and Urticarial-type lesions	7d	Hydrocortisone 0.5%, Naproxen 500 mg

(Continues)

TABLE 1 (Continued)

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31	Kha, C.	70	M	NM	Pityriasis lichenoides chronica, clinically stable	clobetasol 0.05% ointment	1 & 2	erythema, swelling, and pain with movement of the right PIP joints of the 4th and 5th digits for 10d	few scattered pruritic red edematous papules on an erythematous/violaceous background on palmar and lateral aspects of the fingers on right hand	1st: 2d, 2nd: 3d	dense and predominantly perivascular lymphocytic infiltrate (majority of CD31 T cells) within the superficial-to-deep reticular dermis, epidermis normal with no vacuolar changes at the epidermal-dermal junction, notable papillary dermal edema, some slightly thickened vessels walls with trophism of lymphocytes within the superficial dermis	Chilblains	1st: 14d, 2nd: 7d	1st: Clobetasol 0.05% ointment applied twice daily 2nd: Topical Steroid therapy
WithCoronaVac														
32	Selami Aykut Temiz	44	M	Neg, Prior COVID -	Neg	Neg	NM	Neg	Mildly pruritic, edematous violaceous plaques and nodules on the dorsal hands	7d	NM	Acral CBLL	21d	Topical corticosteroids, Antihistamines
32	Selami Aykut Temiz	53	M	Neg, Prior COVID -	Neg	Neg	NM	Neg	Erythematous-to-violaceous, patches on the marginal side of the fingers of both hands	7d	NM	Acral CBLL	21d	Topical corticosteroids, Antihistamines
2.4. Pityriasis rosea ($n = 9$)														
With BNT162b2														
33	Cyrenne, Benoit	20	F	Alopecia areata	NM	Neg	1 & 2	NM	1st: large, pruritic, red and scaly plaque at the inoculation site, small, red, scaly lesions on the trunk, 2nd: increased pruritus and an increasing number of lesions, multiple oval pink-to-tan-colored thin plaques with peripheral scale on the trunk and proximal extremities	2d	Parakeratosis with minimal acanthosis and spongiosis of the epidermis, few scattered dyskeratotic keratinocytes in the lower epidermis, Melanin incontinence, perivascular lymphocytic infiltrate and rare scattered extravasated red blood cells in the papillary dermis	Pityriasis rosea-like eruption	14d	Topical corticosteroid therapy
33	Cyrenne, Benoit	40	M	NM	NM	Neg	2	Neg	2nd: red and scaly plaque on lateral left axilla, widespread eruption of pruritic, symmetrically distributed, smaller plaques with peripheral scale on the trunk and proximal extremities	21d	NM	Pityriasis rosea	21d	Doxycycline and Bilastine
34	Busto-Leis, J.M.	29	M	NM	NM	NM	2	NM	Herald patch, typical oval-shaped macules, appeared along skin tension lines	1d	Mild spongiosis with foci of parakeratosis and a lymphohistiocytic infiltrate around superficial vessels	Pityriasis rosea	NM	NM

TABLE 1 (Continued)

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34	Busto-Leis, J.M.	26	M	NM	NM	NM	2	NM	Herald patch, typical oval-shaped macules appeared along skin tension lines	7d	Mild spongiosis with foci of parakeratosis and a lymphohistiocytic infiltrate around superficial vessels	Pityriasis rosea	NM	NM
35	Carballido Vazquez, A.M.	35	M	NM	NM	NM	1 & 2	NM	Extremely itchy exanthema, a single oval erythematous lesion on the thigh, papulo-squamous rash on the trunk and proximal extremities	NM	NM	Pityriasis rosea like eruption	14d	Antihistamines, Topical Betamethasone
19	Farinazzo, E.	42	F	NM	NM	NM	2	NM	Pityriasis rosea-like rash on the thighs and abdomen	4d	NM	Pityriasis rosea-like rash	NM	NM
19	Farinazzo, E.	64	M	NM	NM	NM	1	NM	Pityriasis rosea-like rash on the neck, upper limbs, and trunk	5d	NM	Pityriasis rosea-like rash	NM	NM
36	Abdullah, Lina	40	M	NM	Neg	Neg	2	Neg	Rash, single larger erythematous patch with scale on the back, papules on the arms, thighs, chest, abdomen, and flanks in a Blaschkoid distribution	7d	Neg	Pityriasis rosea	21d	0.1% Triamcinolone cream
With CoronaVac														
37	Akdas, E.	45	F	Neg	Neg	Neg	1 & 2	NM	Plaques, with a peripheral collarette scaling, herald patch on the right scapula and the right breast, salmon-colored plaques over the trunk and proximal extremities, many of which had peripheral scales; distribution of plaques: along cleavage lines reminiscent of a Christmas tree pattern on the patient's body	1st& 2nd: 4d	Focal parakeratosis in mounds with exocytosis of lymphocytes, spongiosis in the epidermis and extravasated red blood cells in the dermis	Pityriasis rosea	1st:21d	1st: oral Antihistamine, Topical corticosteroid
2.5. Herpes zoster ($n = 8$)														
With BNT162b2														
38	Tessas, Ioannis	44	M	Mild varicella during a stressful period in childhood	Dyslipidemia and active smoking	NM	1	1st: neuropathic pain extending to the neck and the left hand, tiredness	Only after 1st: pain and redness, herpetiform vesicular and erythematous rash on the left upper back and lateral side and inner side of the left arm (C5–C6 dermatomes)	7d	NM	Ipsilateral Herpes zoster	NM	Oral Valaciclovir TDS for 14d
39	Burlando, Martina	42	M	NM	Neg	NM	1	NM	Unilateral small papulovesicular lesions, heralded by a burning sensation, on right hemithorax	2d	NM	Herpes zoster	NM	Acyclovir 800 mg five times a day for 7d

(Continues)

TABLE 1 (Continued)

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40	Nanova, Krassimira	33	F	Chickenpox in childhood	NM	NM	1	High-grade fever	Widespread rash, Multiple vesicular lesions with an erythematous rim, observed on the trunk, scalp, and limbs	7d	NM	Herpes zoster	NM	NM
19	Farinazzo, E.	34	F	NM	NM	NM	1	NM	Herpes Zoster of the scalp	NM	NM	Herpes zoster	NM	NM
19	Farinazzo, E.	48	F	NM	NM	NM	1	NM	Herpes Zoster	NM	NM	Herpes zoster	NM	NM
With CoronaVac														
41	Bostan, E.	78	M	NM	CHD, CVA, HTN, COPD, radical cystectomy, prostatectomy	Neg	NM	Neg	Erythematous, painful, pruritic, stinging crusted, hemorrhagic vesicles upon an erythematous base involving the left mammary region (an area corresponding to T3- T4 dermatomes on the chest and the back)	5d	NM	Herpes zoster	NM	Oral valacyclovir TDS for 7d
With BBV152														
42	Arora, P.	60	M	NM	DM, HTN	NM	NM	Neg	Multiple grouped vesicles on an erythematous base, present over the knee, and anterior aspect of right thigh	4d	Intraepidermal spongiotic vesicle containing acantholytic cells with large vesicular nuclei neutrophils and dyskeratotic cells; Occasional multinucleate cell with ground-glass chromatin and molded nuclei seen within the blister	Herpes zoster	14d	Oral Valacyclovir 1 g TDS for 7d, Topical Fusidic Acid BD
With ChAdOx1 nCoV- 19														
43	Algaadi, S. A.	65	M	Chicken pox at childhood	CHD, HTN, DM	NM	1	NM	Painful grouped vesicles and ulcerations with a burning sensation on the right side of chest	6d	NM	Herpes zoster	NM	7d Acyclovir, Topical Fusidic Acid
2.6. Purpuric lesions ($n = 16$)														
2.6.1. Immune thrombocytopenic purpura (ITP) ($n = 14$)														
With BNT162b2														
44	Ganzel, C.	53	M	NM	Morbid obesity, DM, HTN	Lercanidipin, Losartan, Doxazocin, Hydrochlorothiazide, Aspirin	NM	Epistaxis and low PLT count	Wet purpura on palate and petechial and purpuric rash on the trunk and limbs	14d	NM	ITP	NM	Dexamethasone 20 mg/d and IVIG, 1 g/kg,
45	Tarawneh, O.	22	M	NM	Neg	Neg	NM	Neg	Widespread petechiae and gum bleeding	3d	NM	ITP	3d	Dexamethasone, PLT transfusion, IVIG at 1 g/kg
46	Mazzatenta, C	44	F	NM	NM	NM	2	NM	Asymptomatic purpuric lesions on the right and left eyelid, circumscribed on the upper eyelid	23d	NM	Purpuric lesions on the eyelids	10d	Neg

TABLE 1 (Continued)

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46	Mazzatenta, C	63	M	NM	NM	NM	2	NM	Asymptomatic purpuric lesions on the right and left eyelid, circumscribed on the upper eyelid	14d	NM	Purpuric lesions on the eyelids	15d	Neg
46	Mazzatenta, C	67	F	NM	NM	NM	1	NM	Moderately itchy ecchymotic lesions on upper eyelids	10d	NM	Purpuric lesions on the eyelids	12d	Neg
47	de Bruijn, S.	38	F	NM	previously TTP- naïve	Neg	1 & 2	blurred vision in the left eye (central serous chorioretinopathy)	Bruises after 1st dose, increased bruising and petechiae, diffuse ecchymosis after 2nd dose	14d	NM	Immune- mediated TTP (iTTP)	NM	plasma exchange, methylprednisolone, Asprin, RTX, and caplacizumab
With mRNA-1273														
48	Toom, S.	36	F	Allergy to acetaminophen	ITP	Etonogestrel-Ethinyl Estradiol	1	A mild headache 7d post vaccination	Diffuse petechiae of the extremities and trunk, easy bruising, oral ecchymosis	14d	NM	ITP	3d	Dexamethasone 40 mg IV daily for 4d, IVIG 1 mg/kg for 3d, monitoring
49	Julian, J. A.	72	F	Seasonal contact dermatitis	Gout, DM	Allopurinol, Sitagliptin	NM	NM	Diffuse petechiae across arms, legs, and abdomen and hemorrhagic bullae of the gingival mucosa	1d	NM	ITP	NM	Dexamethasone, IVIG, aminocaproic acid, RTX, PLT transfusions
50	Helms, J. M.	74	M	NM	HTN, gout, hyperlipidemia and nonischemic cardiomyopathy	NM	1	acute epistaxis	diffuse cutaneous purpura	Few hours	NM	Severe, Refractory Immune Thrombocytopenia	NM	High dose Dexamethasone, IVIG, PLT transfusions, RTX, Eltrombopag, plasma exchange, high dose Methylprednisolone, Romiplostim, Cefazolin
With ChAdOx1 nCoV- 19														
51	Candelli, M	28	M	NM	Neg	Neg	1	fatigue and headache for 10 days and fever for 2 days	oral bleeding and the appearance of petechiae over the trunk, arms, and legs for 3d purpura over the trunk, all four limbs, and bleeding lesions within the oral cavity	19d	NM	ITP	NM	dexamethasone (40 mg/day)
52	Ryan, E.	35	F	NM	migraine	Neg	1	general myalgia and extreme fatigue,headache (different from her known migraine headaches	onset of bruising and petechiae	10d	Marrow aspirate revealed some reactivefeatures with no evidence of an underlying infiltrative disorder	VITT	NM	preemptively anticoagulated with apixaban
53	Thaler, J.	62	F	NM	substituted hypothyroidism of unresolved genesis since age 20	NM	1	flu- like symptoms including aching joints, moderate headache, and moderate dizziness, self- medicated with 1 g paracetamol, fever: 400 mg aspirin twice	unusually large hematoma after slight biting of lip, gum bleedings, an atraumatic hematoma at the right ankle, small hematomas and petechiae of the limbs	8d	NM	VIPIT	NM	low dose fibrinogen concentrate (1 g for 2d), danaparoid-sodium 750 IE IV bolus + 1500 IE SC, followed by 1500 IESC every 8 h). high dose IVIG (1 g/kg), prednisolone (0.75 mg/kg)(2d)

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TABLE 1 (Continued)

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With Ad26.COV2.S														
54	Costello, A.	40	F	NM	migraines, obesity	NM	1	sudden headache (intermittent, worsening with sinus pressure, prescribed amoxicillin/clavulanate, methocarbamol, and methylprednisolone), body aches, fever, chills, bilateral lower-extremity pain without edema, intermittent vertigo	swollen red cheeks, petechiae on her right cheek and bilateral breasts and spontaneous bruising in extremities	10-12d	NM	vaccine-induced thrombotic thrombocytopenia	NM	Bivalirudin, Prednisone, (1 mg/kg/day), IVIG (1 g/kg/day), discharged on Rivaroxaban and a Prednisone taper
With CoronaVac														
55	Cebeci, F.	82	F	NM	seronegative RA, HTN	Hydroxychloroquine 3 years, Olmesartan 2 years Prednisolone 5 mg 6 months (discontinued 3 weeks vaccination)	1	weakness, burning in the legs	1st: diffuse petechial rash on both lower extremities 2nd: uneventful	1d	NM	petechial rash as a vaccine- induced hypersensitivity reaction	7d	Prednisolone restarted 1 week after complete remission of the rash
2.6.2. Vasculitis associated purpura ($n = 2$)														
With BNT162b2														
30	Watad A.	53	M	NM	Neg	NM	1	Mild abdominal pain, arthralgia	Palpable purpura	3d	Leukocytoclastic cutaneous vasculitis (IgA and C3 deposits in the vessel walls)	Henoch-Schonlein purpura	NM	Dexamethasone 10 mg, Prednisone 60 mg thereafter
With BBV152														
56	Kharkar, V.	31	F	Neg	Neg	Neg	2	NM	painful palpable purpura on legs, predominantly on the left leg, Dermoscopy: irregularly arranged red blotches, with an orange–red background	4d	Perivascular infiltrate comprised of eosinophils and lymphocytes with a few neutrophils, along with erythrocyte extravasation, perivascular fibrin and perivascular edema	Cutaneous small vessel vasculitis (cSVV)	10d	Wait-and-watch policy
2.7.Inflammatory flare-ups ($n = 27$)														
2.7.1. Autoimmune inflammatory rheumatic diseases ($n = 13$)														
2.7.1.1. Psoriasis ($n = 3$)														
With BNT162b2														
57	Cohen, Stephanie R	46	F	Psoriasis (2 years in remission)	Psoriatic arthritis, IBS, leukocytoclastic vasculitis (biopsy-proven)	Prednisone	1 & 2	Neg	1st: mild exacerbation of palpable purpuric papules on the bilateral lower legs, 2nd: exacerbated again with significant exquisitely tender palpable purpuric papules distributed bilaterally on the lower legs, feet, upper extremities, lower back, and abdomen	1st& 2nd: 2d	Perivascular mixed inflammatory infiltrate with numerous neutrophils, lymphocytes, occasional eosinophils, leukocytoclasia and erythrocyte extravasation, no fibrinoid necrosis of vessels	Small vessel vasculitis such as IgA vasculitis (Leukocytoclastic vasculitis flare)	NM	Topical steroids and a Prednisone taper

TABLE 1 (Continued)

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With mRNA-1273														
30	Watad A.	36	F	Psoriasis since childhood (mild)	NM	NM	1	Dactylitis, stiffness and tightness, finger joint pain	Painful erythematous macules over palmar surfaceof several fingers on both hands, painful chilblains like lesions (CBLL) on fingers	10d	NM	NM	NM	Ibuprofen 800 mg
With CoronaVac														
58	Onsun, Nahide	72	M	Plaque psoriasis	Prerenal acute injury, HTN	Indapamide	1	Fever	Diffuse erythema, desquamation, and coalescing pustules over the entire body	4d	Compatible with generalized pustular psoriasis	Generalized pustular psoriasis	NM	Acitretin (25 mg/d), IV infliximab 5 mg/kg
2.7.1.2. Lichen planus or lichenoid reactions ($n = 2$)														
With BNT162b2														
59	Hiltun, I.	56	F	Lichen planus lesions 7 years prior (successfully treated with topical therapy)	NM	Neg	2	NM	Polygonal, well-delimited, erythematous papules in the ankles, periumbilical area, flexural wrist and forearms and mammary and axillary folds, Dermoscopy: slight desquamation and Wickham's striae, no mucosal or nail involvement	2d	Typical findings of lichen planus with epidermal hyperplasia forming a characteristic saw-tooth appearance with wedge-shaped hypergranulosis, vacuolar degeneration of basal layer and dense lymphocytic infiltrate in the superficial dermis	Lichen planus	NM	High-potency Topical corticosteroids
39	Burlando, Martina	47	M	Previously diagnosed with lichen planus located on both forearms	Neg	NM	1	NM	Sudden worsening of the preexisting papules, which spread to both arms and trunk	1d	Refused by patient	Lichenoid reactions	NM	Topical corticotherapy BD for 10d
2.7.1.3. Behçet's ($n = 4$)														
With BNT162b2														
30	Watad A.	21	M	Behcet's disease for 3 years	NM	Colchicine	1	NM	Oral aphthous ulcers	5d	NM	Behcet's disease flare	NM	20 mg Prednisone for 7d
30	Watad A.	55	M	Behcet's disease for 20 years	Chronic lymphocytic leukemia	Apremilast	2	Synovitis of small joints	Oral aphthous ulcers(on the tongue)	7d	NM	Behcet's disease flare	NM	Colchicine 0.5 mg BD, 5 mg Prednisone
30	Watad A.	20	M	Behcet's disease for 2 years	NM	Colchicine	1	NM	Oral aphthous ulcers	3d	NM	Behcet's disease flare	NM	Colchicine 2 mg daily
30	Watad A.	34	M	Behcet's disease for 10 years	Neg	Colchicine, Humira	1	NM	Pustular skin lesions	5d	NM	Behcet's disease flare	NM	NSAIDs, increase of Colchicine dose
2.7.1.4. Systemic lupus erythematosus (SLE) ($n = 2$)														
With BNT162b2														
30	Watad A.	78	F	Laboratory SLE	NM	NM	1	Fever and arthritis	Erythematous rash (generalized acute cutaneous lupus), purpura, oral aphthous ulcers	2d	Biopsy from purpura: leukocytoclastic vasculitis	Leukocytoclastic vasculitis	NM	Hydroxychloroquine

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TABLE 1 (Continued)

Supplemental references[a]	First author	Case age	Case gender	Patients' mucocutaneous disease history	Patients' other comorbidity	Drug history at the time of vaccination	Vaccine dose	Any sign after vaccine	Description of mucocutaneous reactions	reactions onset	Skin or mucosal biopsy	Diagnosis	Resolution after (time)	Management of reactions
With ChAdOx1 nCoV- 19														
30	Watad A.	50	F	SLEwith arthritis, mucosal ulcers and hemolysis	NM	NM	1	Severe hemolysis and arthralgia	Oral and nasal ulceration	14d	NM	SLE flare	NM	Prednisolone 60 mg daily, RTX
2.7.1.5. Other AIIRDs ($n = 2$)														
With BNT162b2														
30	Watad A.	62	F	Dermatomyositis	NM	Methotrexate, Plaquenil	1	NM	Skin rash similar to the dermatomyositis rash	7d	NM	Dermatomyositis flare	7d	Local Steroid cream
30	Watad A.	42	F	NM	Transient synovitis	NM	1	Migratory arthritis of small joints	Painless hemorrhagic rash on toes, erythema on small joints	4d	NM	Florid clinical arthritis of the PIP joints	7d	Prednisolone 10 mg, daily
2.7.3. Ulcerative colitis (UC) ($n = 1$)														
With BNT162b2														
30	Watad A.	28	M	NM	UC for 10 years, HES for 5 years, (well controlled)	Vedolizumab, Cyclosporin	1	Hemorrhagic diarrhea	Vesicular skin rash, oral aphthosis	4d	NM	Flare of HES and UC	NM	1 gr of Sulomedrol daily for 3d, Prednisone 60 mg/day
2.7.4. BCG scar local skin inflammation ($n = 2$)														
With BNT162b2														
60	Lopatynsky-Reyes, E. Z.	31	F	NM	Neg	NM	1	headaches, chills, myalgias, pain at injection site, lymphadenopathies	Only after 2nd: inflammation area of 1.5 cm on the BCG scar site with erythema, induration, but painless to palpation (5 cm from the COVID vaccine injection site)	2nd: 2d	NM	BCG Scar Local Skin Inflammation	4d	2nd: three doses of Oral Paracetamol
With mRNA-1273														
60	Lopatynsky-Reyes, E. Z.	28	F	NM	NM	NM	1 & 2	1st: pain, redness at the injection site, myalgias, arthralgias, malaise, 2nd: headache, nausea, myalgias, arthralgias, and malaise	1st: redness at injection site, 2nd erythematous reaction followed by pain, induration, and mild edema at BCG scar site (3 cm below COVID vaccine injection site)	2nd: 36 h	NM	BCG Scar Local Skin Inflammation	2d	2nd: four doses of Oral Paracetamol
2.7.5. Radiation recall phenomenon ($n = 3$)														
With BNT162b2														
61	Soyfer, V.	68	M	NM	Metastatic soft tissues sarcoma in the posterior chest wall and 1 lesion in the right lung	Preoperative radiation therapy, resection in the posterior chest wall	2	NM	pain, burning sensation, redness, and mild skin exfoliation in the area of the posterior chest wall electron field (the electron port shape closely resembles the erythematic area)	5d	NM	Radiation Recall Phenomenon	a few days	Topical steroids and painkillers

TABLE 1 (Continued)

Supplemental references[a]	First author	Case age	Case gender	Patients' mucocutaneous disease history	Patients' other comorbidity	Drug history at the time of vaccination	Vaccine dose	Any sign after vaccine	Description of mucocutaneous reactions	reactions onset	Skin or mucosal biopsy	Diagnosis	Resolution after (time)	Management of reactions
61	Soyfer, V.	64	M	NM	Metastatic solitary fibrous tumor	Radiation of lumbar vertebrae after spinal cord surgery	2	NM	Only after 2nd dose (14d after RT): skin redness and itching sensation, sparing the skin covering the lumbar spine	6d	NM	Radiation Recall Phenomenon	7d	Neg
With CoronaVac														
62	Afacan, E	60	F	Melanoma	NM	Dabrafenib/Trametinib combination therapy	1	Sudden onset painful lesion on the medial side of the right leg	Well demarcated, erythematous, indurated plaque confined to an area of previous irradiation	5d	Epidermal intercellular edema, lymphocyte exocytosis, and rare necrotic keratinocytes as well as increased dermal collagenization and fibrosis	Radiation Recall Phenomenon	NM	NM
2.7.6. Inflammatory reaction to hyaluronic acid (HA) soft tissue fillers ($n = 2$)														
With BNT162b2														
63	Michon, A.	39	F	NM	Neg	Neg	1	flu- like illness symptoms (fatigue, headache, myalgias, and anorexia), which resolved within 4d	tender, erythematous swelling at the left tear trough area (areas previously treated with filler)	2d	NM	Delayed inflammatory reaction to HA fillers	5d	Spontaneous resolution
63	Michon, A.	61	F	NM	intermittent benign vertigo	Neg	1	Flu-like illness symptoms	intermittent facial swelling mostly on cheeks and undereye (areas previously treated with filler), lasting for almost 1d per episode, and once for 72 h	1d	NM	Delayed inflammatory reaction to HA fillers	2d after hyaloronidase	75 units of hyaluronidase at a concentration of 150 units/mL
2.7.7. No Flare-up in Autoimmune Disorders ($n = 6$)														
With BNT162b2														
64	Iannone, Michela	48	F	HS for 6 years (vaccination was after 90D of treatment with a single HS flare), anti–TNF-α-induced lupus syndrome	Concomitant endometriosis	Surgical drains, systemic Clindamycin/ Rifampicin, Ixekizumab SC 160 mg	1 & 2	NM	No adverse events and no HS flares	NM	NM	NM	NM	Routine continuation of Ixekizumab
65	Pacifico, A	48	M	Psoriasis, with flares of both PsO and PsA during asymptomatic COVID-19 infection, spontaneous resolution 10 days after COVID-19 remission	Psoriatic arthritis	Apremilast, achieving stable remission, maintained for 8 months	1 & 2	NM	No psoriasis flares with either dose	NM	NM	NM	NM	NM

(Continues)

TABLE 1 (Continued)

Supplemental references[a]	First author	Case age	Case gender	Patients' mucocutaneous disease history	Patients' other comorbidity	Drug history at the time of vaccination	Vaccine dose	Any sign after vaccine	Description of mucocutaneous reactions	reactions onset	Skin or mucosal biopsy	Diagnosis	Resolution after (time)	Management of reactions
65	Pacifico, A	36	F	Plaque psoriasis, concurrent pustular palmoplantar psoriasis area	NM	Apremilast and narrowband UVB for 3 years	NM	Neg	No psoriasis flares with either dose	NM	NM	NM	NM	NM
66	Rama, T. A.	37	F	Adult-onset monomorphic maculopapular cutaneous mastocytosis lesions with generalized pruritus, flare up of lesions, and osteopenia	severe mast cells mediator-related symptoms including abdominal colicky pain, bloating and diarrhea	Antihistamines, Montelukast	1	Neg	No mastocytosis flare	NM	NM	NM	NM	NM
66	Rama, T. A.	47	F	monomorphic maculopapular cutaneous mastocytosis, anaphylaxis with multiple drugs, pruritus	MC mediator-related symptoms including migraines, gastroesophageal reflux, and osteopenia	Antihistamines, montelukast	1	Myalgia	No mastocytosis flare	1d	NM	NM	NM	NM
With ChAdOx1 nCoV-19														
65	Pacifico, A	76	M	Psoriasis for 4 years: stable residual Psoriasis area severity index (PASI) of 3	NM	Apremilast for 4 years	1	1st: fever (38.5°C) and myalgia for 3 days	No psoriasis flares with either dose	NM	NM	NM	NM	NM

Abbreviations: 1st, after the first dose; 2nd, after the second dose; AIIRD, autoimmune inflammatory rheumatic diseases; ASAT, aspartate aminotransferase; BD, twice a day; BPH, benign prostatic hypertrophy; CAD, coronary artery disease; CBLL, chilblain-like lesions; CHD, coronary heart disease; CKD, chronic kidney disease; CVA, cerebrovascular accident; d, days; GGT 2N, gamma-glutamyl transferase twice normal upper limit; HA, hyaluronic acid; HES, hypereosinophilic syndrome; HS, hidradenitis suppurativa; HTN, hypertension; IBS, irritable bowel syndrome; ITP, immune thrombocytopenic purpura; IVIG, intravenous immunoglobulin; MC, mast cell; MOGSD, myelin oligodendrocyte glycoprotein spectrum disorder; Neg, negative; NM, not mentioned; PIP, proximal interphalangeal; PLT, platelet; PO, by mouth; PsA, psoriatic arthritis; PsO, plaque psoriasis; RT, radiation therapy; RTX, rituximab; SC, subcutaneously; SLE, systemic lupus erythematosus; SLE, systemic lupus erythematosus; TDS, three times a day; UVB, ultraviolet B.

[a]Supporting information Table S1.

1:640 in a speckled pattern, anti-Ro/SSA (60), anti-Ro/SSA (52), and anti-La/SSB antibodies within 1 day following vaccination (BNT162b2, 1st dose).

- Two patients (mean age: 56.5 years, F/M: 1) encountered Erythema multiforme (EM)-like eruption following inoculation (100% BNT162b2; 50% 1st dose, 50% both doses); The first patient was a 55-year-old male without previous history of EM who developed symptoms within 10 days and treated with systemic corticosteroids within 10 days, but the second patient was a 58-year-old female with a past medical history of EM and recurrent episodes of herpes labialis, presented her symptoms in 12 h after first and 24 h after the second dose and was cured with topical corticosteroids.
- Two patients were diagnosed with Fixed Drug Eruption (FDE). One a 44-year-old female who developed purplish macule on the third finger of one hand 10 days after her 2nd dose of BNT162b2, and the other, a 66-year-old male who developed painful blistering rashes, violaceous, poorly demarcated patches, large flaccid bullae, and erosions all over his body along with fever, myalgias, malaise, muscle tenderness and stiffness in lower extremity with preserved strength, following his 2nd dose of mRNA-1273 and was diagnosed with extensive bullous FDE. Resolution was achieved in 5 days using ibuprofen, high-dose oral prednisone, along with drainage of patient's bullae, and administration of mupirocin ointment with Vaseline.

Chilblain-like lesions (CBLL) (n = 9)

CBLLs were reported in 9 patients (mean age: 49.8 years, F/M: 1.25) with manifestations as violaceous/ erythematous lesions in the spectrum of macules, nodules to patches or plaques, located on the fingers and/or toes almost symmetrically which could be painful or to a lesser extent, pruritic. The patient's presentation onset was 5.22 days on average after injection (55.6% BNT162b2, 22.2% CoronaVac, and 22.2% mRNA-1273; 44.5% after 1st dose, 11.1% after 2nd dose, 22.2% after both doses and 22.2% dose not mentioned) and their symptoms resolved in an average of 18.2 days, treated with topical corticosteroids (44.5%), antihistamines (22.2%) and NSAIDs (11.1%).

Pityriasis rosea (n = 9)

Nine patients (mean age: 37.9 years, F/M: 0.67) developed pityriasis rosea manifestations (herald patch, oval erythematous thin plaques with peripheral scale dominantly on the trunk and proximal extremities) without previous or relevant history after 6.38 days on average of immunization (88.9% BNT162b2 and 11.1% CoronaVac; 11.1% after 1st dose, 55.6% after 2nd dose and 33.3% after both doses), and resolution took place after 17.5 days on treatment with topical corticosteroids (44.4%) and antihistamines (33.3%) (either separately or in combination).

Herpes zoster (n = 8)

Eight patients (mean age: 50.5 years, F/M: 0.6) presented with painful (burning sensation) grouped vesicles on erythematous background in the various dermatomes and were diagnosed with herpes zoster. 37.5% of them reported a history of varicella infection in childhood, the patients became symptomatic following vaccination (62.5% BNT162b2, 12.5% CoronaVac, 12.5% ChAdOx1S nCoV-19, 12.5% BBV152; 75% 1st dose and 25% doses not mentioned) after 5.17 days on average and mainly managed with Acyclovir.

Purpuric lesions (n = 16)

- Immune thrombocytopenic purpura (ITP) ($n = 14$)

A total of 14 patients (mean age: 51.14 years, F/M: 1.8) developed ITP with the presentation of widespread petechiae, purpura or ecchymosis (78.6%) or local purpuric lesions on the eyelids (21.4%) after 9.14 days on average of vaccination (33.3% BNT162b2, 25% mRNA-1273, 25% ChAdOx1S nCoV-19, 8% Ad26.COV2.S and 8% CoronaVac for diffuse lesions; and 100% BNT162b2 for local eyelid purpuric lesions; 57.1% after 1st dose, 14.4% after 2nd dose, 7.1% after both doses and 21.4% dose not mentioned). ITP was treated mostly by dexamethasone and IVIG and purpuric lesions on the eyelids were managed conservatively.

- Vasculitis associated purpura ($n = 2$)

Two patients encountered vasculitis symptoms: A 31-year-old female without rheumatologic background developed painful palpable purpura on her legs after 4 days of injection (BBV152, dose 2). She was diagnosed with cutaneous small vessel vasculitis (biopsy proven) and her symptoms resolved within 10 days by wait & watch strategy. Another patient was a 53-year-old male who experienced abdominal pain, arthralgia, and palpable purpura after 3 days of vaccination (BNT162b2, 2nddose), received the diagnosis of Henoch Schoenlein Purpura and biopsy revealed leukocytoclastic vasculitis. He was managed with corticosteroids.

Inflammatory flare-ups (n = 27)

- Autoimmune inflammatory rheumatic diseases (AIIRD) ($n = 13$)

A total of 13 patients with AIIRD had flare ups of their disease, including known cases of psoriasis (23%), lichen planus (15.33%), Behcet's disease (31%), SLE (15.33%) and other (dermatomyositis, arthritis)(15.33%),

- Psoriasis ($n = 3$)

Three psoriatic patients (mean age: 51.3 years, F/M: 1.5) experienced disease flare after 4.5 days on average of inoculation (33.3% BNT162b2, 33.3% mRNA-1273 and 33.3% CoronaVac, 75%after 1st dose and 25% after 2nd dose). One of them was a 46-year-old woman with in remission psoriasis (for 2 years, under prednisolone) and leukocytoclastic vasculitis who developed palpable purpuric papules after both BNT162b2 vaccine doses, and biopsy from the lesions revealed leukocytoclastic vasculitis flare, thereafter it was treated by topical and oral corticosteroids. Another patient was a 72-year-old man with a history of plaque psoriasis, who developed biopsy-proven

generalized pustular psoriasis after CoronaVac and was afterward treated by acitretin and infliximab.

- Lichen planus or lichenoid reactions ($n = 2$)

Lichen planus was a medical history of 2 patients (mean age: 51.5 years, F/M:1) who encountered their disease relapse after 1.5 days on average of their immunization (100% BNT162b2, 50% after 1st dose, and 50% after 2nd dose).

- Behçet's ($n = 4$)

In 4 patients with Behcet's disease (mean age: 32.5 years, 100% males), flare occurred with a presentation of aphthous ulcers (75%) and pustular lesions (25%) 5 days on average after injection (100% BNT162b2, 75% after 1st dose, 25% after 2nd dose) and their treatments were with colchicine, oral corticosteroids and NSAID either single or in combination.

- Systemic lupus erythematosus (SLE) ($n = 2$)

Two patients experienced SLE flares. A 78-year-old woman with a past history of Systemic lupus erythematosus, presented with fever and arthritis, besides erythematous rash (generalized acute cutaneous lupus), purpura and oral aphthous ulcers after 2 days of inoculation with 1st dose of BNT162b2; biopsy from purpura showed leukocytoclastic vasculitis and consequently treatment was done with hydroxychloroquine. Another patient with SLE was a 50-year-old woman who received 1st dose of ChAdOx1S nCoV-19 and presented with severe hemolysis and arthralgia in addition to oral and nasal ulceration 14 days post-vaccination. Eventually, she was treated with oral corticosteroid and rituximab.

- Other AIIRDs ($n = 2$)

A 62-year-old woman with a history of dermatomyositis, developed a characteristic rash of dermatomyositis (which she had experienced prior) after 7 days of receiving her 1st dose of BNT162b2 and was subsequently treated by topical corticosteroids leading to the resolution in 1 day.

A 42-year-old woman with history of transient synovitis developed a painless hemorrhagic rash on toes and erythema along with migratory arthritis on small joints 4 days after her 1stdose of BNT162b2, leading to a diagnosis of florid clinical arthritis of the PIP joints. She was treated with daily prednisolone 10 mg, and the symptoms resolved within 7 days.

- Ulcerative colitis (UC) ($n = 1$)

A 28-year-old male with history of UC for 10 years, and hyper eosinophilic syndrome (HES) for 5 years (which were both well controlled under vedolizumab and cyclosporin), experienced vesicular skin rash, oral aphthosis and hemorrhagic diarrhea 4 days following his 1st dose of BNT162b2, which was treated with daily 1 gr of sulomedrol for 3 days and prednisone 60 mg/day.

- BCG scar local skin inflammation ($n = 2$)

Two patients (mean age: 29.5 years, both female) experienced BCG scar local skin inflammation after 1.75 days of their 2nd injection (50% BNT162b2 and 50% mRNA-1273; 50% after 1st dose, 50% after both doses) and it resolved within 3 days on average with paracetamol use.

- Radiation recall phenomenon ($n = 3$)

Three patients with a medical history of malignancy (mean age: 64 years, F/M: 0.5) who had undergone radiotherapy, experienced Radiation Recall Phenomenon 5.3 days on average following injection (66.7% BNT162b2 and 33.3% CoronaVac, 66.7% after 1st dose, 33.3% after 2nd dose).

- Inflammatory reaction to hyaluronic acid (HA) soft tissue fillers ($n = 2$)

Two women, one 39 and the other 61 years old, experienced delayed inflammatory reaction to HA fillers after their 1st doses of BNT162b2, presenting with flu-like symptoms such as headache, fatigue, myalgias, and anorexia, along with tender, erythematous swelling at areas previously treated with filler. One resolved spontaneously after 5 days, but the other was administered 75 units of hyaluronidase (at a concentration of 150 units/mL), as her swelling was intermittent and lasted for 1–3 days at a time, and she had a larger volume of filler injected in her face; her symptoms subsided 2 days after administration of the hyaluronidase.

- No flare-up in autoimmune disorders ($n = 6$)

In the "No flare-up" group, three patients (mean age: 53.3 years, F/M: 0.5) with a history of psoriasis, under control with apremilast (and narrowband type B ultraviolet [UVB] therapy in one of them), did not experience any flare-ups after vaccination (66.7% BNT162b2 and 33.3% ChAdOx1S nCoV-19, either dose). Two patients (mean age: 42 years, both female) with history of mastocytosis and also one patient with a history of hidradenitis suppurativa (HS) did not suffer from a flare-up following inoculation (BNT162b2, 1st dose in patients with mastocytosis and both doses in the one with HS).

In the viewpoint of comparing side-effects following the three most administered vaccine groups, the most common mucocutaneous eruptions among mRNA vaccine recipients presented in case reports ($n = 90$) were generalized eruptions (17.7%), hypersensitivity reactions (15.5%), injection site reactions (14%), purpuric lesions (11%), Pityriasis Rosea (8%), Chilblain-like lesions (7.7%), and inflammatory flare-ups (20%). Among Adenovirus viral vector vaccines ($n = 11$), generalized Eruptions (45%) and purpuric lesions (36%) were most common. Considering inactivated virus vaccines ($n = 9$), Chilblain-like

lesions (22%), Herpes Zoster (22%), and purpuric lesions (22%) were more prevalent.

3.3 | Case series

A total of 10 case series were identified, comprised of 314 cases (mean age: 44.49 years; 83.76% F), as depicted in Table 2. History of previous allergy or allergic reaction was present in 42% to 90% of patients. 63.4% and 36.3% of patients received BNT162b2 and mRNA-1273 vaccines, respectively, and one participant's (3%) vaccine was unknown. The mucocutaneous reactions appeared on first or both doses.

1. Injection site reaction ($n = 17$, 5.4%)

Injection site reactions, including erythema, wheals (some burning, itchy, painful, with axillary lymphadenopathy), swelling, painful and itchy erythematous subcutaneous nodule, painful hardening and itching were present among 17 patients (5.4%)(100% BNT162b2), appearing after an average of 1.7 days (for whom a day of onset was reported).

2. Generalized reaction ($n = 33$, 10.5%) (100% BNT162b2)

Other nonspecific cutaneous reactions were reported in 33 patients (10.5%). They included generalized urticaria, morbilliform rash and widespread erythematous lesions, appearing after an average of almost 4 days (for whom a day of onset was reported).

3. Delayed localized hypersensitivity reactions ($n = 32$, 10.2%) (12.5% BNT162b2 and 87.5% mRNA-1273)

Delayed reactions were reported in 32 patients (10.2%) occurring almost a week after injection. From these, 12 patients developed Delayed large T-cell mediated hypersensitivity presented with rash and pruritis in extremities which persisted for 6 days and left hyperpigmentation in 17% of the patients. A total of 16 patients showed delayed localized hypersensitivity reactions at injection site, characterized with painful erythematous lesions which disappeared within 8.2 days after the 1st dose and in 3 days after the 2nd dose. Four patients developed bullous drug-induced reactions with severe pruritus. Delayed reactions were managed with topical steroids, oral antihistamines and oral antibiotics.

4. Anaphylaxis ($n = 66$, 21%) (71% BNT162b2 and 29% mRNA-1273)

Three articles by Shimabukuro, et al. report anaphylaxis after mRNA vaccines in different time frames.[50–52] The patients in the preceding reports are only counted once, together with the ones reported in the updated article. Anaphylaxis was reported in 66 patients (21%), developed an average of about 13 min (10–16.8 min) after the injections; presenting with respiratory distress, wheezing and nausea, along with generalized urticaria, diffuse erythematous rash and angioedema (facial, tongue, or laryngeal), and they were treated with epinephrine (92%), endotracheal intubation (11%), corticosteroids (86%) and antihistamines (72%). History of prior allergy or allergic reactions was present in 80% of patients, and 30% had a history of prior anaphylaxis. Either vaccine was associated with anaphylaxis and no deaths from anaphylaxis were reported.

5. Non-anaphylaxis allergic reaction ($n = 126$, 40.1%) (65.9% BNT162b2 and 34.1% mRNA-1273)

A total of 126 patients developed rash, pruritus, itchy and scratchy sensations in the throat and mild respiratory symptoms onset 12–15 min, indicative of an allergic reaction, but not to the degree of anaphylaxis. 67% of these people had prior history of allergies or allergic reactions.

6. Herpes zoster ($n = 20$, 5.8%) (30% BNT162b2 and 70% mRNA-1273)

A total of 20 patients (5.8%) developed Herpes Zoster after 10 days of injection, which were treated with antivirals, local or systemic corticosteroids and analgesics.

7. Immune thrombocytopenic purpura (ITP) ($n = 20$, 5.8%) (45% BNT162b2 and 55% mRNA-1273)

A total of 20 patients (5.8%) developed Idiopathic thrombocytopenic purpura (ITP) presented with diffuse petechia and bruising, 8.7 days after injection which were managed with corticosteroids, platelet transfusions, and rituximab so that 88% had improvements and 6% were deceased.

3.4 | RCTs

We included a total of 41 RCTs as depicted in Table 3, having enrolled a cumulative number of 160,464 participants who received vaccines, with a cumulative mean age of 38.28 years (weighted average age from 40 studies), 51.53% of them being women.

The included articles consist of phase 1 ($n = 11$), phase 2 ($n = 3$), phase 1/2 ($n = 17$), phase 2/3 ($n = 3$) and phase 3 ($n = 6$) trials, along with 1 study on all three phases.

The candidate vaccines in order of number of studies on them are ChAdOx1 nCoV-19 (6 studies), BNT162b2 (5 studies), BNT162b1 (4 studies), mRNA-1273 (4 studies), CoronaVac (3 studies), 5 candidate vaccines with 2 studies each and 10 candidate vaccines with one study each.

Among the vaccinated participant groups we included in our study, most had received BNT162b2 ($n = 39,144$), mRNA-1273 ($n = 30,359$), BBIBP-CorV ($n = 27,367$), Ad26.COV2.S ($n = 22,537$),

TABLE 2 Mucocutaneous reaction after COVID-19 vaccination reported in "Case series" studies

Supplemental references[a]	First author	Number of patients	Women percentage	Mean of Age (year)	Patients' mucocutaneous disease history	Dose	Any symptoms after vaccine	Mucocutaneous lesions characteristic	Mean time of onset reaction	Location of mucocutaneous reaction	Duration of reaction	Treatment	Outcome
1. Injection site reaction ($n = 17$)													
With BNT162b2													
1	Farinazzo, E.	17	82.4	47	NM	1 or 2	Fever (24%)	Erythema (30%), wheals (some burning, itchy, painful, with axillary lymphadenopathy [$n = 2$]) (24%), swelling (18%), nodules (painful and itchy erythematous subcutaneous nodule, Painful hardening)(18%), Itching (10%)	1.7d (of those reported)	Injection site	NM	NM	NM
2. Generalized reaction ($n = 33$)													
With BNT162b2													
2	Corbeddu, M.	11	64	50	Allergy or allergic diathesis (72.7%)	1 & 2	Extracutaneous manifestations (36.3%), such as laryngospasm	Erythematous reactions, morbilliform rash, mild erythema, positive dermographism, urticarial rash, periorbital edema, angioedema, an atopic dermatitis flare up	1.66 d	Diffuse (27.5%), Injection site (27.5%), face (9%), chest, trunk (18%), legs (9%), dorsum of foot (9%)	2–3 d	Short oral steroids course	Mostly spontaneous remission
1	Farinazzo, E.	22	95.5	43	NM	1 &/or 2	Fever (4.5%)	Erythema (some itching) (23%), urticarial rash (23%), diffuse urticaria (14%), generalized itching (14%), swelling (eyelids, face, with mandibular lymphadenopathy)(14%), Rash (erythematous macular)(7.5%), Dermatitis (itchy)(4.5%)	5.2 d	Generalized, localized other than injection site	NM	NM	NM
3. Delayed localized hypersensitivity reactions ($n = 32$)													
With BNT162b2													
3	Coto-Segura, P.	4	0	81.5	NM	1	Neg	Bullous drug-induced reactions with severe pruritus Patients 1–3: urticated and erythematous plaques and tense bullae on erythematous base (1–3 cm in diameter), Patient 4: small vesicles-bullae/bleb, some in a rosette-like pattern; (Biopsy: subepidermal/ subcorneal blisters, positivity in DEJ for IgG and C3) (Mucous membranes and eyes spared)	3–17 d	Patients 1–3: trunk, forearms and thighs Patient 4: limited to forearms	NM	NM	NM

TABLE 2 (Continued)

Supplemental references[a]	First author	Number of patients	Women percentage	Mean of Age (year)	Patients' mucocutaneous disease history	Dose	Any symptoms after vaccine	Mucocutaneous lesions characteristic	Mean time of onset reaction	Location of mucocutaneous reaction	Duration of reaction	Treatment	Outcome
With mRNA-1273													
4	Blumenthal, K. G.	12	83.3	43.3	Allergy (42%), rhinitis (20%)	1 & 2	1st: Fatigue (33%), myalgias (17%), headache, chills, lymphadenopathy, fever, Postural tachycardia, HTN 2nd: Fever (67%), myalgias (58%), chills (75%), fatigue (25%), headache (50%), lymphadenitis (17%), lymphadenopathy (9%), nausea (9%)	1st: Pruritus, warmth, burning, swelling, rash, erythema, induration, hyperpigmentation (9%) 2nd:(in 50% of those with 1st dose reactions, either similar or lower grade) rash (50%), erythema (50%), itching (9%), urticaria (9%) Biopsy: Large T-cell–mediated	1st: 8.3 d	Near the injection site, palmar, near elbow	6d	Amoxicillin (875 mg), clavulanic acid (125 mg), cetirizine 10 mg, loratadine 10 mg, diphenhydramine 25–50 mg, triamcinolone 0.1% topical, prednisone, famotidine 20 mg, clobetasol propionate 0.05% topical, hydrocortisone 1% topical	58%resolution, 25% Hyperpigmentation, 17% Pain, Itching
5	Johnston, M. S.	16	81	48.1	NM	1 & 2	1st: Fevers, chills, arthralgias, myalgias, headache, fatigue (19%),Sore arm (38%) 2nd:Nausea, chills (38%), myalgias (31%), headache (63%), sore arm (31%), fatigue (44%),decreased appetite, arthralgias (13%), Lethargy, rigors	1st: (94% skin reaction) pruritic and variably painful erythematous reactions,typically homogenous,less commonly annular 2nd: (75% skin reaction, 73% similar to 1st dose reactions), pruritic, painful, and edematous pink plaques	1st: 7d 2nd: 2.3 d	at or near the injection site	1st: 8.2 d 2nd: 3d	Topical steroids (clobetasol ointment,hydrocortisone cream), oral antihistamines, cool compresses, cephalexin	NM
4. Anaphylaxis ($n = 66$) (those in the preceding reports are counted once)													
With BNT162b2													
6	Shimabukuro, T.	21(first report)	90	40.5	Allergic reactions (81%), anaphylactic episode (33%)	1	Swollen airway, swollen lips (19%) and tongue (10%), wheezing (20%), stridor, nausea (14%), hoarseness (10%), difficulty swallowing, cough (10%)	Diffuse erythematous rash (35%), urticaria (50%), diffuse pruritic rash (10%), pruritus (5%) (of 95% of all patients)	46 min	Generalized	NM	Epi in 90% of patients	recovery
7	Shimabukuro, T.	47(updated)	94	39	allergy or allergic reactions (77%), anaphylaxis (34%)	1 & 2	respiratory and airway obstruction symptoms, and nausea	Generalized urticaria, diffuse erythematous rash; facial, tongue, or laryngeal angioedema	10 min	Generalized	NM	Epi (92%), endotracheal intubation (11%), corticosteroids (86%), antihistamines (72%)	92% recovery

(Continues)

TABLE 2 (Continued)

Supplemental references[a]	First author	Number of patients	Women percentage	Mean of Age (year)	Patients' mucocutaneous disease history	Dose	Any symptoms after vaccine	Mucocutaneous lesions characteristic	Mean time of onset reaction	Location of mucocutaneous reaction	Duration of reaction	Treatment	Outcome
With mRNA-1273													
8	Shimabukuro, T.	10(first report)	100	46.2	allergy or allergic reaction (90%), previous anaphylactic episode (50%)	1	Respiratory failure, vomiting, decreased peripheral perfusion, persistent dry cough, nausea, hypotension, wheezing	(of 50% of all patients): Diffuse erythematous rash (80%),Generalized urticarial rash (20%); Tongue swelling (40%), throat swelling (10%), periorbital edema (20%)	10.8 min	Generalized	NM	Epi in 100% of patients	80% recovery
7	Shimabukuro, T.	19(updated)	100	42.3	allergy or allergic reactions (84%), prior anaphylaxis (26%)	1 & 2	Respiratory and airway obstruction symptoms, nausea	Generalized urticaria, Diffuse erythematous rash Facial, tongue, or laryngeal angioedema	16.8 min	Generalized	NM	Epi (92%), endotracheal intubation (11%), Corticosteroids (86%), Antihistamines (72%)	92% recovery
5. Non-anaphylaxis allergic reaction ($n = 126$)													
With BNT162b2													
6	Shimabukuro, T.	83	90	43	allergies or allergic reactions (67%)	1	mild respiratory symptoms	Rash, pruritus, itchy and scratchy sensations in the throat	12 min	Generalized, throat	NM	NM	NM
With mRNA-1273													
8	Shimabukuro, T.	43	91	43	allergies or allergic reactions (67%)	1	sensations of throat closure	Rash, pruritus, itchy sensations in the mouth and throat	15 min	Generalized, mouth, throat	NM	NM	NM
6. Herpes zoster ($n = 20$)													
6 with BNT162b2 and 14 with mRNA-1273													
9	Lee, C.	20	50	55.9	Psoriasis, Atopic Eczema, Melanoma, Shingles, Chickenpox Actinic keratosis, BCC, SCC, previous vaccination with Zostavax and Shingrix, rubella, measles	NM	Deep painat injection site and body aches	Unilateral dermatomal herpetiform skin eruption, injection site itchiness	6.85 d (itching, burning), 10.2 d (herpetiform eruption)	Generalized	NM	Valacyclovir, gabapentin, LMX, terrasil, shingles cream,prednisone, mupirocin,tramadol, hydrocodone/ acetaminophen, acyclovir, desonide cream	NM
7. Immune thrombocytopenic purpura (ITP) ($n = 20$)													
9 with BNT162b2, 11 with mRNA-1273, 1 unknown													
10	Lee, E. J.	20	58 (of 19 reports)	44.4(of 19 reports)	ITP in remission (2%), mild–moderate thrombocytopenia (10%), inherited thrombocytopenia (2%), autoimmune conditions (hypothyroidism, Crohn's disease, or anti-tg Ab +) (15%)	1 & 2	Thrombocytopenia	Petechiae, bruising or mucosal bleeding (gingival, vaginal, epistaxis)	8.7 d	Generalized	NM	Corticosteroids (70%), IVIG (60%), PLT transfusions (40%), rituximab (10%), romiplostim, vincristine, aminocaproic acid	88% improvement, 6% death, 6% no improvement

Abbreviations: 1st, after the first dose; 2nd, after the second dose; anti-tg Ab, anti-thyroglobulin antibodies; BCC, basal cell carcinoma; d, days; DEJ, dermo-epidermal junction; Epi, epinephrine injection; HF, heart failure; HTN, hypertension; ITP, immune thrombocytopenic purpura; IVIG, intravenous immunoglobulin; KF, kidney failure; NM, not mentioned; PLT, platelet; SCC, squamous cell carcinoma.

[a]Supporting information Table S2.

TABLE 3 Mucocutaneous reaction after COVID-19 vaccination reported in "RCTs" studies

Supplemental references[a]	First author	Phase of RCT	Number of participants (n)	Women percentage	Mean of Age (year)	Participants' comorbidity and (age group in study)	Vaccine dose	Days between doses	Dose number	Any symptoms after vaccine	Percentage of mucocutaneous reaction	Time of onset the reactions (days)
1. mRNA vaccines												
1.1. BNT162b2 ($n = 39{,}144$)												
1	Walsh, E. E.	Phase 1	36	39	36.7	NM (18–55 years)	10, 20, and 30 μg	21	1	Injection site pain, fever, fatigue, chills, small numbers of severe systemic events (fatigue, headache, chills, muscle pain, and joint pain)	Injection site redness: (20 μg:0%, 30 μg:8%) Injection site swelling (10 μg:17%)	Peak at d2
2	Sahin, U.	Phase 1/2 (extended)	12	66.7	34.8	NM	10 μg	21	1&2	Injection site pain, fever, chills, headache, fatigue, muscle pain, joint pain, diarrhea	Injection site: swelling (8%)	0–7, 22–28
2	Sahin, U.	Phase 1/2 (extended)	12	33.3	46.7	NM	30 μg	21	1&2	Injection site pain, chills, headache, fatigue, muscle pain, joint pain, diarrhea	Injection site: swelling (58.3%), redness(8%)	0–7, 22–28
3	Polack	Phase 2/3	18,860	48.9	51.2	Obesity (34.8%)	30 μg	21	1	Injection site pain, fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, jointpain, severe systemic events (<2%)	Injection site: redness (16-55 years:5%, ≥55 years: 5%), swelling (16-55 years:6%, ≥55 years: 7%, lymphadenopathy (0.3%),	NM
3	Polack	Phase 2/3	18,556	48.9	51.2	Obesity (34.8%)	30 μg	21	2	Injection site pain, fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, jointpain, severe systemic events: <2% except for fatigue (3.8%) and headache (2.0%)	Injection site: redness (16-55 years:6%, ≥55 years: 7%), swelling (16-55 years:6%, ≥55 years: 7%)	NM
4	Frenck, R. W., Jr.	Phase 3	1131	49.9	13.6	Baseline COVID +(4.1%) (12–15 years)	30 μg	21	1&2	Injection site pain, fatigue, headache, chills, vomiting, diarrhea, muscle pain, joint pain,fever	Injection site: redness(1st:6%, 2nd:5%), swelling(1st:7%, 2nd:5%)	0–7
4	Frenck, R. W., Jr.	Phase 3	537	52.5	19.4	Baseline COVID +(5.6%) (16–25 years)	30 μg	21	1&2	Injection site pain, fatigue, headache, chills, vomiting, diarrhea, muscle pain, joint pain,fever	Injection site: redness(1st:6%, 2nd:6%), swelling(1st:8%, 2nd:7%)	0–7
1.2. BNT162b2 booster in ChAdOx1-S-primed participants (CombiVacS) ($n = 450$)												
5	Borobia, A. M.	Phase 2	450	57	43.93	Hypothyroidism, Allergies, Asthma, HTN, Hypercholesterolaemia, Psychiatric, Migraine, Insomnia, Arthralgia, Back pain, Drug hypersensitivity, baseline COVID + (0%)	30 μg	50–84	2	Injection site pain and discomfort, malaise, pyrexia, headache, myalgia, arthralgia, chills, cough, nausea	Injection site: erythema(31%), pruritus(10.9%), urticaria (15%), hardness(35.5%), pustule(0.2%), general pruritus (2%), rash (1.3%) (among 448 subjects)	0–7
1.3. BNT162b1 ($n = 324$)												
6	Li, J.	Phase 1	24	50	37.9	Cardiac Ischemia,Sinus Bradycardia, Hyperuricemia, Nasopharyngitis, Increasedblood uric acid, HTN (18–55 years)	10 μg	21	1&2	Injection site pain, fever, headache, fatigue, malaise, joint pain, muscle pain, chills, nausea, anorexia, diarrhea,	Injection site: redness (1st:12.5%, 2nd:16.7%), swelling(1st: 12.5%, 2nd:8.3%)	0–7

(Continues)

TABLE 3 (Continued)

Supplemental references[a]	First author	Phase of RCT	Number of participants (n)	Women percentage	Mean of Age (year)	Participants' comorbidity and (age group in study)	Vaccine dose	Days between doses	Dose number	Any symptoms after vaccine	Percentage of mucocutaneous reaction	Time of onset the reactions (days)
6	Li, J.	Phase 1	24	50	70.5	Hyperuricemia, HTN, DM (65–85 years)	10 μg	21	1&2	Injection site pain, fever, headache, fatigue, malaise, chills	Injection site: redness (1st:12.5%)	0–7
6	Li, J.	Phase 1	24	50	39.7	Sinus Bradycardia, Hyperuricemia, Blood uric acid increased (18–55 years)	30 μg	21	1&2	Injection site pain, fever, headache, fatigue, malaise, joint pain, muscle pain, chills, nausea, anorexia, diarrhea, vomiting	Injection site: redness (1st:25% 2nd:20.9%), swelling (1st:20.8%, 2nd:16.7%), induration(1st:8.3%, 2nd:4.2%)	0–7
6	Li, J.	Phase 1	24	50	68.5	Hyperuricemia, HTN, DM (65–85 years)	30 μg	21	1&2	Injection site pain, fever, headache, fatigue, malaise, joint pain, muscle pain, chills, anorexia	Injection site: redness (1st: 16.6%),swelling(2nd: 21.7%), induration(1st: 4.2%)	0–7
1	Walsh, E. E.	Phase 1	36	39	36.7	NM (18–55 years)	10 μg, 20 μg, 30 μg	21	1	Injection site pain, fever, fatigue, chills	Injection site redness: (30 μg:17%) Injection site swelling: (10 μg:25%, 20 μg:17%)	Peak at d2
1	Walsh, E. E.	Phase 1	36	39	36.7	NM (18–55 years)	10 μg, 20 μg, 30 μg	21	2	Injection site pain, fever, fatigue, chills *dose-dependent (greater after the 2nd dose than after the 1st dose, both systemic and local reactions)	Injection site redness: (30 μg:17%) Injection site swelling: (20 μg:8%, 30 μg:25%)	Peak at d2
1	Walsh, E. E.	Phase 1	36	67	70.1	NM (65–85 years)	10 μg, 20 μg, 30 μg	21	1	Injection site pain, fever, fatigue, chills (systemic events milder than in the younger participants)	Injection site swelling: (10 μg:8%, 20 μg:8%, 30 μg:17%)	Peak at d2
1	Walsh, E. E.	Phase 1	36	67	70.1	NM (65–85 years)	10 μg, 20 μg, 30 μg	21	2	Injection site pain, fever (33% after the 2nd dose, 1 severe), fatigue, chills	Injection site redness: (20 μg:8%, 30 μg:8%) Injection site swelling: (10 μg:8%, 20 μg:17%, 30 μg:25%)	Peak at d2
7	Sahin, U.	Phase 1/2	12	58.3	38.21	NM	1 μg	21	1&2	Injection site pain, fever, chills, headache, fatigue, muscle pain, joint pain, diarrhea	Injection site: swelling(17%)	0–7, 22–28
7	Sahin, U.	Phase 1/2	12	66.7	43.62	NM	10 μg	21	1&2	Injection site pain, fever, chills, headache, fatigue, muscle pain, joint pain, diarrhea	Injection site: swelling(4%)	0–7, 22–28
7	Sahin, U.	Phase 1/2	12	33.3	35.74	NM	30 μg	21	1&2	Injection site pain, fever, chills, headache, fatigue, muscle pain, joint pain, diarrhea	Injection site: redness(54.1%), swelling(41.6%)	0–7, 22–28
7	Sahin, U.	Phase 1/2	12	50	33.88	NM	50 μg	21	1&2	Injection site pain, fever, chills, headache, fatigue, muscle pain, joint pain, diarrhea, vomiting	Injection site: redness(62.5%), swelling(50%)	0–7, 22–28
7	Sahin, U.	Phase 1/2	12	41.7	35.81	NM	60 μg	21	1	Injection site pain, fever, chills, headache, fatigue, muscle pain, joint pain, diarrhea, vomiting	Injection site: swelling(33%)	0–7, 22–28

TABLE 3 (Continued)

Supplemental references[a]	First author	Phase of RCT	Number of participants (n)	Women percentage	Mean of Age (year)	Participants' comorbidity and (age group in study)	Vaccine dose	Days between doses	Dose number	Any symptoms after vaccine	Percentage of mucocutaneous reaction	Time of onset the reactions (days)
8	Mulligan, M. J.	Phase 1&2	12	50	35.8	NM	30 μg	21	1&2	Injection site pain, fever, fatigue, headache, chills, diarrhea, muscle pain, joint pain Severe adverse events: (8.3%)	Injection site redness:(both doses: <20%) Injection site swelling: (1st: <20%, 2nd:<30%)	0–7, Peak at d2
8	Mulligan, M. J.	Phase 1&2	12	58.3	38.3	NM	100 μg	21	1	Injection site pain, fever, fatigue, headache, chills, diarrhea, muscle pain, joint pain Severe adverse events: (8.3%)	Injection site redness(<40%), Injection site swelling(<50%)	0–7, Peak atd2
1.4. mRNA-1273 ($n = 30,359$)												
9	Anderson, E. J.	Phase 1	10	70	65.8	NM (56–70 years)	25 μg	28	1&2	Injection site pain, fever, headache, fatigue, arthralgia, myalgia, chills, nausea,	Injection site erythema/redness (2nd ≤ 10%), swelling/induration(1st ≤ 10% and 2nd ≤ 20%)	0–1
9	Anderson, E. J.	Phase 1	10	20	72.8	NM (≥71 years)	25 μg	28	1&2	Injection site pain, headache, fatigue, arthralgia, myalgia	Injection site erythema/redness (2nd ≤ 20%), swelling/induration(2nd ≤ 20%), skin and subcutaneous tissue disorders (collective $n = 3$ in age group)	0–1
9	Anderson, E. J.	Phase 1	10	50	63.8	NM (56–70 years)	100 μg	28	1&2	Injection site pain, fever, headache, fatigue, arthralgia, myalgia, chills, nausea,	Injection site erythema/redness (2nd ≤ 10%), swelling/induration(2nd ≤ 20%)	0–1
9	Anderson, E. J.	Phase 1	10	70	72.6	NM (≥71 years)	100 μg	28	1&2	Injection site pain, fever, headache, fatigue, arthralgia, myalgia, chills, nausea,	Injection site erythema/redness (2nd ≤ 20%), swelling/induration(2nd ≤ 30%), skin and subcutaneous tissue disorders(collective $n = 3$ in age group)	0–1
10	Jackson, L. A.	Phase 1	15	51	33	NM	25 μg	28	1	Injection site pain, fatigue, headache, myalgia, nausea	Transient urticaria on both legs in one participant	5
10	Jackson, L. A.	Phase 1	15	51	33	NM	100 μg	28	1	Injection site pain, arthralgia, fatigue, chills, headache, myalgia,	Erythema/redness (13.4%), induration/swelling (13.3%)	NM
10	Jackson, L. A.	Phase 1	15	51	33	NM	100 μg	28	2	Injection site pain, fever, nausea, arthralgia, fatigue, chills, headache, myalgia	Erythema/redness (13.4%), induration/swelling (6.7%)	NM
10	Jackson, L. A.	Phase 1	15	51	33	NM	250 μg	28	1	Injection site pain, arthralgia, fatigue, chills, headache, myalgia, nausea	Erythema/redness (6.7%), induration/swelling (13.4%)	NM
10	Jackson, L. A.	Phase 1	14	51	33	NM	250 μg	28	2	Injection site pain, fever, arthralgia, fatigue, chills, headache, myalgia, nausea	Erythema/redness (21.4%), induration/swelling (21.4%)	NM
11	Chu, L.	Phase 2	100	64	36.6	NM (≥18 - < 55 years)	50 μg	28	1&2	Injection site pain,headache, fatigue,myalgia,arthralgia, nausea/vomiting,chills	Local: erythema(1st:2%, 2nd:5%), swelling(1st:5%, 2nd:6%), axillary swelling /tenderness(1st:7%, 2nd:7%), generalized rash(1st:4%, 2nd:7%)	0–7

(Continues)

TABLE 3 (Continued)

Supplemental references[a]	First author	Phase of RCT	Number of participants (n)	Women percentage	Mean of Age (year)	Participants' comorbidity and (age group in study)	Vaccine dose	Days between doses	Dose number	Any symptoms after vaccine	Percentage of mucocutaneous reaction	Time of onset the reactions (days)
11	Chu, L.	Phase 2	100	73	64.6	NM (≥55 years)	50 μg	28	1&2	Injection site pain,headache, fatigue,myalgia,arthralgia, nausea/vomiting,chills	Local: erythema (1st:3%, 2nd:5%), swelling(1st:3%, 2nd:6%), axillary swelling /tenderness(1st:3%, 2nd:12%), generalized rash (1st:2%, 2nd:3%)	0–7
11	Chu, L.	Phase 2	100	53	38.3	NM (≥18 - < 55 years)	100 μg	28	1&2	Injection site pain,headache, fatigue,myalgia,arthralgia, nausea/vomiting,chills	Local: erythema (1st:3%, 2nd:8%), swelling(1st:5%, 2nd:11%), axillary swelling /tenderness(1st:15%, 2nd:10%), generalized rash (1st:4%, 2nd:4%)	0–7
11	Chu, L.	Phase 2	100	71	63.9	NM (≥55 years)	100 μg	28	1&2	Injection site pain, fever, headache, fatigue, myalgia, arthralgia, nausea/vomiting, chills	Local: erythema(1st:2%, 2nd:7%), swelling(1st:3%, 2nd:10%), axillary swelling /tenderness(1st:3%, 2nd:10%), generalized rash (1st:1%, 2nd:2%)	0–7
12	Baden, L. R.	Phase 3	15,168	47.8	51.4	CLD, Cardiac disease, Obesity, DM, Liver disease, HIV	100 μg	28	1	Injection site pain, fever, headache, fatigue, myalgia, arthralgia, nausea or vomiting, chills, serious adverse events: (<0.1%)	Erythema (2.8%), swelling (6.1%), lymphadenopathy (10.2%), hypersensitivity (1.1%), urticaria (0.2%), rash (0.2%), contact dermatitis (0.2%)	2.6
12	Baden, L. R.	Phase 3	14,677	47.8	51.4	CLD, Cardiac disease, Obesity, DM, Liver disease, HIV	100 μg	28	2	Injection site pain, fever, headache, fatigue, myalgia, arthralgia, nausea or vomiting, chills, serious adverse events: (<0.1%)	Erythema (8.6%), swelling (12.2%), lymphadenopathy (14.2%), hypersensitivity (1.1%), urticaria (0.2%), rash (0.2%), contact dermatitis (0.2%)	3.2
2. Adenovirus viral vector vaccines												
2.1. ChAdOx1 nCoV-19 ($n = 13{,}995$) (*SD*: 3.5–6.5 [mostly 5] $\times$ 10^{10} virus particles, LD: 2.2 $\times$ 10^{10} viral particles)												
13	Barrett, J. R.	Phase 1/2	20	70	36	NM	SD/SD	56	1&2	Injection site pain, chills, fatigue, fever, feverish, headache, joint pain, malaise, muscle ache, nausea	Itch(1st& 2nd), tenderness (1st&2nd), warmth(1st& 2nd)	0–7
13	Barrett, J. R.	Phase 1/2	32	52	44	NM	SD/LD	56	1&2	Injection site pain, chills, fatigue, fever, feverish, headache, joint pain, malaise, muscle ache, nausea	Induration(1st), itch(1st& 2nd), redness(1st& 2nd), swelling (2nd), tenderness(1st& 2nd), warmth(1st& 2nd)	0–7
14	Folegatti, P. M.	Phase 1/2	487	49	34	NM	SD	single	1	Injection site pain, feverishness, fever, chills,joint pain,muscle ache,fatigue,headache, malaise,nausea	Local: redness(3%), warmth (25%), itch(7%), swelling(4%), induration(3%), tenderness (83%)	0-7 peak at d1
14	Folegatti, P. M.	Phase 1/2	56	49	34	NM	SD + prophylactic paracetamol	single	1	Injection site pain, feverishness, fever, chills,joint pain,muscle ache,fatigue,headache, malaise,nausea	Local: redness(2%), warmth (20%), itch(12%), swelling (2%), tenderness(77%)	0–7 peak at d1

TABLE 3 (Continued)

Supplemental references[a]	First author	Phase of RCT	Number of participants (n)	Women percentage	Mean of Age (year)	Participants' comorbidity and (age group in study)	Vaccine dose	Days between doses	Dose number	Any symptoms after vaccine	Percentage of mucocutaneous reaction	Time of onset the reactions (days)
14	Folegatti, P. M.	Phase 1/2	10	49	34	NM	SD	single	1&2	Injection site pain, feverishness, fever, chills,joint pain,muscle ache,fatigue,headache, malaise,nausea	Local: warmth(20%), itch(10%), tenderness(50%) (after both doses)	0–7 peak at d1
15	Madhi, S. A.	Phase 1b–2	10[11]	43.2	31	Obesity(18.8%), current smoker (42.9%), HTN (3.1%), Chronic respiratory condition (3.5%), DM (0.4%)	SD	21–35	1&2	Cough, feverish, headache, joint pain, muscle pain, sweating, tenderness, weakness	Injection site: redness, swelling, bruising, hardness,mild itching, epidermal and dermal conditions(0.9%), skin appendage conditions(0.5%), angioedema and urticaria (0.2%), dental and gingival conditions(0.2%), oral soft tissue conditions(0.4%), allergic conditions(0.2%)	0–6
16	Frater, J.,	Phase 2/3	54	0	42.5	HIV +	NM	28–56	1&2	Injection site pain,feverish, fever, chills, joint pain, muscle ache, fatigue, headache, malaise, nausea	Local: warmth(1st:11.3%, 2nd:5.9%), itch(1st:3.8%, 2nd:2%), swelling(1st:1.9%), induration(1st:1.9%), tenderness(1st:62.3%, 2nd:43.1%)	0–7
16	Frater, J.,	Phase 2/3	50	48	38.5	HIV -	NM	28–56	1&2	Injection site pain,feverish, fever, chills, joint pain, muscle ache, fatigue, headache, malaise, nausea	Local: redness(2nd:2.0%), warmth(1st:16%, 2nd:12.2%), itch(1st:4.0%, 2nd:12.2%), tenderness (1st:76.0%, 2nd:61.2%)	0–7
17	Ramasamy, M. N.	Phase 2/3	50	70	44.5	NM (18–55 years)	SD/SD	28	1&2	Injection site pain,tenderness, feverish, fever, chills, joint pain, muscle ache, fatigue, headache, malaise, nausea	Injection site: redness(2nd:2%), warmth(1st:14%, 2nd:12%), itch(1st:4%, 2nd:12%)	0–7
17	Ramasamy, M. N.	Phase 2/3	30	33	60.4	NM (56–69 years)	SD/SD	28	1&2	Injection site pain,tenderness, feverish, chills, joint pain, muscle ache, fatigue, headache, malaise, nausea	Injection site: warmth(1st:7%, 2nd:14%), itch(1st:7%, 2nd:3%)	0–7
17	Ramasamy, M. N.	Phase 2/3	46	35	73	NM (≥70 years)	SD/SD	28	1&2	Injection site pain,tenderness, feverish, chills, joint pain, muscle ache, fatigue, headache, malaise, nausea	Injection site: redness(1st:2%, 2nd:2%), warmth(1st:14%, 2nd:4%), itch(1st:4%, 2nd:2%), swelling(1st:4%, 2nd:4%), induration(1st:2%, 2nd:2%)	0–7
17	Ramasamy, M. N.	Phase 2/3	49	47	39	NM (18–55 years)	LD/LD	28	1&2	Injection site pain,tenderness, feverish, chills, joint pain, muscle ache, fatigue, headache, malaise, nausea	Injection site: redness(2nd:2%), warmth(1st:18%, 2nd:6%), itch(1st:4%, 2nd:2%)	0–7
17	Ramasamy, M. N.	Phase 2/3	30	53	59.5	NM (56–69 years)	LD/LD	28	1&2	Injection site pain,tenderness, feverish, fever, chills, joint pain, muscle ache, fatigue, headache, malaise, nausea	Injection site: warmth(1st:3%), itch(1st: 7%)	0–7
17	Ramasamy, M. N.	Phase 2/3	49	43	73	NM (≥70 years)	LD/LD	28	1&2	Injection site pain,tenderness, feverish, fever, chills, joint pain, muscle ache, fatigue, headache, malaise, nausea	Injection site: redness(1st:2%, 2nd:4%), warmth(1st:2%, 2nd:2%), itch(1st:2%), swelling(1st:2%, 2nd:4%), induration(1st:2%, 2nd:4%)	0–7

(Continues)

TABLE 3 (Continued)

Supplemental references[a]	First author	Phase of RCT	Number of participants (n)	Women percentage	Mean of Age (year)	Participants' comorbidity and (age group in study)	Vaccine dose	Days between doses	Dose number	Any symptoms after vaccine	Percentage of mucocutaneous reaction	Time of onset the reactions (days)
18	Voysey, M.	Different phases (1,2,3)	12,021	56	NM	CVD, Respiratory disease, DM, some Baseline COVID + (18–55 years, 56–69 years, 70+ years)	SD/SD or LD/SD	28	1&2	Cardiac, sensory, GI, general and injection site, procedural complications, infections and infestations, neoplasms, nervous system, renal and urinary, musculoskeletal and connective tissue, reproductive, respiratory side effects	Cellulitis1 (<0.1%),anaphylactic reaction1 (<0.1%),psoriasis 1 (<0.1%), rosacea 1 (<0.1%), vitiligo 1 (<0.1%), Raynaud's phenomenon 1 (<0.1%), uveitis 2 (<0.1%)	any time during study
2.2.Gam-COVID-Vac ($n = 15{,}011$) (all 1×10^{11} viral particles)												
19	Logunov, D. Y.	Phase 1/2	9	78	27	NM	LyophilisedrAd5-S	21	1&2	Injection site pain, hyperthermia,headache, muscle and joint pain, changes in laboratory variables	Local: edema(11%), hyperthermia(11%),mucosal abnormality	0–28
19	Logunov, D. Y.	Phase 1/2	9	0	27.8	NM	rAd26-S	21	1&2	Injection site pain, hyperthermia,headache, asthenia,muscle and joint pain,heartbeat (subjective palpitation),diarrhea,loss of appetite,changes in laboratory variables	Local: itch(11%), generalized: hives(11%)	0–28
19	Logunov, D. Y.	Phase 1/2	9	44	31.4	NM	LyophilisedrAd26-S	21	1&2	Injection site pain, hyperthermia,headache, muscle and joint pain, changes in laboratory variables	Local: edema(22%)	0–28
19	Logunov, D. Y.	Phase 1/2	20	30	26.4	NM	rAd26-S plus rAd5-S (heterologous prime-boost)	21	1&2	Injection site pain, hyperthermia,headache, asthenia,muscle and joint pain,diarrhea,rhinorrhea,loss of appetite,pain in the oropharynx, malaise,sore throat, nasal congestion, cough, sneezing, changes in laboratory variables	Local: hyperthermia(10%), swelling(5%)	0–28
20	Logunov, D. Y.	Phase 3	14,964	38.9	45.3	DM, HTN, IHD, Obesity	rAd26-S plus rAd5-S (heterologous prime-boost)	21	1&2	Vascular disorders, infections and invasions, reproductive, heart disorders, injury, intoxication and complications of procedures, GI, renal, liver and biliary tract, muscle, skeletal and connective tissue and nervous system side effects	Hypersensitivity (0.01%), acne-form dermatitis (0.01%), allergic skin reaction(0.01%), allergic rash(0.05%), alopecia (0.02%), itching (0.04%), skin rash (0.1%), petechial rash (0.01%), rash(0.03%), eczema (0.01%), keratoconjunctivitis (0.01%),chalazion (0.01%), allergic reaction (0.15%), herpes (0.09%), benign neoplasm of the eyelid (0.01%), axillary lymphadenitis (0.07%)	any time during study

TABLE 3 (Continued)

Supplemental references[a]	First author	Phase of RCT	Number of participants (n)	Women percentage	Mean of Age (year)	Participants' comorbidity and (age group in study)	Vaccine dose	Days between doses	Dose number	Any symptoms after vaccine	Percentage of mucocutaneous reaction	Time of onset the reactions (days)
2.3. Ad5-nCoV ($n = 490$) (LD: 5×10^{10} viral particles, MD: 1×10^{11} viral particles, HD: 1.5×10^{11} viral particles)												
21	Zhu, F. C.	Phase 1	36 of 108	49	36.3	Baseline COVID + (0%)	LD	single	1	Injection site pain, fever, headache, fatigue, vomiting, diarrhea, muscle pain, joint pain, throat pain, cough, nausea, impaired appetite, functional gi disorder, dizziness	Injection site: induration(6%), redness(6%), swelling(11%), itch (6%), general pruritis: (3%)	0–7
21	Zhu, F. C.	Phase 1	36 of 108	49	36.3	Baseline COVID + (0%)	MD	single	1	Injection site pain, fever, headache, fatigue, diarrhea, muscle pain, joint pain, throat pain, cough, nausea, impaired appetite	Injection site: induration(3%), redness(3%), swelling(11%), itch(8%), general pruritis:(3%)	0–7
21	Zhu, F. C.	Phase 1	36 of 108	49	36.3	Baseline COVID + (0%)	HD	single	1	Injection site pain, fever, headache, fatigue (6% grade 3), vomiting, diarrhea, muscle pain (3% grade 3), joint pain (3% grade 3), muscular weakness, throat pain, cough, nausea, impaired appetite, dyspnoea (3% grade 3), dizziness	Injection site: induration(3%), redness(3%), general pruritis: (3%), mucosal abnormality (3%)	0–7
22	Zhu, F. C.	Phase 2	253	50	40	Underlying diseases (3%), Baseline COVID + (0%)	MD	single	1	Injection site pain, fever, headache, fatigue, vomiting, diarrhea, muscle pain, joint pain, oropharyngeal pain, cough, nausea, dyspnoea, appetite impaired, syncope	Injection site reactions: induration (5%), redness (2%), swelling (4%), itching (6%), general: pruritus (2%)	0–14
22	Zhu, F. C.	Phase 2	129	50	39.7	Underlying diseases (6%), Baseline COVID + (0%)	LD	single	1	Injection site pain, fever, headache, fatigue, vomiting, diarrhea, muscle pain, joint pain, oropharyngeal pain, cough, nausea, dyspnoea, appetite impaired, syncope	Injection site reactions: induration (2%), redness (1%), swelling (4%), itching (2%), general: pruritus (3%) mucosal abnormality	0–14
2.4. Ad26.COV2.S ($n = 22,537$) (LD: 5×10^{10} viral particles, HD: 1×10^{11} viral particles)												
23	Sadoff, J.,	Phase 1–2a	162	52	36.1	NM 18–55 years	LD	56	1&2	Injection site pain, fatigue, headache, myalgia, nausea, pyrexia	Local: erythema (<5%), swelling (<5%)	0–28
23	Sadoff, J.,	Phase 1–2a	158	54	34.8	NM 18–55 years	HD	56	1&2	Injection site pain, fatigue, headache, myalgia, nausea, pyrexia	Local: erythema(<5%), swelling (<5%)	0–28
23	Sadoff, J.,	Phase 1–2a	161	48	69.6	NM ≥ 65 years	LD	56	1&2	Injection site pain, fatigue, headache, myalgia, nausea, pyrexia	Local: erythema(<10%), swelling (<10%)	0–28
23	Sadoff, J.,	Phase 1–2a	161	51	70	NM ≥ 65 years	HD	56	1&2	Injection site pain, fatigue, headache, myalgia, nausea, pyrexia	Local: erythema(<10%), swelling (<10%)	0–28
24	Sadoff, J.	Phase 3	21,895	44.9	52	Baseline COVID + (9.8%), Obesity (28.6%)	LD	56	1	Injection site pain, headache, fatigue, myalgia, nausea, fever	Local: erythema (0.23%), swelling(0.2%), urticaria ($n = 8$), hypersensitivity($n = 9$)	0–7

(Continues)

TABLE 3 (Continued)

Supplemental references[a]	First author	Phase of RCT	Number of participants (n)	Women percentage	Mean of Age (year)	Participants' comorbidity and (age group in study)	Vaccine dose	Days between doses	Dose number	Any symptoms after vaccine	Percentage of mucocutaneous reaction	Time of onset the reactions (days)
3. Protein subunit vaccines												
3.1. NVX-CoV2373 ($n = 1060$) (Ad: Adjuvant 50 μg Matrix-M1)												
25	Shinde, V.	Phase 1	334	43.1 (all 2199)	31.9 (all 2199)	HTN, DM, HIV, Baseline COVID + (0%)	5 μg + Ad	21	1	Injection site pain and tenderness, fever, headache, fatigue, malaise, joint pain, muscle pain,nausea or vomiting	Injection site: erythema(1.5%), swelling(1.2%)	0–6
25	Shinde, V.	Phase 1	329	43.1 (all 2199)	31.9 (all 2199)	HTN, DM, HIV, Baseline COVID + (0%)	5 μg + Ad	21	2	Injection site pain and tenderness, fever, headache, fatigue, malaise, joint pain, muscle pain,nausea or vomiting	Injection site: erythema(1.8%), swelling(2.7%)	21–27
25	Shinde, V.	Phase 1	150	43.1 (all 2199)	31.9 (all 2199)	HTN, DM, HIV, Baseline COVID +(100%)	5 μg + Ad	21	1	Injection site pain and tenderness, fever, headache, fatigue, malaise, joint pain, muscle pain,nausea or vomiting	Injection site: erythema(1.3%), swelling(4%)	0–6
25	Shinde, V.	Phase 1	142	43.1 (all 2199)	31.9 (all 2199)	HTN, DM, HIV, Baseline COVID +(100%)	5 μg + Ad	21	2	Injection site pain and tenderness, fever, headache, fatigue, malaise, joint pain, muscle pain,nausea or vomiting	Injection site: swelling(0.7%)	21–27
26	Keech, C.	Phase 1/2	25	52	27.2	NM	25 μg, Un-adjuvanted	21	1&2	Injection site pain, arthralgia, fatigue,malaise,headache, myalgia,nausea or vomiting	Local: erythema or redness (2nd:4%), induration or swelling(2nd:4%)	0–7
26	Keech, C.	Phase 1/2	26	50	29.5	NM	5 μg + Ad	21	1&2	Injection site pain, arthralgia, fatigue,malaise,headache, myalgia,nausea or vomiting	Local: erythema or redness (2nd:7.6%), induration or swelling(2nd:3.8%),skin and subcutaneous tissue disorders(3.8%)	0–7
26	Keech, C.	Phase 1/2	3	33.3	23.7	NM	5 μg + Ad	21	1&2	Injection site pain, fatigue, malaise,headache,myalgia	Local: erythema or redness (1st:33.3%,2nd:33.3%)	0–7
26	Keech, C.	Phase 1/2	25	32	35.6	NM	25 μg + Ad	21	1&2	Injection site pain, arthralgia, fatigue,malaise,fever, headache,myalgia,nausea or vomiting	Local: induration or swelling (2nd:8.3%)skin and subcutaneous tissue disorders(4%), rash(4%)	0–7
26	Keech, C.	Phase 1/2	26	65.4	33	NM	1st: 25 μg + Ad 2nd: placebo	21	1&2	Injection site pain, arthralgia, fatigue,malaise,headache, myalgia,nausea or vomiting	Local: erythema or redness (1st:3.8%,2nd:3.8%)skin and subcutaneous tissue disorders(7.7%)	0–7
3.2. MF59-adjuvanted sclamp ($n = 96$)												
27	Chappell, K. J.	Phase 1	24	54	34.1	NM	5 μg	28	1&2	Injection site pain, chills, nausea, vomiting, fever, headache, fatigue/somnolence, myalgia, arthralgia, malaise	Local: tenderness(1st:50.0%, 2nd:62.5%), induration/ swelling(1st:8.3%); Alopecia (4.2%), pruritis (4.2%)	0–7
27	Chappell, K. J.	Phase 1	24	54	31	NM	15 μg	28	1&2	Injection site pain, nausea, vomiting, headache, fatigue/ somnolence, diarrhea, myalgia, arthralgia, malaise	Local: tenderness(1st:54.2%, 2nd:58.3%), induration/ swelling(1st:8.3%)	0–7

TABLE 3 (Continued)

Supplemental references[a]	First author	Phase of RCT	Number of participants (n)	Women percentage	Mean of Age (year)	Participants' comorbidity and (age group in study)	Vaccine dose	Days between doses	Dose number	Any symptoms after vaccine	Percentage of mucocutaneous reaction	Time of onset the reactions (days)
27	Chappell, K. J.	Phase 1	1st: $n = 48$ 2nd: $n = 24$	33.5	32.3	NM	45 μg	28	1&2	Injection site pain, chills, nausea, vomiting, headache, fatigue/somnolence, diarrhea, myalgia, arthralgia, malaise	Local: tenderness(1st:47.9%, 2nd:58.3%), erythema/redness (1st:2.1%), induration/swelling (1st:4.2%); Macular rash(4.2%), contact dermatitis(4.2%)	0–7
3.3. SCB-2019 ($n = 88$)												
28	Richmond, P.	Phase 1	8	38	35.8	NM (18–54 years)	3 μg + AS03	21	1&2	Injection site pain, fever, headache, myalgia, nausea, vomiting, fatigue	Local: erythema (12.5%)	0–7
28	Richmond, P.	Phase 1	8	38	62.8	NM (55–75 years)	3 μg + AS03	21	1&2	Injection site pain, headache, fatigue	Local: erythema (6.25%), swelling(6.25%)	0–7
28	Richmond, P.	Phase 1	8	100	41.9	NM (18–54 years)	3 μg + CpG/Alum	21	1&2	Injection site pain, headache, myalgia, nausea, fatigue	Local: erythema (6.25%), swelling(6.25%)	0–7
28	Richmond, P.	Phase 1	8	50	37	NM (18–54 years)	9 μg + AS03	21	1&2	Injection site pain, fever, headache, myalgia, fatigue	Local: erythema (6.25%), swelling (18.75%)	0–7
28	Richmond, P.	Phase 1	8	38	59.1	NM (55–75 years)	9 μg + AS03	21	1&2	Injection site pain fever headache myalgia fatigue	Local: erythema (25%), swelling (18.75%)	0–7
28	Richmond, P.	Phase 1	8	50	36.1	NM (18–54 years)	9 μg + CpG/Alum	21	1&2	Injection site pain, headache, myalgia, fatigue	Local: erythema (12.5%), swelling(6.25%)	0–7
28	Richmond, P.	Phase 1	8	38	60.3	NM (55–75 years)	9 μg + CpG/Alum	21	1&2	Injection site pain, fever, headache, myalgia, fatigue	Local: erythema (6.7%), swelling (6.7%)	0–7
28	Richmond, P.	Phase 1	8	75	31.3	NM (18–54 years)	30 μg + AS03	21	1&2	Injection site pain, fever, headache, myalgia, diarrhea, nausea, vomiting, fatigue	Local: erythema (6.25%), swelling(18.75%)	0–7
28	Richmond, P.	Phase 1	8	75	59.8	NM (55–75 years)	30 μg + AS03	21	1&2	Injection site pain, headache, myalgia, diarrhea nausea, vomiting	Local: erythema (6.25%), swelling(6.25%)	0–7
28	Richmond, P.	Phase 1	8	75	39.1	NM (18–54 years)	30 μg + CpG/Alum	21	1&2	Injection site pain, headache, fatigue	Local: erythema (18.75%), swelling(6.25%)	0–7
28	Richmond, P.	Phase 1	8	50	61.5	NM (55–75 years)	30 μg + CpG/Alum	21	1&2	Injection site pain, myalgia, fatigue	Local: swelling(6.25%)	0–7
3.4. CoV2 preS dTM ($n = 336$) (LD: 1.3 μg, HD: 2.6 μg)												
29	Goepfert, P. A.	Phase 1/2	18	50	35.3	NM (18–49 years)	LD + AF03	21	1&2	Injection site pain, fever, headache, malaise, myalgia	1st: injection site: erythema (6.3%) 2nd: injection site: erythema (12.5%), swelling(18.8%)	0–7
29	Goepfert, P. A.	Phase 1/2	54	46	33.7	NM (18–49 years)	LD + AS03	21	1&2	Injection site pain, fever, headache, malaise, myalgia	1st: injection site:swelling(2%) 2nd: injection site: erythema (19.6%), swelling(15.7%)	0–7
29	Goepfert, P. A.	Phase 1/2	28	39	59.8	NM (≥50 years)	LD + AS03	21	1&2	Injection site pain, fever, headache, malaise, myalgia	1st: injection site: erythema (3.6%) 2nd: injection site: erythema (32.1%),swelling(25%)	0–7
29	Goepfert, P. A.	Phase 1/2	17	65	32.5	NM (18–49 years)	HD + AF03	21	1&2	Injection site pain, fever, headache, malaise, myalgia	2nd: injection site: erythema (17.6%), swelling(17.6%)	0–7

(Continues)

TABLE 3 (Continued)

Supplemental references[a]	First author	Phase of RCT	Number of participants (n)	Women percentage	Mean of Age (year)	Participants' comorbidity and (age group in study)	Vaccine dose	Days between doses	Dose number	Any symptoms after vaccine	Percentage of mucocutaneous reaction	Time of onset the reactions (days)
29	Goepfert, P. A.	Phase 1/2	10	70	58.7	NM (≥50 years)	HD + AF03	21	1&2	Injection site pain, headache, malaise, myalgia	1st: injection site: erythema (11.1%) 2nd: injection site: erythema (11.1%),swelling(11.1%)	0–7
29	Goepfert, P. A.	Phase 1/2	54	43	34.9	NM (18–49 years)	HD + AS03	21	1&2	Injection site pain, fever, headache, malaise, myalgia	1st: injection site: erythema (3.7%),swelling(7.4%) 2nd: injection site: erythema (50%),swelling(33.3%)	0–7
29	Goepfert, P. A.	Phase 1/2	31	68	61.7	NM (≥50 years)	HD + AS03	21	1&2	Injection site pain, fever, headache, malaise, myalgia	1st: injection site: erythema (6.5%),swelling(3.2%) 2nd: injection site: erythema (32.3%),swelling(25.8%)	0–7
29	Goepfert, P. A.	Phase 1/2	18	56	34.8	NM (18–49 years)	HD Un-adjuvanted	21	1&2	Injection site pain, headache, malaise, myalgia	2nd: injection site: erythema (5.9%),swelling(5.9%)	0–7
29	Goepfert, P. A.	Phase 1/2	24	58	36	NM (18–49 years)	LD + AF03	single	1	Injection site pain, headache, malaise, myalgia	Injection site: erythema(3.8%), swelling(3.8%)	0–7
29	Goepfert, P. A.	Phase 1/2	10	80	59.3	NM (≥50 years)	LD + AF03	single	1	Injection site pain, headache, malaise, myalgia	Injection site: erythema(10%)	0–7
29	Goepfert, P. A.	Phase 1/2	24	38	35.4	NM (18–49 years)	LD + AS03	single	1	Injection site pain, headache, malaise, myalgia	Injection site: swelling(7.7%)	0–7
29	Goepfert, P. A.	Phase 1/2	24	54	32	NM (18–49 years)	HD + AF03	single	1	Injection site pain, headache, malaise, myalgia	Injection site: swelling(4.3%)	0–7
29	Goepfert, P. A.	Phase 1/2	24	58	29.7	NM (18–49 years)	HD + AS03	single	1	Injection site pain, headache, malaise, myalgia	Injection site: erythema(12.5%), swelling(8.3%)	0–7
3.5. ZF2001($n = 640$)												
30	Yang, S.	Phase 1	20	30	31.7	NM	25 μg	30	1&2&3	Injection site pain, fever, headache, cough, muscle pain	Swelling(5%), induration(10%), redness(20%), itch(20%)	0–7
30	Yang, S.	Phase 1	20	45	33.6	NM	50 μg	30	1&2&3	Injection site pain, headache, fatigue, weakness, cough, nausea	Swelling(15%), induration(25%), redness(20%, 5% grade ≥3), rash(5%), itch(35%)	0–7
30	Yang, S.	Phase 2	150	57	43.04	NM	25 μg	30	1&2	Injection site pain, fever, headache, fatigue, cough, nausea, muscle pain	Swelling(4%), induration(3%), redness(8%), rash(2%), itch (6%)	0–7
30	Yang, S.	Phase 2	150	62	44.4	NM	50 μg	30	1&2	Injection site pain, fever, headache, fatigue, cough	Swelling(6%), induration(5%), redness(8%, 1% grade ≥3), rash(3%), itch(9%)	0–7
30	Yang, S.	Phase 2	150	53	42.7	NM	25 μg	30	1&2&3	Injection site pain, fever, headache, cough, muscle pain	Swelling(14%), induration(9%), redness(16%, 1% grade ≥3), rash(1%), itch(19%)	0–7
30	Yang, S.	Phase 2	150	58	43.2	NM	50 μg	30	1&2&3	Injection-site pain, fever, nausea	Swelling(13%, 2% grade ≥3), induration(7%, 1% grade ≥3), redness(14%, 3% grade ≥3), rash(1%, grade ≥3), itch(17%)	0–7
3.6. V-01 ($n = 24$)												
31	Zhang, J.	Phase 1	24	75	40	NM	10 μg	21	1&2	Injection site pain, fever, anorexia, vomiting, nausea, headache, fatigue	Local: pruritus(4.17%)	0–30

TABLE 3 (Continued)

Supplemental references[a]	First author	Phase of RCT	Number of participants (n)	Women percentage	Mean of Age (year)	Participants' comorbidity and (age group in study)	Vaccine dose	Days between doses	Dose number	Any symptoms after vaccine	Percentage of mucocutaneous reaction	Time of onset the reactions (days)
4. Inactivated virus vaccines												
4.1. CoronaVac ($n = 7497$)												
32	Wu, Z.	Phase 1	24	54	65.6	NM	3 μg	28	1&2	Injection site pain, muscle pain, fatigue, nausea, fever, abdominal distention	Injection site pruritus(4.2%), hypersensitivity(4.2%)	0–28
32	Wu, Z.	Phase 1	24	46	67.5	NM	6 μg	28	1&2	Injection site pain, muscle pain, fatigue,headache, decreased appetite, cough	Injection site pruritus(4.2%), mucocutaneous eruption (8.3%), rash(4.2%)	0–28
32	Wu, Z.	Phase 2	100	51	66.8	NM	1.5 μg	28	1&2	Injection site pain,fever, fatigue, diarrhea, cough	Injection site: erythema(2%), pruritus(1%)	0–28
32	Wu, Z.	Phase 2	100	51	66.5	NM	3 μg	28	1&2	Injection site pain, fever, fatigue, diarrhea, cough	Injection site: swelling(1%)	0–28
32	Wu, Z.	Phase 2	99	55	66.2	NM	6 μg	28	1&2	Injection site pain	Injection site: erythema(1%), swelling(1%)	0–28
33	Zhang, Y.	Phase 1	24	58.3	45	NM	6 μg	14	1&2	Injection site pain, fatigue, diarrhea, fever, abdominal pain	Injection site discoloration (4.2%), acute hypersensitivity with manifestation of urticaria (1st dose, one case, 4% of 24), general hypersensitivity(4.2%)	Mostly 0–2
33	Zhang, Y.	Phase 2	120	55	42	NM	3 μg	14	1&2	Injection site pain, fatigue, fever, diarrhea, nausea, headache, muscle pain, vomiting, chest pain, dizziness, decreased appetite	Injection site: swelling(1.7%), redness(0.8%)hypoaesthesia (0.8%),pruritus(0.8%), induration(0.8%)	Mostly 0–2
33	Zhang, Y.	Phase 2	120	60	42.4	NM	6 μg	14	1&2	Injection site pain, fatigue, fever, diarrhea, nausea, headache, muscle pain, cough,chest pain, drowsiness,palpitations	Injection site: swelling (2.5%), redness (1.7%), hypoaesthesia (0.8%), discoloration (0.8%), pruritus (0.8%), general hypersensitivity (0.8%)	Mostly 0–2
33	Zhang, Y.	Phase 2	120	47.5	41.5	NM	3 μg	28	1&2	Injection site pain, fatigue, fever, diarrhea,headache, muscle pain,cough	General hypersensitivity (0.8%)	Mostly 0–2
33	Zhang, Y.	Phase 2	120	47.5	40.6	NM	6 μg	28	1&2	Injection site pain, fatigue, fever, diarrhea,headache, muscle pain,decreased appetite	Injection site: swelling (0.8%), redness (0.8%), discoloration (0.8%), pruritus (0.8%)	Mostly 0–2
34	Tanriover, M. D.	Phase 3	6646	42.6	45	HTN, CVD, Chronic respiratory disease, DM, Malignancy, Autoimmune	3 μg	14	1&2	Injection site: pain and paraesthesia, fatigue, headache, myalgia, chill, fever, diarrhea, cough, arthralgia, nausea, vomiting, seizure($n = 1$),encephalitis ($n = 1$)	Injection site: erythema(0.18%), swelling(0.06%), induration (0.05%), pruritus(0.03%), generalized: rash(0.11%), allergic reaction(0.08%), pruritis and swelling (<0.0%), redness and swelling in the mouth($n = 1$)	0-unblinding

(Continues)

TABLE 3 (Continued)

Supplemental references[a]	First author	Phase of RCT	Number of participants (n)	Women percentage	Mean of Age (year)	Participants' comorbidity and (age group in study)	Vaccine dose	Days between doses	Dose number	Any symptoms after vaccine	Percentage of mucocutaneous reaction	Time of onset the reactions (days)
4.2. WIBP-CorV ($n = 132$)												
35	Xia, S.	Phase 1	24	54.2	36	Baseline COVID + (0%)	2.5 μg	28	1&2&3	Injection site pain	Local: swelling(4.2%)	0–28
35	Xia, S.	Phase 1	24	54.2	43.1	Baseline COVID + (0%)	10 μg	28	1&2&3	Injection site pain,fever,nausea and vomiting, anorexia	Local: redness(4.2%), swelling (4.2%)	0–28
35	Xia, S.	Phase 2	84	61.9	43.8	Baseline COVID + (0%)	5 μg	21	1&2	Injection site pain, diarrhea, fever, nausea and vomiting	Local: itching(1.2%), swelling (1.2%)	0–28
4.3. BBIBP-CorV ($n = 27,367$)												
36	Xia, S.	Phase 1	24	66	42.7	NM (18–59 years)	2 μg, HB02 strain	28	1&2	Injection site pain, fever,fatigue, headache	Injection site: redness(4%), mucocutaneous abnormalities(4%),itch (non-injection site)(4%)	0–7
36	Xia, S.	Phase 1	24	50	37.7	NM (18–59 years)	4 μg, HB02 strain	28	1&2	Injection site pain, fever, vomiting	Injection site: itch (4%)	0–7
36	Xia, S.	Phase 1	24	47	40.1	NM (18–59 years)	8 μg, HB02 strain	28	1&2	Injection site pain, fever, inappetence, nausea, constipation	Injection site: swelling (8%)	0–7
36	Xia, S.	Phase 1	24	72	67.5	NM (≥60 years)	8 μg, HB02 strain	28	1&2	Injection site pain, fever, fatigue,headache	Injection site: induration (8%)	0–7
36	Xia, S.	Phase 2	84	54	40.8	NM (18–59 years)	8 μg, HB02 strain	single	1	Injection site pain, fever, fatigue,headache, diarrhea, muscle pain, dizziness, anaphylaxis(1%)	Injection site: swelling(2%),itch (2%),redness(1%),rash(1%)	0–7
36	Xia, S.	Phase 2	84	55	41	NM (18–59 years)	4 μg, HB02 strain	14	1&2	Injection site pain, fever, fatigue,headache, diarrhea, muscle pain	Injection site:itch(1%),itch (non-injection site)(2%)	0–7
36	Xia, S.	Phase 2	84	53	41.7	NM (18–59 years)	4 μg, HB02 strain	21	1&2	Injection site pain, fever, fatigue,nausea,headache, drowsiness	Injection site: swelling(4%), redness(1%)	0–7
36	Xia, S.	Phase 2	84	57	43.7	NM (18–59 years)	4 μg, HB02 strain	28	1&2	Injection site pain, fever fatigueheadache, cough	Injection site: swelling(1%),itch (1%),redness(1%), itch (non-injection site)(1%)	0–7
37	Al Kaabi, N.	Phase 3	13,464	15.9	36.2	Baseline COVID PCR + (0.2%), Baseline IgG +(5.0%)	5 μg, WIV04 strain	21	1&2	Injection site pain, headache, fatigue, myalgia, diarrhea, coughing, fever, dyspnea, arthralgia, constipation, nausea, vomiting, dysphagia, anorexia	Injection site: induration(1.0%), swelling(1.5%), rash(0.7%), redness (1.1%), itching(0.4%), pruritus (non-inoculated site) (1.3%), skin and mucosal abnormalities(0.2%), acute allergic reactions(0.3%)	0–7
37	Al Kaabi, N.	Phase 3	13,471	15.4	36.2	Baseline COVID PCR + (0.2%), Baseline IgG +(5.2%)	4 μg, HB02 strain	21	1&2	Injection site pain, headache, fatigue, myalgia, diarrhea, coughing, fever, dyspnea, arthralgia, constipation, nausea, vomiting, dysphagia, anorexia	Injection site: induration(0.6%), swelling(0.8%), rash(0.7%), redness(0.9%), itching(0.5%), pruritus (non-inoculated site) (1.5%), skin and mucosal abnormalities(0.2%), acute allergic reactions(0.3%)	0–7

TABLE 3 (Continued)

Supplemental references[a]	First author	Phase of RCT	Number of participants (n)	Women percentage	Mean of Age (year)	Participants' comorbidity and (age group in study)	Vaccine dose	Days between doses	Dose number	Any symptoms after vaccine	Percentage of mucocutaneous reaction	Time of onset the reactions (days)
4.4. BBV152 ($n = 380$)												
38	Ella, R.	Phase 1/2	190	26	34	NM	3 μg + Algel-IMDG	14	1&2	Injection site pain, body ache, fever, headache, malaise	Redness at injection site (1st:1%), itching (1st:1%), stiffness in upper arm (1st:1%)	0–7
38	Ella, R.	Phase 1/2	190	24	35	NM	6 μg + Algel-IMDG	14	1&2	Injection site pain, weakness in injection arm, body ache, fever, headache, malaise, weakness	Redness at injection site (1st:1%), itching(1st:1%, 2nd:1%),rashes(1st:1%)	0–7
4.5. KCONVAC ($n = 424$)												
39	Pan, H. X.	Phase 1	24	50	38	NM	5 μg	14	1&2	Injection site pain,myalgia, fatigue	Injection site:induration(4%), erythema(8%)	0–28
39	Pan, H. X.	Phase 2	100	47	45.5	NM	5 μg	14	1&2	Injection site pain,fever, inappetence, myalgia, headache, fatigue	Injection site:induration(2%), erythema(1%), pruritus(2%)	0–28
39	Pan, H. X.	Phase 2	100	55	44.9	NM	10 μg	14	1&2	Injection site pain,fever, diarrhea, inappetence, vomiting, myalgia, headache, cough, dyspnea, fatigue	Injection site:pruritus(1%), skin or mucosa abnormality(1%)	0–28
39	Pan, H. X.	Phase 2	100	62	42.4	NM	5 μg	28	1&2	Injection site pain,fever, diarrhea, myalgia, headache, cough, fatigue	Injection site:erythema(1%), pruritus(1%)	0–28
39	Pan, H. X.	Phase 2	100	54	44.5	NM	10 μg	28	1&2	Injection site pain,fever, diarrhea, nausea, cough, fatigue	Injection site:induration(%3), swelling(2%), erythema(5%), pruritus(2%)	0–28
4.6. IBMCAMS vaccine ($n = 96$) (LD: 50EU, MD: 100EU)												
40	Pu,J.	Phase 1	24	54	37	NM	LD	14	1	Injection site pain, fatigue, fever, serious adverse events (8.3%)	Injection site itching (8.3%), rash (4.2%)	0–7
40	Pu,J.	Phase 1	24	54	37	NM	LD	14	2	Injection site pain, fatigue	Injection site redness (4.2%)	0–7
40	Pu,J.	Phase 1	24	67	38.2	NM	MD	14	2	Injection site pain, fatigue, diarrhea	Injection site itching (4.2%)	0–7
40	Pu,J.	Phase 1	24	50	40.1	NM	MD	28	2	Injection site pain, fatigue, fever, serious adverse events (8.3%)	Injection site swelling (4.2%)	0–7
5. Virus-like particle vaccines												
5.1. CoVLP ($n = 180$)												
41	Ward, B. J.	Phase 1	20	55	34.9	NM	3.75 μgUn-adjuvanted	21	1&2	Injection site pain, headache, fatigue, chills, discomfort or uneasiness	Injection site: redness (5%), swelling(5%), swelling in neck (5%) 0-21d: allergicconjunctivitis (5%), maculo-papular rash (5%)	0–7
41	Ward, B. J.	Phase 1	20	50	35.3	NM	3.75 μg + CpG	21	1&2	Injection site pain, fever, headache, muscle aches fatigue, chills, discomfort or uneasiness	Injection site: redness (5%), swelling(1st:5%, 2nd: 15%) swelling in neck(1st:20%, 2nd: 5%), chest wall (5%); 0-21d: hordeolum(5%), plantar fasciitis(5%)	0–7

(Continues)

TABLE 3 (Continued)

Supplemental references[a]	First author	Phase of RCT	Number of participants (n)	Women percentage	Mean of Age (year)	Participants' comorbidity and (age group in study)	Vaccine dose	Days between doses	Dose number	Any symptoms after vaccine	Percentage of mucocutaneous reaction	Time of onset the reactions (days)
41	Ward, B. J.	Phase 1	20	75	34.7	NM	3.75 μg + AS03	21	1&2	Injection site pain, fever, headache, muscle aches, joint aches, fatigue, chills, discomfort or uneasiness	Injection site: redness (1st:5%, 2nd:31.6%), swelling (1st:15%, 2nd: 31.6%), swelling in neck(5.3%); 0-21d: bacterial vaginosis(5%), vaginal infection (5%)	0–7
41	Ward, B. J.	Phase 1	20	50	35.6	NM	7.5 μg Un-adjuvant	21	1&2	Injection site pain, headache, muscle aches, joint aches fatigue, chills	Injection site: swelling(5%); swelling in neck (5%), axilla (5%), groin(5%); 0-21d: rash(5%)	0–7
41	Ward, B. J.	Phase 1	20	60	32.4	NM	7.5 μg + CpG	21	1&2	Injection site pain, fever, headache, muscle aches, fatigue, chills, discomfort or uneasiness	Injection site: redness (5%), swelling(1st:20%, 2nd:15%), swelling in neck (5%) 0-21d: vulvovaginal pruritus (5%), contact dermatitis (5%), erythema(5%)	0–7
41	Ward, B. J.	Phase 1	20	60	37.2	NM	7.5 μg + AS03	21	1&2	Injection site pain, fever, headache, muscle aches, joint aches, fatigue, chills, discomfort or uneasiness	Injection site: redness(35%), swelling(1st:30%, 2nd:40%); swelling in neck(1st:5, 2nd:10), axilla(5%), groin(5%), chest wall(5%); 0-21d: lymphadenopathy(5%), injection site papule(5%)	0–7
41	Ward, B. J.	Phase 1	20	65	34.1	NM	15 μg Un-adjuvanted	21	1&2	Injection site pain, headache, muscle aches, fatigue	Swelling in neck (10%); 0-21d: oral herpes(5%), dyshidrotic eczema(5%)	0–7
41	Ward, B. J.	Phase 1	20	50	32	NM	15 μg + CpG	21	1&2	Injection site pain, fever, headache, muscle aches, joint aches, fatigue, chills, discomfort or uneasiness	Injection site: swelling(1st:10%, 2nd:5.3%); swelling in neck (1st:5%, 2nd:5.3%), axilla (5.3%), chest wall (5%); 0-21d:hot flush(5%)	0–7
41	Ward, B. J.	Phase 1	20	45	32.7	NM	15 μg + AS03	21	1&2	Injection site pain, fever, headache, muscle aches, joint aches, fatigue, chills, discomfort or uneasiness	Injection site: redness (1st:5%, 2nd:20%), swelling(1st:20%, 2nd:25%); swelling in neck (1st:10%, 2nd:15%), axilla (1st:10%, 2nd:10%); 0–21 d:injection sitebruising (5%), erythema(5%), warmth (5%), swelling(5%)	0–7

Abbreviations: 1st, after the first dose; 2nd, after the second dose; CLD, chronic lung disease; CVD, cardiovascular disease; d, days; DM, diabetes mellitus; GI, gastrointestinal; HIV, human immunodeficiency virus positive; HTN, hypertension; IHD, ischemic heart disease; NM, not mentioned.

[a]Supporting information Table S3.

Gam-COVID-Vac ($n = 15{,}011$), and ChAdOx1 nCoV-19 ($n = 13{,}995$), in descending order.

For intervals between the two (or three) doses, studies on BNT162b2, BNT162b1, Gam-COVID-Vac, NVX-CoV2373, SCB-2019, V-01 and CoVLP used an interval of 21 days; studies on mRNA-1273 and MF59-adjuvanted sclamp used 28 days; and studies on Ad26.COV2.S used 56-day intervals or single doses. Other trials also tested different regimens or single doses, sometimes comparing the two. For example, studies on ChAdOx1 nCoV-19 tested day 0–21, 0–28, 0–56 regimens or intervals anywhere between 21 to 35 days (the rest are noted in the table). Most of these trials used the same candidate vaccines for both the primer and booster doses, some using different doses of the same vaccine for each dose. Three of the studies had administered heterologous primer-booster vaccines; rAd26 with rAd5 (making up the Gam-COVID-Vac),[15,16] and ChAdOx1-S with BNT162b2 (named the CombiVacS).[53]

Among our included groups, only one study which was on BNT162b2 had individuals under the age of 18, set in two groups, 12 to 15-year-olds and 16 to 25-year-olds.[4] The rest had only included individuals above the age of 18, some extending their age groups up to 85-year-olds. Also, the trials often had groups with different age ranges, measuring the side effects in each age group, which are all noted in Table 3.

We must bear in mind that the earlier expeditious vaccination with mRNA vaccines and their larger number of RCT participants is also reflected in the net number of observed side-effects, as the number of participants in RCTs on mRNA vaccines (70,277), is almost comparable to the number of participants in the collective rest of the vaccine RCTs (90,353). This earlier jumpstart in mRNA vaccination also warrants more time for researchers to observe the side effects. We believe that these reasons have led to the larger number of studies on mRNA vaccines and therefore when evaluating the different vaccine categories, the relative risk of side-effects should be compared between the groups, not the number of reported cases or articles.

3.5 | Analytical observational studies

A total of 27 observational articles, consisting of case-control, cohort and cross-sectional studies were included, with a total population of 467,577 participants, as illustrated in Table 4. The studies came from different countries such as United States, the UK, Italy, Poland, Czech Republic, Jordan, Spain, South Korea, Malta, Scotland, Argentina, China and international registries. The administered candidate vaccines in these studies in order of number of collective number participants having received them were Ad26.COV2.S ($n = 338{,}765$),[54] mRNA-1273 ($n = 55{,}944$),[47,55] BNT162b2 ($n = 33{,}539$),[45,47,55–66] ChAdOx1 nCoV-19 ($n = 26{,}862$),[56,60,62,63,66–68] CoronaVac ($n = 1855$),[69,70]Gam-COVID-Vac ($n = 683$),[71] and BBIBP-CorV ($n = 89$).[56]In addition, seven studies reported combined results on more than one vaccine, collectively comprised of 9851 participants. Five of these studies were on BNT162b2 and mRNA-1273,[72–76] one study with the addition of ChAdOx1 nCoV-19 to the two previous vaccines,[77] and one study with BNT162b2 and ChAdOx1 nCoV-19.[78] We categorized the studies base on the vaccines administered in Table 4.

3.6 | Recommendations and guidelines for vaccination in specific groups

A total of 37 articles regarding recommendations, guidelines and consensus opinion of experts on COVID vaccination in specific groups, such as those with underlying dermatologic or autoimmune disorders (with worries of potential flare-ups[79,80]), those with allergies, and those on immunosuppressive, immunomodulatory or biologic therapies (with worries of inefficient immunization[79,81]), along with articles on certain precautions to be taken with regard to possible anaphylaxis or vaccine-induced thrombotic thrombocytopenia (VITT) were found and their key points were extracted, as highlighted in Table 5.

These points have been categorized in the table as depicted below:

1. For patients with autoimmune disorders
   - 1.1 Autoimmune inflammatory rheumatic diseases[82–87]
     - 1.1.1 Psoriasis[88,89]
   - 1.2 Hidradenitis suppurativa[90]
   - 1.3 Patients with pemphigus on rituximab[91]
   - 1.4 Inflammatory bowel diseases[92]
2. For patients with allergic or atopic disorders
   - 2.1 Atopic dermatitis[93–95]
   - 2.2 Mastocytosis[96,97]
   - 2.3 Urticaria[93,94]
   - 2.4 Allergic diseases (general)[98–103]
   - 2.5 Precautions for anaphylaxis[104–108]
3. For dermatology patients on Immunosuppressive, immunomodulatory or biologic therapies[109–113]
4. Precautions for vaccine-induced thrombotic thrombocytopenia[72,114]
5. For delayed reactions to hyaluronic acid soft tissue fillers[115–117]

4 | DISCUSSION

With the emerging knowledge of the adverse events following COVID-19 immunization, an arising demand has been put on clinicians to be updated on the various mild to severe or potentially life- threatening manifestations of COVID vaccines, and whether or not certain patient groups can be vaccinated, or what precautions are to be taken with regard to their medical status. Much attention has been focused on hot topics regarding COVID-19 prognostic and therapeutic options during the pandemic, with special focus on dermatologic concerns,[118–135] and now with the wide distribution of the COVID vaccines, a comprehensive assessment of the mucocutaneous eruptions associated with COVID-19 immunization is an issue of great

TABLE 4 Mucocutaneous reaction after COVID-19 vaccination reported in "Observational Analytical" studies

Supplemental references[a]	Patients No	Woman ratio	Mean of Age (year)	Participants' characteristics or comorbidities	Dose	Any symptoms after vaccine	Mucocutaneous lesions characteristic	Time of onset the reactions	Location of mucocutaneous reaction	Duration of reaction
With BNT162b2										
1	141	70.7	34.99	NM	1	Fever(6.4%), fatigue (31.9%), myalgia(21.3%), bone pain(7.1%), joint pain (13.5%), headache (27.7%), injection site pain(75.9%), arm numbness (12.1%), diarrhea(1.4%), shortness of breath (1.4%)	Herpes zoster (0.7%), redness and swelling (0.7%)	NM	Injection site	1.39 days
2	803	86.55	43	NM	1 & 2	Injection site pain(88.04%), weakness(58.9%), myalgia(45.7%), headache(44.83%), chills (35.99%), fever(22.04%), joint pain(16.56%), nausea(15.94%), spasm (9.59%), sweating (9.22%), dizziness (8.34%), musculoskeletal (53.3%), GI (21.42%), neurological (12.7%), cardiovascular (5.98%), respiratory(2.61%), allergy(1.24%) lymphadenopathy (3.36%)	Swelling(5.48%), itching (5.35%), rash(2.49%), skin discoloration (1.25%), hives(0.62%), bleeding(0.37%), mouth/ throat swelling(0.37%), atopic eczema(0.25%), Hair loss(0.12%), Swelling of the lips (0.12%), Flushing(7.1%)	NM	Injection site, Mouth, Lips	NM
3	877	88.5	42.56	Allergy(5.9%), baseline COVID + (19.3%), HTN (36.9%), thyroid disease (25.6%), asthma(21.8%), DM(9.6%), CVD(5.9%), RA(4.8%), bowel disease (4.4%), Neurologic disease(4.1%), Psychological distress (3%), Renal disease (2.2%), COPD(1.8%), Cancer(1.5%), Hepatologic disease (0.7%), Ophthalmologic disease(0.4%)	1 & 2	Injection site pain(89.8%), fatigue(62.2%), headache(45.6%), muscle pain(37.1%), chills(33.9%), fever (21.7%), lymphadenopathy (16.2%), nausea(13%), taste disturbance(3.5%)	At least one skin-related side effect(5.2%): swelling(25.6%), redness (23%), rash(62.2%), urticaria(22.2%); At least one oral side effect (13%): blisters(36%), halitosis(25.4%), ulcers (14%), bleeding gingiva (11.4%), white/red plaque(10.5%), burning gingiva(8.8%), angular cheilitis(4.4%), tongue tingling(4.4%), vesicles (3.5%), swollen lips (3.5%), xerostomia(2.6%)	1–3 days (26.8%), 1st week (28.6%), 2nd week (16.1%), 3rd week (18.8%), 4th week (9.8%)	Upper limb (60%), chest/ trunk(33.3%), lower limb (22.2%), face(20%), back (17.8%), lips(74.1%), labial/buccal(14.8%), tongue(13%), palate (9.3%), gingiva(9.3%)	1 day (45.1%), 3 days (35.8%), 5 days (9.4%), 1 week (5.3%), >1 week (3.0%), >4 week (1.4%)
4	103	88.3	40.4	NM	1 & 2	(47.6%) of reactions After 1st dose, (52.4%) of reactions after 2nd dose, (18.4%) of participants had reactions after both doses	Delayed injection-site reaction (COVID-arm) (100%), itching (68%), disseminated lesions (4.9%), slightly indurated erythematous targetoid patch(1%)	NM	Injection site, Generalized	<8 h(22.3%), 8-24 h(27.1%), 24-72 h(36.9%), >72 h(13.6%)

TABLE 4 (Continued)

Supplemental references[a]	Patients No	Woman ratio	Mean of Age (year)	Participants' characteristics or comorbidities	Dose	Any symptoms after vaccine	Mucocutaneous lesions characteristic	Time of onset the reactions	Location of mucocutaneous reaction	Duration of reaction
4	4775	83.4	43.2	NM	1 & 2	NM	Vaccine-related urticaria (0.04%)	NM	NM	<7d
5	57	71	48.9	Psoriatic arthritis(17.5%), Spondylo-arthritis(5%), RA(10%), systemic sclerosis(8.7%), SLE (1.5%), Sjogren syndrome(1.7%), HTN (15.7%), obesity(8.7%), DM(3.5%)	1 & 2	1st: injection site pain (29%), fatigue(8.7%), headache(28%), fever (5.2%), tachycardia (3.5%), paresthesia (3.5%), 2nd: injection site pain(41%), fatigue (58%), headache(58%), fever(58%), paresthesia (5.8%), itchy scratchy throat(5.8%), diarrhea (23.5%), lymphadenopathy(5.8%)	2nd: cutaneous vasculitis (5.8%)	NM	NM	NM
6	282,103	61·6	62	NM	1	Headache(7.8%), fatigue (8.4%), chills(2.5%), diarrhea(1.4%), fever (1.5%), arthralgia(3.2%), myalgia(2.3%), nausea (2.1%)	Local side-effects(71.9%), rash(0.2%), skin burning (0.7%)	0–8 days	NM	NM
	28,207	69·6	61		2	Headache(13.2%), fatigue (14.4%), chills(6.4%), diarrhea(1.5%), fever (3.8%), arthralgia(7%), myalgia(5%), nausea (3.5%)	Local side-effects(68.5%), Rash(0.4%), Skin burning (1.1%)	0–8 d	NM	NM
7	131	85.5	47	CVD(21.4%), respiratory disease(26%), autoimmunity(16%), chronic skin conditions (2.2%), anaphylaxis (92.4%), asthma(34.4%), chronic urticaria(5.3%), contact dermatitis(9.9%)	1	Mild immediate reaction in (0.7%) with history of severe asthma, Nasal obstruction, Rhinolalia	Pruriginous erythematous macules (0.7%)	10 min	Neck and upper thorax	1 h
8	34	85 85%	42 42	Atopic dermatitis(7%), contact dermatitis (2.8%), psoriasis(4.2%), urticaria(2.8%), acne vulgaris(2.8%), HTN (11%), COPD(2.8%), morbid obesity(4.2%), DM(1.4%), CVD(2.8%), rheumatologic disease (5.6%), malignancy(4.2%)	1	Fatigue(32%), Myalgia (29%), Headache(26%), Fever(12%), Arthralgia (15%), Nausea(12%), Chills(12%), Lymphadenopathy (5.9%), Diarrheal(2.9%), Injection site pain(24%)	Delayed large local reaction (15%), Local injection site reaction(24%), swelling(18%), erythema (18%), urticaria(26%), morbilliform(18%), erythromelalgia(2.9%), Flare of existing dermatologic condition (2.4%), vesicular(8.8%), pernio/chilblains(8.8%), VZV(2.9%), pityriasis rosea(5.9%), vasculitis (2.9%), reaction in breastfed infant(5.9%), petechiae(2.9%)	Urticarial:3d, morbilliform:3d, Erythromelalgia:7d	Urticaria: arms (68%), trunk (57%), legs(46%), morbilliform: arms(62%), trunk (42%), legs(27%), erythromelalgia: arms (69%), face(31%), hands (23%), feet(15%)	Urticaria:5 days, Morbilliform:4.5 days, Erythromelalgia: 5.5 days

(Continues)

TABLE 4 (Continued)

Supplemental references[a]	Patients No	Woman ratio	Mean of Age (year)	Participants' characteristics or comorbidities	Dose	Any symptoms after vaccine	Mucocutaneous lesions characteristic	Time of onset the reactions	Location of mucocutaneous reaction	Duration of reaction
	40				2	Fatigue(33%), myalgia (25%), headache(15%), fever(10%), arthralgia (20%), nausea(7.5%), chills(13%), lymphadenopathy(7.5%), injection site pain(18%)	Delayed large local reaction (18%), local injection site reaction(25%), swelling (15%), erythema(20%), urticaria(20.5%), morbilliform(7.5%), erythromelalgia(5%), flare of existing dermatologic condition (7.5%), vesicular(5%), pernio/chilblains(5%), VZV(10%), angioedema (2.5%), pityriasis rosea (2.5%), filler reaction (2.5%), contact dermatitis(5%), reaction in breastfed infant (2.5%), onset of new dermatologic condition (5%)	Urticarial:2 days, morbilliform: 2 days, Erythromelalgia: 1 day	Urticaria: arms(68%), trunk (57%), legs(46%); morbilliform: arms (62%), trunk (42%), legs 27%); erythromelalgia: arms(69%), face(31%), hands(23%), feet(15%)	Urticaria: 3 days, Morbilliform: 2.5 days, Erythromelalgia:3 days
9	277	66.8	NM	NM	1	Injection site pain(70.0%), fever(6.9%), chills (15.9%), muscle ache (33.6%), joint pain(9.4%), headache(24.2%), dizziness(14.4%), confused mentality (3.6%), anxiety(4.7%), dyspepsia(6.1%), abdominal pain(4.7%), vomiting(6.1%), diarrhea (5.8%), fatigue(37.5%), palpitation(4.3%), HTN (3.6%), hypotension (3.6%), paralysis(3.6%), paraesthesia(4.3%), nasal obstruction(5.8%), parageusia(1.4%), foreign body sensation in the throat(9.7%), hoarseness(2.2%), odynophagia(2.5%), wheezing(0.7%), chest discomfort(0.4%)	Injection site: redness (2.5%), swelling(5.1%), itch(6.1%), angioedema (4.3%), tongue edema (3.6%), throat swelling and tightness(5.8%), urticaria(0.7%), skin rash (1.8%)	3 days	Injection site, diffuse	NM
10	93	74.1	29	NM	1&2	Injection site pain, fatigue, muscle pain, headache, diarrhea, headache, chills, joint pain, fever (only after 2nd dose)	Injection site: redness (<10%),swelling (<10%)	0–7 days	Injection site	NM

TABLE 4 (Continued)

Supplemental references[a]	Patients No	Woman ratio	Mean of Age (year)	Participants' characteristics or comorbidities	Dose	Any symptoms after vaccine	Mucocutaneous lesions characteristic	Time of onset the reactions	Location of mucocutaneous reaction	Duration of reaction
11	1480	66.69	NM	NM	1&2	Pain at injection site (49.85%), fever(10.11%), chills(10.20%), fatigue (21.79%), muscle pain (24.16%), joint pain (11.00%), headache (21.91%), vomiting (12.90%), diarrhea (13.75%)	Injection site: redness (31.07%),swelling (36.44%)	Peak 1–2d	Injection site	NM
12	151	48	73	CVD(41%), DM(15%), underlying lung pathology(8%), malignancy (100%: solid cancer [63%], hematological cancer [37%])	1&2	Injection-site pain, flu-like symptoms, headaches, chills, fatigue, arthralgia, nausea/vomiting, fever, diarrhea, deranged liver function tests	Injection site: erythema (<10%), swelling(<10%)	0–30 days	Injection site	NM
13	10,445	85	41	(Study only on cutaneous reactions after mRNA COVID-19 vaccination)	1	NM	Dose 1 reaction: cutaneous reaction(1.4%), itching or rash(1.2%), hives/urticaria(0.2%), swelling/angioedema(0.2%)	0–3 days	Injection site, diffuse	NM
	124				2		Recurrent dose 2 reaction: cutaneous reaction (16%), Itching or rash (14%), hives/urticaria (2.4%), swelling/angioedema(2.4%)			
	9055				2		New dose 2 reaction: cutaneous reaction (1.4%), itching or rash (1.1%), hives/urticaria (0.3%), swelling/angioedema(0.2%)			
14	4953 reports	NM	NM	NM	1	Thrombocytopenia (excluding ITP)(0.003%), venous thromboembolic events (including CVST) (0.03%), Arterial thromboembolic events) (0.03%), hemorrhagic events)(0.01%)	ITP (<0.001%)	0–27 days	NM	NM
With mRNA-1273										
8	267	92 92%	45 45	Atopic dermatitis(3.5%), contact dermatitis (2.9%), psoriasis(1.7%), urticaria1.5%), acne vulgaris(1.2%), HTN (16%), COPD(5.2%), morbid obesity(4.1%), DM(4.1%), CVD(2.3%), rheumatologic disease (1.7%), malignancy(1.5%)	1	Fatigue(22%), myalgia (21%), headache(17%), fever(6.7%), arthralgia6%), nausea (5.6%), chills(5.2%), lymphadenopathy(4.9%), diarrheal(3.4%), injection site pain(35%)	Delayed large local reaction (66%), injection site reaction(54%), swelling (44%), erythema (49%), urticaria(5.9%), morbilliform(4.1%), erythromelalgia(1.9%), flare of existing dermatologic condition (1.1%), vesicular(1.5%), pernio/chilblains(1.1%),	Urticarial:3 days, morbilliform:3 days, Erythromelalgia:7 days, delayed large local reactions:7 days	Urticaria: arms(68%), trunk (57%), legs(46%), morbilliform: arms(62%), trunk(42%), legs(27%), erythromelalgia: arms (69%), face(31%), hands (23%), feet (15%)	Urticaria: 5 days, morbilliform: 4.5 days, delayed large local reaction: 4 days, erythromelalgia: 5.5 days

(Continues)

TABLE 4 (Continued)

Supplemental references[a]	Patients No	Woman ratio	Mean of Age (year)	Participants' characteristics or comorbidities	Dose	Any symptoms after vaccine	Mucocutaneous lesions characteristic	Time of onset the reactions	Location of mucocutaneous reaction	Duration of reaction
							VZV(1.9%), angioedema (1.9%), pityriasis rosea (0.4%), erythema multiforme (1.1%), filler reaction (1.1%), vasculitis (0.7%), contact dermatitis (1.1%), onset of new dermatologic condition (0.7%), petechiae(0.4%)			
	102				2	Fatigue(62%), myalgia (62%), headache53%), fever(41%), arthralgia (27%), nausea(27%), chills(46%), lymphadenopathy(8.8%), diarrheal(3.9%), injection site pain(59%)	Delayed large local reaction (30%), Local injection site reaction(70%), swelling(68%), erythema (67%), urticaria(6.9%), morbilliform(6.9%), erythromelalgia(5.9%), Flare of existing dermatologic condition (1%), vesicular(1%), filler reaction(4.9%), contact dermatitis(1%), petechiae(2%)	Urticarial:2 days, Morbilliform:2 days, Erythromelalgia:1 day, Delayed large local reactions:2 days	Urticaria:arms(68%), trunk (57%), legs(46%); morbilliform: arms(62%), trunk(42%), legs(27%); erythromelalgia: arms (69%), face(31%), hands (23%), feet(15%)	Urticaria: 3 days, morbilliform: 2.5 days, erythromelalgia: 3 days
13	30,195	85	41	(Study only on cutaneous reactions after mRNA COVID-19 vaccination)	1	NM	Dose 1 reaction: cutaneous reaction(2.1%), itching or rash(1.6%), hives/ urticaria(0.5%), swelling/ angioedema(0.3%)	0–3 days	Injection site, diffuse	NM
	485				2		Recurrent dose 2 reaction: cutaneous reaction (17%), itching or rash (13%), hives/urticaria (3.5%), swelling/ angioedema(2.7%)			
	24,884				2		New dose 2 reaction: Cutaneous reaction (2.6%), Itching or rash (1.8%), Hives/urticaria (0.7%), Swelling/ angioedema(0.4%)			
With ChAdOx1 nCoV-19										
1	179 409 409	70.7 70.7%	34.99 34.99	NM	1	Fever(73.7%), fatigue (84.9%), myalgia(79.9%), bone pain(44.1%), joint pain (57.0%), headache (68.7%), injection site pain(91.1%), arm numbness(22.9%), diarrhea(9.5%), shortness of breath (9.5%), dizziness (3.4%), vomiting(3.4%), nausea (6.1%)	Urticaria (0.6%)	NM	NM	1.39 d

TABLE 4 (Continued)

Supplemental references[a]	Patients No	Woman ratio	Mean of Age (year)	Participants' characteristics or comorbidities	Dose	Any symptoms after vaccine	Mucocutaneous lesions characteristic	Time of onset the reactions	Location of mucocutaneous reaction	Duration of reaction
15	92	77.2	35.37	Allergy(1.1%), Baseline COVID + (8.7%), thyroid disease(5.4%), asthma (4.3%), neurologic disease (3.3%), psychologic distress(2.2%), RA(1.1%), bone disease(1.1%), HTN(1.1%)	1 & 2	Injection site pain(72.8%), fatigue(73.9%), muscle pain(55.4%), chills (48.9%), feeling unwell (46.7%), nausea(45.7%), headache(29.3%), fever (15.2%), lymphadenopathy(5.4%), taste alterations (5.4%)	Injection site: swelling (10.9%), redness(10.9%); skin rash(4.3%); oral: oral ulcers/blisters/ vesicles(7.6%), halitosis (3.3%), bleeding gingiva (3.3%), white/red plaque (1.1%), Swollen lips (1.1%)	1–3 days (82.6%), 1st week (13%), 4th week (4.3%)	Injection site, lips (1.1%), labial/buccal mucosa (4.3%), tongue (2.2%)	1–3 days
6	345,280	57·7	63·3	NM	1	Headache (22.8%), fatigue (21.1%), chills(14.7%), diarrhea(2.2%), fever (8.2%), arthralgia(11.5%), myalgia(7%), nausea (5.7%)	Local side-effects (58.7%), Rash (0.4%), Skin burning (1.7%)	0–8 days	NM	NM
16	994	76.7	35.7	NM	1	Injection site: tenderness (94.5%) resting pain(88%); fatigue (92.9%), headache (77.7%), malaise(83.8%), arthralgia(61.5%), chills (67.2%), fever(27.6%), nausea/vomiting(36.4%), diarrhea(19.9%)	Injection site: redness (34.1%), swelling(48.7%); reports of urticaria at both arms, both legs, itching sense or warmth at the injection site	2.2 days, peak at 4 days	Injection site, diffuse	1 day, for many
9	5589	77	NM	NM	1	Injection site pain(81.2%), fever(51.3%), chills (65.8%), muscle ache (79.9%), joint pain (48.6%), headache (69.5%), dizziness (46.8%), confused mentality(19.1%), anxiety(22.4%), dyspepsia(30.9%), abdominal pain (24.3%), vomiting (22.8%), diarrhea (24.1%), fatigue (76.5%), palpitation (28.3%), HTN (18.1%), hypotension(18.0%), paralysis(17.7%), paraesthesia (19.3%), nasal obstruction (27.2%), parageusia (8.1%), foreign body sensation in the throat (24.3%), hoarseness (10.4%), odynophagia (11.0%), wheezing (6.4%), chest discomfort (6.3%)	Injection site: redness (7.0%), swelling (9.6%), itch (22.2%), angioedema (19.1%), tongue edema (18.0%), throat swelling and tightness (21.1%), urticaria (5.8%), skin rash(5.7%)	3 days	Injection site, diffuse	NM

(Continues)

TABLE 4 (Continued)

Supplemental references[a]	Patients No	Woman ratio	Mean of Age (year)	Participants' characteristics or comorbidities	Dose	Any symptoms after vaccine	Mucocutaneous lesions characteristic	Time of onset the reactions	Location of mucocutaneous reaction	Duration of reaction
10	42	90.5	36	NM	1	Injection site pain (93%), fatigue (81%), muscle pain (79%), headache (62%), vomiting (<20%), diarrhea (<20%), headache (~60%), chills (~60%), joint pain (~30%), fever (<40%)	Injection site: redness (<20%), swelling (<20%)	0–7 days	Injection site	NM
14	19,148 reports	NM	NM	NM	1	Thrombocytopenia (excluding ITP) (0.002%), Venous thromboembolic events (including CVST) (0.02%), Arterial thromboembolic events (0.07%), Hemorrhagic events (0.01%)	ITP (0.001%)	0–27 days	NM	NM
With Ad26.COV2.S										
17	13,725	66.2	42	(Percentages are among all 338,765 participants receiving the vaccine, 13,725 of which experienced adverse events)	1	Fatigue (59.1%), injection site pain (57.9%), headache (52.2%), myalgia (47.8%), fever (34.7%), chills (34.2%), joint pain (26.1%), nausea (18.7%), diarrhea (9.4%), abdominal pain (7.4%), vomiting (2.1%)	Swelling (9.3%), redness (7.4%) itching (7.1%) rash (1.9%) (serious adverse reactions: 3%, including 3 reports of non-CVST TTS) cerebral venous sinus thrombosis thrombocytopenia syndrome	0–7 days	Injection site, diffuse	NM
With BBIBP-CorV										
1	89	65.6	39.27	NM	2	Headache (12.4%), fever (4.5%), fatigue (16.9%), myalgia1 (4.6%), injection site pain (37.1%), injection site numbness (5.6%), joint pain (3.4%), diarrhea (1.1%), shortness of breath (2.2%), bone pain (4.5%)	Herpes zoster (1.1%)	NM	NM	NM
With CoronaVac										
18	329	48.5	35.77	NM	2	Injection site pain, headache (16.8%), fever (3.6%), state of sleep/ fatigue (13.8%), nausea/ vomiting (10.8%), myalgia (3.9%), (tachycardia, loss of taste, feeling of throat swelling, vertigo) (5.1%)	Injection site: redness/ swelling/pain (9.0%), allergy (0.9%), extensive itchiness (0.6%) (serious adverse reactions: 33.2%)	1.14 days (for serious events)	Injection site, diffuse	1.68 days (for serious events)

TABLE 4 (Continued)

Supplemental references[a]	Patients No	Woman ratio	Mean of Age (year)	Participants' characteristics or comorbidities	Dose	Any symptoms after vaccine	Mucocutaneous lesions characteristic	Time of onset the reactions	Location of mucocutaneous reaction	Duration of reaction
19	1526	79.3	35.4	Allergic history (6.3%), adverse reactions to other vaccines (5.6%), BMI ≥ 28 (5.1%)	1	Fatigue (8.3%), Muscle pain (8.1%), headache/ dizziness(6%), fever (2.9%), vomiting/ diarrhea(1.6%), appetite impaired/nausea (1.4%), cough/throat pain (1.2%), stuffy runny nose(0.9%), non-solicited adverse reactions (menstruation, chest pain, numbness of limbs): (0.6%)	Injection site adverse reactions (pain, induration, redness, swelling, or itch): (9.6%), allergic reaction/ urticaria/rash(1%), lymphadenopathy(0.7%)	NM	Injection site, diffuse	NM
					2	Fatigue (6.5%), muscle pain (7.8%), headache/ dizziness (3.4%), fever (1%), vomiting/diarrhea (0.9%), appetite impaired/nausea (0.9%), cough/throat pain (0.5%), stuffy runny nose (0.4%), non-solicited adverse reactions (menstruation, chest pain, numbness of limbs): (0.3%)	Injection site adverse reactions (pain, induration, redness, swelling, or itch): (10.7%), lymphadenopathy (0.3%) (129 did not receive the 2nd dose, 16.3% of which had an adverse reaction after the 1st dose)	NM	Injection site, diffuse	NM
With Gam-COVID-Vac										
20	683	68.2	35	Allergies (5.3%), DM (0.9%), hepatic disease (0.6%), renal failure (0.1%), corticosteroid treatment (0.1%), autoimmune disease (1.6%), baseline COVID-19 + (5.0%), any vaccinations 4 months prior (1.5%), family history of reaction to vaccines (0.9%)	1	New or worsened muscle pain (58%, 10% severe, 1% grade 4), pain at injection site (57%, 2% severe), fever (40%), headache (33%), diarrhea (5%, $n = 1$ severe), vomiting (3%, $n = 2$ severe), breathing difficulty (2%)	Local redness or swelling (11%), swelling of face or throat (1%) 33% of all reported adverse events were local (serious adverse events: 5%)	0–3 days	Injection site, diffuse	NM
Results on more than one vaccine in a study (received by noted percentage of participants)										
With BNT162b2 (54%), mRNA-1273 (46%)										
21	741	57	60	Study conducted only on solid organ transplant recipients, kidney (49%), liver (19%), heart (15%), lung (11%), pancreas (1%), multiple organs (5%) (median 7 [Refs. 3–14] years since transplant, on maintenance immunosuppression) Prior COVID +(2%)	1&2	Pain at the injection site (80%), fatigue (46%) (severe:2.5%), headache (49%), myalgia, chills, fever, diarrhea, vomiting	Local swelling and erythema <20%	0–7 days	Injection site	NM

(Continues)

TABLE 4 (Continued)

Supplemental references[a]	Patients No	Woman ratio	Mean of Age (year)	Participants' characteristics or comorbidities	Dose	Any symptoms after vaccine	Mucocutaneous lesions characteristic	Time of onset the reactions	Location of mucocutaneous reaction	Duration of reaction
With BNT162b2 (93%), mRNA-1273 (7%)										
22	708	65	44	(Study conducted only on nephrologists) Prior COVID +(17%)	1&2	Local reaction (68%), followed by myalgia (44%), tiredness (39%) and headache (34%) chills (28%), Low-grade fever (21%)(75% of all included) (69%) after the first dose (57%) after the second dose	Lymphadenopathy (6%), rash (<1%)	0–7 days	Diffuse	NM
With BNT162b2 (51%), mRNA-1273 (49%)										
23	325	96	43	Only on patients with rheumatic and musculoskeletal diseases (RMD): inflammatory arthritis (38%), SLE (28%), overlap connective tissue disease (19%) Treated with: non-biologic disease modifying antirheumatic drugs (44%), biologic therapy (19%) and combination therapy (37%)	1	Systemic symptoms (69%), fatigue: the most common systemic event, 7.4% severe), headache, myalgia, chills, fever, diarrhea, vomiting	Local symptoms (89%) including pain (<90%), swelling (<30%), and erythema (∼20%)	0–7 days	Injection site	NM
With BNT162b2 (95.16%), mRNA-1273 (4.81%), unknown (0.03%)										
24	3908	80.33	42.75	NM	1&2	(79.68%) reported after the first dose, general disorders (48.80%), such as fatigue, pain, and chills nervous system disorders (46.39%) headache (46.39%), dizziness (38.67%), and paraesthesia (25.48%) syncope (2.04%), facial nerve paralysis (0.99%), and seizure (0.66%) Gastrointestinal disorders (25.54%) nausea (56.41%), vomiting (14.73%), and diarrhea (14.13%) anaphylactic or anaphylactoid reactions (∼4.15%)	Skin and subcutaneous tissue disorders: 24.08% (rash: 40.28%)	3 days	Diffuse	NM

TABLE 4 (Continued)

Supplemental references[a]	Patients No	Woman ratio	Mean of Age (year)	Participants' characteristics or comorbidities	Dose	Any symptoms after vaccine	Mucocutaneous lesions characteristic	Time of onset the reactions	Location of mucocutaneous reaction	Duration of reaction
With mRNA-1273 (90%), BNT162b2 (7%), other or unknown (3%)										
25	510	93	50	(Results only on Black, Indigenous, or People of Color [BIPOC])	1&2	(96%) after 1st dose and (85%) after mRNA-1273	Delayed large local reactions (100%, 11% reported in BIPOC patients), diffuse itching, hives or other rash, or angioedema (20%)	8 days	Injection site, diffuse	NM
With BNT162b2 (94.9%), ChAdOx1 nCoV-19 (3.9%) and mRNA-1273 (1.2%)										
26	1657	79	NM	NM	1	Soreness (78%), limb pain (46.6%), fatigue (30%), malaise (21.3%), headache (16.65%), muscle and joint pain (15%), fever (17.3%), chills (11.5%), lymphadenopathy (4.2%), seizures (1.6%), insomnia (4.3%), nausea (3.9%), vomiting (0.8%), allergic reactions (0.6%), migraine (2.6%), diarrhea (1.3%), cough (0.9%)	Swelling (24.5%), redness (18.3%), hair loss (0.8%)	NM	Injection site	NM
					2	Soreness (64.7%), fatigue (45.7%), malaise (43%), pain in the limb (38.7%), muscle and joints pain (33%), chills (31%), headache (30%), fever (42.3%), lymphadenopathy (9.5%), insomnia (7%), nausea (6.8%), migraine (3.6%), seizures (3.2%), cough (1.9%), diarrhea (1.7%), fainting (1.2%), vomiting (1.1%), allergic reaction (0.5%)	Swelling (20%), redness (16.6%), pruritus (4.8%), hair loss (0.9%)	NM	Injection site	NM

(Continues)

TABLE 4 (Continued)

Supplemental references[a]	Patients No	Woman ratio	Mean of Age (year)	Participants' characteristics or comorbidities	Dose	Any symptoms after vaccine	Mucocutaneous lesions characteristic	Time of onset the reactions	Location of mucocutaneous reaction	Duration of reaction
A comparison of mRNA and viral vector vaccines: BNT162b2 (83.6%), ChAdOx1 nCoV-19 (14.1%), other or unknown (2.3%)										
27	2002	72.1	45	Prior COVID-19 + (26.6%)	1 1	More common in viral vector vaccines: Fever, flu-like illness, shortness of breath, fatigue or tiredness	More common in viral vector vaccines: Skin rash, tingling, face and mouth swelling, generalized swelling, anaphylaxis (less common among those without a prior COVID infection)	0–7 days	Injection site, diffuse	NM
						More common in mRNA vaccines: Any side effect	More common in mRNA vaccines: Localized reaction (mostly mild in mRNA vaccines)			

Abbreviations: 1st, after the first dose; 2nd, after the second dose; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; GI, gastrointestinal; HTN, hypertension; NM, not mentioned; RA, rheumatoid arthritis; SLE, systemic lupus erythematous; VZV, Varicella-zoster virus.

[a]Supporting information Table S4.

TABLE 5 Guidelines and recommendations of experts about COVID-19 vaccination in special categories

Supplemental references[a]	FA	Recommendations	Reason for recommendation	Drug dose adjustments	Any added drugs or monitoring
1. For patients with autoimmune disorders					
1.1. Autoimmune inflammatory rheumatic diseases					
1	Curtis, J.R.	• Vaccinate AIIRD patients with stable, low-activity disease, and those receiving immunomodulatory treatments, with either vaccine available to them (suggest the 2nd dose of the same vaccine) • Vaccinate AIIRD patients with life-threatening disease, only after controlling their disease • Consider patients with SLE receiving cytotoxic therapy and higher-dose glucocorticoids, or patients receiving RTX therapy as high risk AIIRD patients and advised to get vaccinated	AIIRD patients are at a higher risk for incident viral infections hospitalization due to COVID- 19 compared to the general population	• Withhold MTX and JAK inhibitors 1 week after each vaccine dose, for those with controlled disease • Withhold ABT SC both 1 week prior to and 1 week after only the 1st dose of vaccination • Schedule ABT IV infusion 4 weeks only before the 1st vaccination, and postpone the subsequent ABT infusion by 1 week (5 week interval in total) (no adjustments needed for 2nd vaccine dose) • Schedule CP administration 1 week after each vaccine dose • Delay RTX 2–4 weeks after 2nd vaccine dose if disease activity allows	Prophylaxis with Acetaminophen or NSAIDs to prevent post-vaccination symptoms is not recommended
2	Park, J.K.	• Suggest patients with AIIRD and their family members to receive a COVID-19 vaccine • Administer the vaccination, ideally when the patient's AIIRD is in a quiescent state, and before beginning immunosuppressive therapy • Continue DMARDs during vaccination; and to improve vaccine efficacy, adjust the timing of RTX, MTX, and ABT administration • Consider immediate, severe allergic reaction to a previous COVID-19 vaccine or its components, the only contraindication to COVID-19 vaccination	Patients with AIIRD are immunocompromised due to underlying immune dysfunction and concomitant immunosuppressive treatment	• Continue DMARDs during vaccination since withholding DMARDs can increase disease activity, which is associated with worse COVID-19 infection severity and outcomes • Temporarily discontinue MTX for 1–2 weeks after each dose • Start the next cycle of RTX 4 weeks after the 2nd vaccine dose • Schedule ABT 1 week after the 1st vaccine dose and continue after the 2nd vaccine dose • Schedule CP IV 1 week after each vaccine dose • Withhold JAK inhibitors 1 week after each vaccine dose	• Monitor patients for at least 15 min after being vaccinated for signs of anaphylaxis • Patients should continue general public health measures against COVID-19, such as wearing masks, hand hygiene, and social distancing, even after vaccination
3	Moutsopoulos, H.M. Moutsopoulos	• Delay initiation of immunosuppressive therapy until vaccination is completed • Vaccinate patients on monthly IV pulse CP/methyl prednisone therapy either prior to therapeutic scheme or 1 month after the completion of 6 months pulse therapy • Perform immunization after the anti-cytokine drug therapy has reached baseline sera levels • Vaccinate reluctant patients without withholding their immunoregulatory/immunosuppressive therapy • Check antibody titers against SARS-CoV-2, 2–4 weeks after the final vaccination dose and at 3 and 6 months thereafter, in all of the mentioned cases	Serum antibodies against PF-4 in patients with SLE and APS display an association with thrombotic events	• Hold anti-metabolites, calcineurin and JAK inhibitors for 10 days before and 10 days after each vaccine dose • Decrease Prednisone dosage (of >0.5 mg/kg body weight or an equivalent synthetic steroid dose) to <10 mg/daily for 10 days before and after each vaccine dose • Vaccinate patients on RTX therapy either 1 month prior to initiation of the therapeutic scheme or 6–8 months after the RTX infusion • Continue anti-cytokine therapies, AZA and calcineurin inhibitor therapy in patients • Temporarily hold MTX and JAK inhibitors only after and not prior to administration of each vaccine dose	• Suggest a constant vigilance following vaccination in patients with SLE and APS due to possible thrombotic events
4	Tam, L.S.	For rheumatic and musculoskeletal diseases (RMD) (including SLE): • Vaccinate RMD patients with normal or altered immunocompetence as soon as it becomes available to them based on current country, regional and/or international guidelines • Initiate immunosuppressive therapies in patients with newly diagnosed RMD at least 2 weeks after the completion of COVID-19 vaccination (with 2nd dose administered after minimum interval), if disease activity allows	To allow an adequate immune response to the vaccine and also to minimize the delay in the administration of immunosuppressive therapy	• Consider a temporary discontinuation of MTX for 2 weeks post-vaccination in well-controlled rheumatoid arthritis patients	NM

(Continues)

TABLE 5 (Continued)

Supplemental references[a]	FA	Recommendations	Reason for recommendation	Drug dose adjustments	Any added drugs or monitoring
5	Santosa, A.	For connective tissue disorders, Psoriatic arthritis, SLE, Immune mediated inflammatory myositis, Sjogren's syndrome, Systemic sclerosis: • Making individualized decisions is suggested • If possible, administer the vaccine when the disease is quiescent • Continue immunomodulatory drugs, other than RTX, alongside COVID-19 vaccination • Vaccinate household contacts	B cell depleting therapy with RTX is associated with significant reduction in immunogenicity.	• Administer the vaccine a minimum of 6 months after the last dose, and/or 4 weeks prior to the next dose of RTX • Do not delay vaccination in patients on or planned for RTX, with an ideal interval of vaccination 4–8 weeks after the last dose of RTX or 2 weeks prior to a planned dose of RTX, if possible	NM
6	Bechman, K.	For immunosuppressed patients with rheumatic disorders • If immunosuppressive treatment has not been started, administer the 1st dose at least 2 weeks prior to initiation of the therapy course and administer 2nd dose before starting the treatment with a minimum interval of 3–4 weeks after 1st dose • If patients are already on immune modulation, vaccinate at least 6 months after administration and 4 weeks before the next course of B cell–depleting therapy • No universal decision on DMARD interruption has been made yet	To have a more adequate immune response	• Adjust conventional synthetic DMARD therapy on an individual basis	NM
1.1.1 Psoriasis					
7	Gelfand, J.M.	• Recommend an mRNA-based COVID-19 vaccine to patients without contraindications, as soon as possible	Comorbidities leading to more severe COVID-19 are more frequent among patients with psoriasis	• Continue the biologic or oral therapies for psoriasis and/or psoriatic arthritis during the vaccination period	NM
8	Mease, P. J.	Consensus opinion from rheumatologists, dermatologists, infectious disease specialists, and patient research partners: • Data does not suggest that having psoriatic diseases or being under treatment significantly increases the risk of COVID infection, or a more severe disease course • The telehealth experience for patients with psoriatic diseases has been a success overall	Concerns of more severe outcomes of COVID-19 among those with psoriatic diseases	Before getting the chance to vaccinate, treatment should continue without concerns of a more severe COVID course.	NM
1.2. Hidradenitis Suppurativa (HS)					
9	Giamarellos-Bourboulis, E.J.	• Vaccinate HS patients without specific contraindications • Consider HS patients with metabolic diseases as a priority group to get vaccinated • Patients treated with biologics should not be given vaccines containing living microorganisms • Serological confirmation of adequate immune response is still not recommended as routine practice • Treatment of HS with ADA and antibiotics seems not to increase the chance of contraction or a more severe course of COVID-19	Metabolic diseases, which are more common in HS, may induce an increased risk of a severe course of COVID-19 and possible fatalities. Biological drugs reduce the hyperactivity of the immune system which might result in suboptimal immunization.	• Treatment with ADA should not be interrupted especially in moderate-to-severe HS, and patients can be vaccinated with non-living virus vaccines, • but ADA may be suspended around the vaccination periodat the discretion of the responsible physician, who knows the patient's clinical situation best	• Initiation of HS treatment with therapies other than ADA and antibiotics should be carefully evaluated at an individual level • Recommend self-protection with masks, even after vaccination

TABLE 5 (Continued)

Supplemental references[a]	FA	Recommendations	Reason for recommendation	Drug dose adjustments	Any added drugs or monitoring
1.3. Patients with pemphigus on RTX					
10	Waldman, R. A.	Individuals who have not initiated RTX therapy: • Typically vaccinated at least 4 weeks before RTX infusion. Individuals who are actively receiving RTX: • Often vaccinated 12–20 weeks after completion of a treatment cycle,so there is a 4-week or longer period prior to next their infusion (assuming dosing every 6 months) to mount an immune response (this is the common pattern for influenza vaccines and could be used for COVID vaccination as well)	Concerns of the effect of RTX on immune response after vaccination	• Before getting the change to vaccinate, encourage careful use of anti-CD20 (RTX) therapy for skin diseases. • When vaccines are available, consider vaccination 12–20 weeks after the completion of a treatment cycle, or extending RTX dosing intervals • Extending RTX dosing intervals to enhance the immune response after vaccination should be weighed against the risk of disease recurrence.	• Although vaccine response may be attenuated, and may have lower rates in RTX recipients, it can be quantified with titers, which may then be helpful for further decisions to revaccinate patients.
1.4. Inflammatory bowel diseases					
11	Siegel, C. A.	• Patients with IBD should be vaccinated against COVID as soon as possible. • Patients with IBD are at the same risk of COVID as the general population. • Patients with IBD, whether or not receiving immune-modifying therapies, can safely receive all non-live vaccinations for any vaccine-preventable illness. If on immune they should not receive live virus vaccines. • Do not defer vaccination for a patient with IBD receiving immune-modifying therapies. • Inform patients that they will mount an immune response to vaccination, however, vaccine efficacy may be blunted when receiving systemic corticosteroids.	Concerns of inefficient immunization	Patients with IBD receiving Infliximab infusions can receive non-live vaccinations: • on the day of their infusion • or in mid-cycle with no reduction in efficacy and safety of vaccination. Patients can be vaccinated during induction or maintenance of biologic therapies irrespective of timing within their treatment cycle.	NM
2. For patients with allergic or atopic disorders					
2.1. Atopic dermatitis					
12	Pfaar, O.	• Vaccination is possible at any time • No increased risk of allergic reactions, only short-term aggravation of eczema is possible after vaccination • Suggest vaccination of patients receiving systemic therapy with CYSP, MTX, Systemic Steroids and/or CYSP, AZA, or Baricitinib at any time, but a temporary interruption of treatment or a reduced dosage of the medication is recommended	General immune stimulation in AD, and immune suppression under drugs	• Vaccination is recommended between two injections of biologics with 1 week interval between vaccination and the treatment; however, vaccination can be done at any time under dupilumab	Apply topical anti-inflammatory locally, using both steroids and calcineurin inhibitors
13	Ring	• Vaccinate according to their local or national vaccination plan • Suggest to do a diagnostic work-up for allergy prior to vaccination in patients with a history of anaphylaxis to drugs in general or vaccinations, and in patients with systemic mastocytosis or idiopathic anaphylaxis	The protein or the vector, one possible elicitor of anaphylaxis could be other ingredients such as PEG, present both in the BNT162b1 and the mRNA-1273 vaccines	NM	NM
14	Thyssen, J.P.	AD is not a contraindication to vaccination • recommend a case-by-case approach considering the specific drug and vaccine product • recommend to strictly follow guidelines and decisions issued by the local and national health authorities in each country • Suggest at least 3 weeks between the two COVID-19 vaccine doses	AD worsening is unlikely after vaccination, as the vaccination response is mainly skewed toward T helper cell 1. The risk of AD flares and loss of AD control increases if the systemic AD therapy is withheld or reduced in dose for longer than 3 weeks.	Most clinicians pause these therapies as follows: • JAK-inhibitors and CYSP from the vaccination day until 1 week after • MTX and AZA until 2 weeks after vaccination (to possibly improve chances or appropriate vaccination response) • suggest using the lowest dose possible: 2.5 mg/kg/day CYSP,1 mg/kg/day AZA and 7.5 mg/week MTX	NM

(Continues)

TABLE 5 (Continued)

Supplemental references[a]	FA	Recommendations	Reason for recommendation	Drug dose adjustments	Any added drugs or monitoring
2.2. Mastocytosis					
15	Bonadonna, P.	Mastocytosis alone is not a contraindication to vaccines but some patients have a high risk of anaphylaxis: • Uncontrolled MC-mediator induced symptoms (intense flushing, episodes of hypotension, other uncontrolled symptoms from cardiovascular, respiratory, gastrointestinal, neurological systems): first treat symptoms accordingly, and vaccination should be delayed until treatment and proper control of symptoms • Unstable mastocytosis and severe uncontrolled MCAS symptoms should first be treated until the symptoms are well controlled before receiving vaccination. • known or suspected allergy to PEG or polysorbate 80/20 • previous anaphylaxis to vaccination • Brighton consensus anaphylactic reaction grade 1 and 2 to the 1st dose of COVID -19 vaccine	NM	Continue anti-mediator-based treatment, like omalizumab, during the time of vaccination	• Allergy evaluation prior to vaccination • Skin test to PEG and polysorbate 80/20 and vaccine • H1-antihistamines 30 to 60 min before vaccination (also consider corticosteroids, H2-antihistamines, and montelukast) • Supervision for 60 min after vaccination
16	Stingeni, L.	For cutaneous and systemic mastocytosis in general, the following criteria are suggested as contraindications for vaccination: • Severe anaphylaxis on 1st administration of SARS-cov-2 vaccine • History of severe immediate reactions (urticaria-angioedema syndrome, anaphylaxis) and/or delayed reactions (maculo-papular eruptions, severe adverse drug reactions) to drugs containing PEG, polysorbate 80/20, and tromethamine • Documented immediate and/or delayed allergy to PEG, polysorbate 80/20, and tromethamine	Excipients with known sensitizing potential in COVID-19 vaccines: • PEG-2000 in BNT162b2 • PEG-2000 tromethamine in mRNA-1273 • polysorbate 80 in ChAdOx1S/nCoV-19	NM	• Evaluate individually • Premedicate with antihistamine (cetirizine oral drops 10 mg: 24 h before the vaccination day, on the vaccination day, and on the following 5 days)
2.3. Urticaria					
12	Pfaar, O.	For chronic spontaneous urticaria: • Vaccination is possible at any time • No increased risk of allergic reactions; but vaccination may result in transient aggravation • Patients on systemic steroids and/or CYSP can be vaccinated at any timeHowever, if applicable, adequate immunological response to vaccination should be verified by serum antibody levels	Effect of vaccination may be reduced by systemic immunosuppression	Vaccination is recommended between two injections of biologics with 1 week interval between vaccination and the treatment; however, vaccination can be done at any time under Omalizumab	• Systemic antihistamines can be used during vaccination and do not impact the effect of the vaccination
13	Ring, J.	• Groups that should undergo a drug allergy diagnostic work-up before vaccination: ○ Patients with a history of anaphylaxis to drugs in general, especially to vaccines ○ Patients with systemic mastocytosis or idiopathic anaphylaxis • Consider severe allergic reactions to ingredients of the vaccine as contraindication	Systemic allergic reactions to vaccines are rare, and are due to hypersensitivity to components of the formulation of the vaccine	• For patients with urticaria, acute flare of eczema, and other allergic diseases, do not delay vaccination, but they should be actively treated for their disease	• Consider anti-allergic medication such as combined histamine H1 and H2 receptor antagonists + oral glucocorticoids prior to vaccination • Observe for 30 min after vaccination • In the case of anaphylaxis: main acute treatment includes IM Epinephrine

TABLE 5 (Continued)

Supplemental references[a]	FA	Recommendations	Reason for recommendation	Drug dose adjustments	Any added drugs or monitoring
2.4. Allergic diseases (general)					
17	Klimek, L.	• Consider common allergies due to medications, food, inhalants, venoms and latex as general public • Consider patients with history of allergy to oral medications or family history of severe allergic reaction as general public • Vaccinate in a healthcare setting with appropriate equipment • Do not vaccinate if a patient has a history of severe reaction to the 1st dose or to the vaccine's component (PEG) • Recommend to use non-live vaccines in chronic rhinosinusitis with nasal polyps or AD patients whom are under immunomodulator medications	No evidence of immunosuppressive effects in dupilumab and omalizumab	• Defer vaccination for 90 days after receiving convalescent plasma or monoclonal antibody treatment for COVID-19 • Administer any other vaccines with a minimum interval of 14 days before and after mRNA COVID-19 vaccines • No need to hold allergen immunotherapy and biologics • Do not administer SC immunotherapy injections or biologics on the same day as mRNA vaccine • No need to adjust the dose for sublingual forms of immunotherapy	Monitor patients with history of severe allergic reaction for 30 min and others for 15 min
18	Peter, J.	Consider following conditions as contraindications to vaccinationin allergic or immune-based diseases: • Patients with inborn errors of immunity, malignancies (hematological cancers with immunoparesis), hematopoietic stem cell and solid organ transplant • Patients with a prior anaphylactic reaction to either the 1st dose of COVID-19 vaccine or an ingredient in the vaccine formulation, like PEG	Increased risk for severe COVID-19 disease is considered in contraindicated conditions. The majority of drug- or vaccine-induced anaphylactic reactions occur within the first 30 min following vaccination.	Suggest a case-by-case risk assessment	• Observe patients with prior anaphylaxis or severe allergic disorders for 30 min after vaccination • Suggest an allergy assessment and review by a specialist in patients with prior vaccine-associated anaphylaxis • suggest vaccination in a fully equipped setting with experienced staff to manage
19	Murphy, K.R.	• Known history of a severe allergic reaction to any component of the vaccine (e.g., polysorbate, PEG) is a contraindication for vaccination • In case of immediate allergic reaction of any severity happening within 4 h of receiving the 1st dose, do not vaccinate with 2nd dose • State that there is an experimental option for vaccine administration in patients with higher risk for developing serious or fatal COVID-19 infections and who have previously experienced a suspected or confirmed severe allergic reaction to a COVID-19 vaccine (explained in the adjustment column)	Adjuvants and other excipients/components in the vaccine are generally responsible for allergic reactions	The graded vaccine administration protocol as an experimental protocol: administer 0.05 ml of 1:10 dilution, and 10%, 20%, 30%, and 40% of the full dose in ascending order, in alternate arms at 15-min intervals, followed by a minimum 30-min observation period	• Screen patients by asking several questions to determine the possible risk for an allergic reaction to the mRNA COVID-19 vaccines • Observe patients with a history of systemic reactions to food, drugs, or venoms for 30 min, others for 15 min
20	Kleine-Tebbe, J.	For atopic and/or eosinophilic airway diseases with type 2 inflammation: • Consider a 1–2 week interval between vaccination and allergen immunotherapy injections, on manufacturer's recommendations • Continue sublingual immunotherapy as usual	NM	• Do not interrupt biologics such as Benralizumab, Dupilumab, Mepolizumab, Omalizumab, Reslizumab; continue as planned • Schedule vaccination approximately midway through the treatment interval	NM
21	Tanno, L.K.	Consider following conditions as contraindication for COVID-19 vaccination: • History of allergy to one of the components of the vaccine (PEG) • History of immediate reaction to first injection of a COVID-19 mRNA vaccine or another vaccine or unidentified drug Vaccinate with precaution in following conditions: • Possible Mast Cell Activation Syndrome (MCAS)/mastocytosis • History of immediate allergic reaction to multiple drug classes, with the trigger unidentified	Concerns of allergies	• NM	• Observe patients for 15–30 min • In local reactions: use local treatment and carry on • In systemic mild reaction (like acute urticaria): treat accordingly, take precise clinical history, and refer immediately to the allergist/immunologist (count them as contraindicated patients for 2nd injection until allergy work up) • In anaphylaxis: measure tryptasemia between 30 min to 2 h after the onset of reaction,

(Continues)

TABLE 5 (Continued)

Supplemental references[a]	FA	Recommendations	Reason for recommendation	Drug dose adjustments	Any added drugs or monitoring
		• History of "immediate allergy" or anaphylaxis to a vaccine or a parenteral biological therapy, an injected corticosteroid, colonoscopy preparation, or laxatives • History of idiopathic anaphylaxis, latex allergy or topical disinfectant allergy, bradykinin related angioedema or inhibitor angiotensin agent induced anaphylaxis			then >24 h after the onset of reaction, to exclude other diagnosis like mast cell activation
22	Untersmayr, E.	• Recommendation clearly speaks in favor of COVID-19 vaccination • In times of vaccine shortage, high-risk patients as well as patients under immunosuppressive therapy should be prioritized. • Although further detailed assessment of the protective effect of vaccination is warranted, especially for patients receiving immunomodulatory or immunosuppressive therapy, vaccination is expected to be beneficial. • Patients should be clearly informed that vaccination reactions are to be expected.	Concerns of vaccination among patients under immunomodulatory and immunosuppressive therapy or those with immunodeficiencies		• Prophylactic paracetamol (in not contraindicated), about 6 h after vaccination can attenuate reactions to vaccination. • If necessary, paracetamol can be continued every 6 h for 24 to 48 h.
2.5. Precautions for anaphylaxis					
23	Turner, P.J.	Recommend special precaution for following conditions: • history of immediate allergic reaction like anaphylaxis to multiple different drug classes, with the trigger unidentified (which may indicate PEG allergy) • history of anaphylaxis to a vaccination or parenteral monoclonal antibody preparation • Mast cell disease (systematic mastocytosis) Vaccination contraindications: • prior allergic reaction to the vaccine itself or to its components such as PEG In these cases, vaccination should be proceeded as normal: • Local (non-systemic) reaction to prior vaccination, stable asthma on biologics, hypersensitivity to NSAIDs, prior history of allergy to an identified food, venom or a defined group of medication	Adjuvants and other excipients/components in the vaccine are generally responsible for allergic reactions	NM	• Assessment of possible risk of PEG-allergy, and referral to allergist-immunologist • 30 min observation after vaccine injection • No pretreatment with antihistamine, as it may mask initial symptoms of a reaction • Consider obtaining venous access prior to skin testing with PEGs • Recommend a blood sample for evaluation of mast cell tryptase to diagnose vaccine-associated anaphylaxis after a reaction
24	Kim, M. A.	Those excluded from or candidates for a delayin vaccination: • Current COVID-19 infection or fever ≥37.5°C • Pregnant • ≤18 years old Special considerations: • Patients with chronic illness or immunocompromised conditions • Breast-feeding mothers Past history of COVID-19 infection: vaccinate at least 4 weeks after recovery In asymptomatic cases: vaccinate 4 weeks after first PCR test Patient on systemic steroids for more than 2 weeks: • vaccinate at least 4 weeks after stopping systemic steroids	Concerns of vaccination after a COVID infection or in special groups	• Subjects treated with monoclonal antibodies or therapeutic plasma exchange for COVID-19 infection: defer vaccination for at least 90 days, to avoid the potential interference of immune responses	• Patients with inherited coagulopathy: factor replacement on the day of vaccination is necessary

TABLE 5 (Continued)

Supplemental references[a]	FA	Recommendations	Reason for recommendation	Drug dose adjustments	Any added drugs or monitoring
		• If patients cannot stop steroids due to underlying diseases, vaccinate based on the risk-to-benefit ratio.			
25	Klimek, L.	Contra-indications to vaccination: • Immediate- or late-type allergy, or anaphylaxis to one or more ingredients of the vaccine or to substances that are cross-reactive to them • Patients with an anaphylactic reaction to the first dose of vaccine • Previous anaphylaxis of unclear cause • Known mastocytosis or anaphylaxis to different drugs or other vaccines No allergy sufferer should be excluded from COVID-19 vaccination without sufficient reason, except those with contra-indications or high-risk groups. High risk patients should undergo an "allergological evaluation" prior to COVID vaccination.	Concerns of allergies in vaccination	Provide an interval of 7 days between allergologically relevant biologics and vaccination	Monitor patients with allergies or those who belong to a defined risk groups for 30 min after vaccination. Vaccinators and vaccination staff must be prepared and have the appropriate expertisefor the recognition and treatment of anaphylaxis and severe allergic reactions and vaccination sites must have a minimum equipment of drugs and instruments. In case of (supposed) allergic reactions to vaccination, an allergological work-up in a specialized center is indicated.
26	Klimek, L.	• Regularly inform patients about possible severe allergic/anaphylactic reactions • Ask patients about such incidents in the past, including allergic reactions to additives, in particular PEG and cross-reactive PEG analogues • In suspected cases, perform an allergological clarification (skin prick test, laboratory diagnostics) and consult an allergist • More precise definitions of the type, cause, and severity of severe allergic reactions are needed not over-exclude people from vaccination and possibly damage the achievement of herd immunity	Concerns of allergies in vaccination	NM	Vaccination personnel must always be prepared for the possibility and treatment of severe allergic/anaphylactic reactions and anaphylaxis
27	Worm, M.	A recommended set of questions for the assessment of the "allergological riskpotential" for COVID-19 vaccination should be asked, finding details on • Previous (possibly repeated) severe allergic reactions to medications, vaccines, or PEG-macrogol or polysorbate-containing drugs (e.g., macrogol or cold medications) • (Repeated) severe general reactions during medical procedures such as colonoscopies or operations under general anesthesia • Severe general reaction to an unknown trigger • Known mastocytosis in patients with previous severe immediate drug reactions or anaphylaxis to an unknown trigger • For the second dose: possible a = severe general reaction after the first dose	Concerns of allergies prior to vaccination	NM	NM
3. For dermatology patients on immunosuppressive, immunomodulatory or biologic therapies					
28	Ferretti, F.	• Consider patients with systemic comorbidities related to immune-mediated chronic skin diseases, such as cardiovascular diseases, diabetes and obesity, and those under treatment with conventional therapy or biologics as a priority group to get vaccinated • A case-by-case approach to any therapeutic decision is recommended, but it is suggested to withdraw or delay immunosuppressant drugs or	Due to high risk of severe COVID-19 or hospitalization	• Taper systemic corticosteroids to ≤20 mg/day of prednisone or equivalent to administer live vaccines • Withhold MTX and JAK inhibitors 1 week after each vaccine dose • For patients with an autoimmune bullous disease treated with RTX; if RTX is not started, patient needs to be vaccinated ≥4 weeks prior to RTX	NM

(Continues)

TABLE 5 (Continued)

Supplemental references[a]	FA	Recommendations	Reason for recommendation	Drug dose adjustments	Any added drugs or monitoring
		biologics in case of COVID-19 diagnosis up to infection recovery, except for patients on systemic corticosteroids therapy		infusion, otherwise they need to be vaccinated 12–20 weeks after completion of a cycle of therapy	
29	Gresham, L.M.	• Advise to check antibody titers after vaccination, and use additional vaccinations if needed, to boost the level of protective antibodies • Consider nonviral or inactivated SARS-CoV-2 vaccine subtypes before, during, or after receiving systemic immunosuppressant, immune-targeting therapy and biologic therapy without significant modification of ongoing treatments	Concerns of immune therapies	NM	Consider anti-IL-17 biologics, anti-IL-12/23 biologics, Omalizumab, MTX and JAK inhibitors as safe therapies during the COVID-19 pandemic
30	Wang, C.	• Consider atopic dermatitis, immune-bullous disorders, vasculitis and cutaneous drug eruptions as high-risk patients and advise to get vaccinated • if immunomodulator or biologic therapy have not been started, vaccinate prior to initiation of the therapy course • Advise to administer vaccines other than those against COVID at least 7 days either before or after the completion of the two-dose COVID-19 vaccine regimen	To maximize vaccine response and decrease the frequency of local and systemic reactions	if patient is already on a biologic or immunomodulatory agent: • administer the vaccine (non-live COVID-19 vaccines strongly recommended) at least 7 days on either side of biologic or immunomodulator dose, and at a different anatomical location	NM
31	Hauptman, M.	For patients on biologic therapies (including patients with psoriasis): • Administer an inactivated vaccine if it is a possible option • Consider discontinuation of biologics prior to receiving an inactivated vaccine in patients who prioritize high titer immunity over potential skin flare • Discontinue the biologic therapy, if only live attenuated vaccines are available	Concerns of immune therapies	NM	NM
32	Chakravarthy, K.	• There is no evidence that patients receiving epiduralsteroid therapy for pain management are more at risk of adverse reactions to COVID vaccination • There is no evidence that bolus steroids in theepidural space will impact the immune response to vaccination	Concerns of those receiving steroids	There is no need to defer neuraxial steroid injections when indicated in the context of COVID-19 vaccination There is no specific guidance suggesting withholding NSAIDs or other anti-inflammatories before vaccination	NM
4. Precautions for vaccine-induced thrombotic thrombocytopenia					
33	Elalamy, I.	• Rapidly vaccinate those under 60 years of age with comorbidities (like cancer, CVD, kidney or liver impairment, immunosuppressant use, obesity, DM) and patients on long-term anticoagulant treatment for APS or other reasons • IM injection should be done correctly at the appropriate lower site of deltoid muscle and not intravascularly • Minimal systemic signs, low-grade fever, or muscular pain are expected in varying degrees for each individual and should decrease in 48 to 72 h • Check for extensive ecchymotic or purpuric local reaction that is particularly painful • In case of thrombocytopenia (PLT < 120 G/L): investigate for HIT by screening for heparin-PF4 antibodies	on a Principle of Precaution	• Recommended labs after physical exam:CBC with PLT count, D-dimers (>1000 ng/mL), and schistocytes to rule out a hypercoagulable state with PLT consumption (PLT < 120 G/L) or DIC with a decrease in fibrinogen (<2 g/L), and other tests depending on the clinical state • Use imaging to detect thrombosis in various sites (venous ultrasound, MRI, CTA) • Patients presenting more than 4 days (4–28 days) after the vaccination with symptoms suggestive of thrombosis and thrombocytopenia should be admitted with a low threshold so an immediate and thorough work-up is possible • Symptoms include: intense and persistent headaches, dizziness, visual disorders, impaired speech, acute pain or worsening muscular pain,	• In the event of major thrombotic events, infuse immunoglobulins (1 g/kg) + antithrombotics for 48 h • Steroids and plasma exchange are also options to reduce the autoantibodies • inhibitors of Bruton's tyrosine kinase (like Ibrutinib), can be another potential option in treatment of VITT • Implement an effective non-heparin antithrombotic treatment without delay: By injectable anticoagulant (Fondaparinux, Danaparoid, Argatroban), and

TABLE 5 (Continued)

Supplemental references[a]	FA	Recommendations	Reason for recommendation	Drug dose adjustments	Any added drugs or monitoring
		• Do not take these steps for everyone systematically: management of vaccination with thromboprophylaxis (LMWH or direct oral anticoagulant or aspirin, screening for thrombophilia before vaccination, measuring of anti-PF4 antibodies after vaccination, monitoring of D-dimer changes before and after vaccination, venous ultrasound before and after vaccination; use a case-by-case basis • Do not contraindicate vaccination in case of history of thrombosis, autoimmune disease, history of HIT (but mRNA vaccines are preferable), history of allergy (except for allergy after 1st dose of any vaccine), immune thrombocytopenia		edema of a limb suggestive of phlebitis, significant changes in a limb temperature (heat or cold), difficulty breathing, sudden heart rate acceleration, unusual bleeding signs, especially petechiae)	depending on the clinical evolution, switching to direct oral anticoagulant (dabigatran, rivaroxaban, apixaban) can be an option • In case of flu-like symptoms, it is advisable for the patient to drink lots of fluids and take Paracetamol
34	Oldenburg, J.	• The positive effects of vaccination with ChAdOx1 nCoV-19 outweigh the negative effects, so its administration is welcome to be resumed in Germany. • Considering the immunogenesis of thrombosis in intracranial veins or other atypical locations, patientswith a history of thrombosis and/or known thrombophilia do not have a higher risk for this specific and very rare complication with ChAdOx1 nCoV-19. • Flu-like symptoms (joint and muscle pain or headache) persisting for 1 to 2 days after vaccination are a common side effect and not a cause for concern • If side effects persist or recur more than 3 days after vaccination (dizziness, headache, visual disturbances, nausea, vomiting, shortness of breath, acute pain in chest, abdomen, or extremities), further medical diagnostics should be carried out to clarify a thrombosis • Anticoagulation is necessary to treat the thrombosis. While heparins are contraindicated in (autoimmune) HIT, IV anticoagulation with heparins is likely possible in confirmed VIPIT. • Diagnostics for HIT/VIPIT should be ordered before administering IVIG, since high-dose IVIGs may lead to false-negative test results. • There is no indication for routine thromboprophylaxis with anticoagulants or antiplatelet agents following vaccination with ChAdOx1 nCoV-19. • Regardless of (autoimmune) HIT/VIPIT test results, alternative causes of thrombocytopenia and/or thrombosis must be considered and further clarified, including: thrombotic microangiopathies ITTP or atypical HUS, APS, paroxysmal nocturnal hemoglobinuria, and underlying hematological malignancies	Concerns of thromboses after ChAdOx1 nCoV-19	Labs: CBC with PLT count, blood smear, D-dimers, further imaging in indicated (cranial MRI, ultrasound, chest and abdomen CT). • In the case of thrombocytopenia and/or evidence of thrombosis (regardless of previous exposure to heparin): antibodies against the PF4/heparin complex • In case of a negative screening test: an HIT-like cause of thrombosis/thrombocytopenia can be ruled out. • In case of a positive screening test for PF4/heparin antibodies: order classical HIPA assayor SRA, as a functional confirmatory test; • if positive: establishment of the diagnosis of autoimmune HIT (in the absence of previous heparin exposure) • if negative: order a modified HIPA assay; if positive: establishes the diagnosis of VIPIT • Patients receiving oral anticoagulation (e.g., for AF, VTE): continue treatment during and after vaccination. • Patients with no indication for oral anticoagulation at significant risk of VTE: thromboprophylaxis over several days may be indicated individually, in case of severe flu-like symptoms with fever and immobilization	• Until (autoimmune) HIT is ruled out: anticoagulation with heparins should be avoided, alternated to danaparoid, argatroban, direct oral anticoagulants, and possibly fondaparinux (with very specific considerations) • The authors of this guidance document advise against the use of LMWH or fondaparinux for thromboprophylaxis, as it cannot be safely ruled out that these IV anticoagulants foster the production of platelet-activating antibodies. • As an off-label alternative, general measures (exercise, fluid replacement, compression stockings) + prophylactic doses of direct oral anticoagulants (rivaroxaban 10 mg once daily or apixaban 2.5 mg BD), maybe be considered. • In case of confirmed (autoimmune) HIT/VIPIT and critical thromboses such as sinus/cerebral or splanchnic vein thrombosis: high dose IVIG is very likely to interrupt the prothrombotic pathomechanism.

(Continues)

TABLE 5 (Continued)

Supplemental references[a]	FA	Recommendations	Reason for recommendation	Drug dose adjustments	Any added drugs or monitoring
5. For delayed reactions to hyaluronic acid soft tissue fillers					
35	Gotkin, R. H.	Collected data does not support the concern for a higher risk of adverse reactions following soft tissue filler injections associated with COVID vaccination, compared to other previously described triggers or the default of adverse reactions following soft tissue filler injections	Concerns of reactions to fillers	NM	NM
36	Rice, S. M.	• Emerging reports of delayed-type hypersensitivity reactions (DTRs) to facial fillers after COVID vaccination may cause patients to become confused by potential side effects and possibly postpone vaccination as a result. • Vaccination must be encouraged and patients should be informed about the temporary and treatable nature of these side effects. • Do not discourage patients with a history of treatment with dermal fillers from vaccination A time frame should be suggested: • longer than 2 weeks between vaccination and filler procedures, dental procedures or for with recent infections, • potentially longer windows for those with risk factors such as prior sensitivity to dermal fillers, autoimmune disorders, or those on immunomodulatory medications	Concerns of DTRs to fillers	Dilution of fillers with saline or lidocaine or use of non-HA fillers around the time of vaccination may also be suggested to minimize the risk of DTRs	In case of facial swelling lasting longer than 48 h: treat with antihistamines, steroids, and/or hyaluronidase, with resolution both alone or in combination, without altering the vaccine efficacy ACE-Is(lisinopril) have been recommended (not strongly) for the treatment of facial edema following COVID-19 vaccination In case of symptoms after first vaccine dose, manage the side effects, reassure the patient and advise them to obtain their second dose, with pretreatment considerations (including antihistamines), and instruct them to present to the emergency department if a more severe reaction is suspected
37	Rice, S. M.	Pre-vaccine counseling in cosmetic patients seeking fillers: • Patients with allergies, history of injection site reactions, or urticaria may benefit from antihistamines and topical medications. • COVID-19 vaccine–related planning (procedures could be planned with a time window to minimize the risk of reactions), along with screening for dental procedures and the herpes simplex virus • Cutaneous implications of both COVID-19 infection and vaccination may become part of standard medical counseling prior to aesthetic procedures • Patients seeking filler injection may be counseled regarding vaccine options not associated with adverse reactions; especially for patients with risk factors discussed	Concerns of DTRs to fillers	• In cases of facial swelling: short courses of oral steroids (<2 weeks) can achieve resolution, and do not appear to alter vaccine effectivity • In case of residual or prolonged edema: hyaluronidase • Consider a 4 –8 week window between filler injections and vaccination for the general population, and potentially longer for those with risk factors: autoimmune or immunologic disorders, chemotherapy or immunomodulatory medications, history of sensitivity to dermal fillers (more pronounced and delayed swelling than expected for a given filler)	• Inform patients to contact their physicians for treatment if facial swelling or nodules develop, or present to the emergency room in case of more serious reactions. • Fillers containing HA and polymethylmethacrylate may be more likely to cause reactions, so other filler options (e.g., calcium hydroxyapatite, polylactic acid, or laser resurfacing) may be prioritized, especially during the months surrounding vaccination • Dilution of filler is another reasonable consideration, for both polylactic acid and HA with saline, sterile water, or lidocaine can decrease the risk of adverse reactions and DTRs

Abbreviations: ABT, abatacept; ACE-I, angiotensin converting enzyme inhibitors; AD, atopic dermatitis; ADA, adalimumab; AF, atrial fibrillation; AIIRD, autoimmune inflammatory rheumatic diseases; APS, antiphospholipid syndrome; AZA, azathioprine; CBC, complete blood count; CP, cyclophosphamide; CT, computed tomography; CTA, computed tomography angiography; CVD, cardiovascular disease; CYSP, cyclosporine; DIC, disseminated intravascular coagulation; DM, diabetes mellitus; DMARD, disease-modifying anti-rheumatic drugs; DTRs, delayed-type hypersensitivity reactions; FA, first author; HIPA, heparin-induced platelet activation; HIT, heparin-induced thrombocytopenia; HUS, hemolytic uremic syndrome; IM, intramuscular; ITTP, immune thrombotic thrombocytopenic purpura; IV, intravenous; Lab, laboratory investigations; LMWH, low-molecular-weight heparin; MC, mast cell; MCAS, mast cell activation syndrome; MRI, magnetic resonance imaging; MTX, methotrexate; NM, not mentioned; NSIAD, non-steroidal anti-inflammatory drugs; PEG, polyethylene glycol; PF4, platelet factor 4; PLT, platelet; RMD, rheumatic and musculoskeletal diseases; RTX, rituximab; SC, subcutaneous; SLE, systemic lupus erythematosus; SRA, serotonin-release assay; VTE, venous thromboembolism.

[a]Supporting information Table S5.

importance, so that with concrete knowledge, vaccination is not hindered by hesitancy through false beliefs about the extension or prevalence of adverse events or worries of flare-ups or inefficient immunization, and that critical or potentially fatal adverse reactions are safely avoided.

We extracted any side effects of COVID-19 vaccines reported in these studies with a special emphasis on mucocutaneous manifestations, comorbidities, lesion characteristics, time of onset, location, and duration of reactions, along with vaccine types, and further details regarding dosage, conjugated materials and age groups for the RCTs. It is important to mention that studies with no mucocutaneous manifestations were not included in our systematic review. Also, among the studies we did include, we did not extract the data on groups or subgroups that had no mucocutaneous reactions to the vaccines, so the results and numbers presented here are only on groups with mucocutaneous side effects.

Regarding the case reports and case series, we would like to also emphasize the importance of reporting registries and helping the medical community gather data on more unsolicited adverse events related to vaccination, that were perhaps less commonly observed in the initial trials, and through this cumulative international effort to report these events, many less solicited adverse reactions are now well-known and clinicians are well aware of their potential emergence, and as expressed earlier, many guidelines, consensus recommendations and position papers have been written since.

Regarding the RCTs, the most common side effect among all trials was injection site pain, present in 95% of studies. Among the common systemic reactions were fatigue, fever, headache, chills, malaise, arthralgia, myalgia, nausea, vomiting and diarrhea. Among the common local (injection site) reactions reported in the RCTs were redness, swelling, induration, pruritis and warmth. Generalized pruritis, rash, hypersensitivity and lymphadenopathy (axillary) were also among the solicited general side effects. Less solicited or unsolicited mucocutaneous adverse events reported in the RCTs were mucocutaneous eruptions like pustules (at injection site or elsewhere), macular or maculo-papular allergic rashes, petechial rash, urticaria, injection site discoloration or bruising, alopecia, contact dermatitis, acne-form dermatitis, allergic conjunctivitis, hordeolum, chalazion, keratoconjunctivitis, uveitis, benign neoplasm of the eyelid, plantar fasciitis, swelling in the neck, chest wall or groin, oral herpes, dyshidrotic eczema, bacterial vaginosis, vaginal infection, vulvovaginal pruritus, anaphylactic reactions, cellulitis, psoriasis, rosacea, vitiligo, Raynaud's phenomenon, among other epidermal and dermal conditions, skin appendage conditions, dental and gingival conditions and oral soft tissue conditions. These side effects were sometimes more common in lower dose groups or younger age groups, which is an interesting observation. There was the same pattern with the primer and booster doses where sometimes side effects were more common after the booster doses and sometimes after the primers, so the trials' results were not all in the same direction on this matter. Among patients' comorbidities were obesity, hypertension, diabetes, history of or current COVID-19, metabolic and endocrine conditions, allergies and hypersensitivities, asthma, cardiac and pulmonary conditions, psychiatric disorders, joint and back pain, positive HIV, malignancy and autoimmune illnesses. Moving on to safety assessments, most studies had observed the side effects within 7 days after vaccination, others extending the watch period to 14, 21, 28, or more days.

Regarding the analytical observational studies, a wide range of side effects after vaccination were reported in the studies. Among these studies, the most common reaction after COVID-19 vaccination was local adverse events such as injection site pain and numbness. Apart from local events, systematic reactions such as fatigue followed by fever, myalgia, headache, bone pain, joint pain represented as the most common symptoms. Other mild adverse effects such as nausea, sweating, dizziness, diarrhea, vomiting, taste disturbance, itchy scratchy throat, insomnia, spasm, migraine, nasal obstruction, and rhinolalia were also observed in the reported results. To further categorize the reported adverse events, they mostly fell into seven groups; musculoskeletal, gastrointestinal, cardiovascular, neurological, respiratory, allergic reactions, and mucocutaneous symptoms. The mucocutaneous reactions ranged a broad spectrum from mild local reactions including swelling, redness, pruritus, rash, urticaria, and burning sensation of the skin, to more rare reactions such as erythromelalgia, morbilliform rash, contact dermatitis, oral ulcers, blisters and vesicles, bleeding and burning gingiva, angular cheilitis, swollen lips, xerostomia, flare of existing dermatologic conditions such as varicella-zoster or herpes simplex flares, and pityriasis rosea-like reactions. The rare mucocutaneous effects were efficiently controlled with steroids, antihistamines, and pain-relievers. The side effects were most frequently reported within the first 3 days after vaccination, but there were also some studies reporting delayed adverse reactions, up to 4 weeks after vaccination. Duration of reactions varied from most frequently almost 1 day to as long as 4 weeks or more. The most common location of mucocutaneous lesions was upper limbs (injection site), trunk and face. Almost half of these studies reported participants' comorbidities. The most commonly reported comorbidities were hypertension, prior COVID-19, diabetes mellitus, cardiovascular disorders, autoimmune, rheumatologic or allergic disorders, malignancies, obesity, and anaphylaxis.[47,57,59,65,67,70–74,78,118,136–139] In addition, less common co-morbidities including asthma, thyroid disorder, psychological distress, hepatologic disease, and ophthalmologic disease were also mentioned in these studies.

Regarding the recommendations and guidelines for vaccination in specific groups, a generally positive view toward vaccination was expressed, inviting most groups to vaccinate, while having the necessary precautions in mind, and clarifying the contra-indications so those with higher risks could safely avoid any severe adverse reactions or modify their vaccination and/or treatment schedules to achieve peak immunization, all the while having their underlying diseases under control.

In some cases, a true causality between proposed adverse events and vaccination was not concluded. In these situations, we relied on the authors' original statement, while considering patient's past medical history, notably previous allergic/hypersensitivity reactions to other vaccines or drugs, and the temporal course between vaccine administration and onset of the eurptions. Based on provided

evidence, in patients with no alternative underlying source for the adverse eurptions, and in case the onset of reactions were compatible with our experience and current literature, usually occurring from 2–3 days to 3–4 weeks, a vaccine induced adverse reaction was ascertained.

The authors of this study have worked on various clinical aspects of COVID-19, COVID-19 vaccination and dermatology[118–135,140,141] and it seems that this hot topic could answer some questions and concerns about the most encountered specific disorder in the field of dermatology.

We hope the present article provides its audience with the state-of-the-art knowledge that is essential in today's standard of care regarding the mucocutaneous adverse reactions following COVID-19 vaccination.

5 | CONCLUSION

Mild, moderate, severe, and potentially life-threatening adverse events have been reported following immunization with COVID-19 vaccines. It appears that although in the assessment of the pros and cons of vaccination, mucocutaneous adverse events could be one of the causes of vaccine hesitancy, they are nonetheless mostly non-significant, self-limiting reactions, and for the more uncommon moderate to severe reactions, guidelines and consensus position papers can be of great importance to provide those at higher risks and those with specific worries of flare-ups or inefficient immunization, with sufficient recommendations to safely schedule their vaccine doses, or avoid vaccination if they have the discussed contra-indications.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHORS CONTRIBUTION

All authors contributed to the preparation and finalization of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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