SYSTEMATIC REVIEW

Global prevalence and clinical manifestations of cutaneous adverse reactions following COVID-19 vaccination: A systematic review and meta-analysis

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Abstract

Although vaccination is widely accepted as an effective method of preventing and controlling the COVID-19 pandemic, many people are concerned about possible cutaneous side-effects, which can delay or prevent them from being vaccinated. The objectives of this systematic review were to assess the global prevalence and clinical manifestations of cutaneous adverse reactions following COVID-19 vaccination. PubMed and Scopus databases were searched for articles published from 1 January 2019 to 31 December 2021, and reference lists for each selected article were screened. Case reports, case series, observational studies and randomized controlled trials that provided information on cutaneous adverse reactions following COVID-19 vaccines were included. A total of 300 studies were included in a systematic review of which 32 studies with 946,366 participants were included in the meta-analysis. The pooled prevalence of cutaneous manifestations following COVID-19 vaccination was 3.8% (95% CI, 2.7%–5.3%). COVID-19 vaccines based on the mRNA platform had a higher prevalence than other platforms at 6.9% (95% CI, 3.8%–12.3%). Various cutaneous manifestations have been reported from injection site reactions, which were the most common (72.16%) to uncommon adverse reactions such as delayed inflammatory reactions to tissue filler (0.07%) and flares of pre-existing dermatoses (0.07%). Severe cutaneous reactions such as anaphylaxis have also been reported, but in rare cases (0.05%). In conclusion, cutaneous adverse reactions are common, especially in those receiving mRNA vaccines. Most reactions are mild and are not contraindications to subsequent vaccination except for anaphylaxis, which rarely occurs. COVID-19 vaccination may also be associated with flares of pre-existing dermatoses and delayed inflammatory reactions to tissue filler.

Conclusion: Cutaneous reactions are common, especially in those receiving mRNA vaccines. Most reactions are mild and are not contraindications to subsequent vaccination except for anaphylaxis, which rarely occurs. COVID-19 vaccination may also be associated with flares of pre-existing dermatoses and delayed inflammatory reactions to tissue filler. Patients with a history of allergies, pre-existing skin conditions or scheduled for filler injections should receive additional pre-counselling and monitoring. A better understanding of potential side-effects may strengthen public confidence in those wary of new vaccine technologies.

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Conflict of interest

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Introduction

The emergence of the novel coronavirus known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is currently a global pandemic and public health crisis. COVID-19 causes significant morbidity and mortality with millions of deaths reported worldwide.1

COVID-19 vaccination represents a safe and effective way for disease prevention and mortality reduction. This public health emergency required urgent efforts globally to develop vaccines. More than 180 vaccine candidates using a wide range of
technology platforms including nucleic acid (DNA and RNA), virus-like particles, peptides, viral vectors (replicating and non-replicating), recombinant protein, live attenuated virus and inactivated virus approaches are currently in development or have received emergency approval for use.\(^2\)

Establishing the safety of the COVID-19 vaccines is crucial and plays an important role in gaining public trust for vaccinations since emergency approval is being granted without completing all phases of clinical trials. Speculations and reports about vaccine-related side-effects have arisen due to these very large-scale vaccination programmes. Cutaneous adverse reactions to SARS-CoV-2 vaccinations are one of the most frequently reported adverse effects.\(^3,4\)

This study performed a systematic review and meta-analysis of previously published studies to ascertain the prevalence of cutaneous adverse events associated with the COVID-19 vaccine. Additionally, we summarized all clinical manifestations and therapeutic considerations, which may help guide clinicians with prevaccine counselling, prevention and management.

**Methods**

**Data sources and search strategy**

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Table S1). A systematic search was conducted on studies published from 1 January 2019 to 31 December 2021, in PubMed and Scopus databases. Search terms, such as “COVID-19 vaccines”, “skin”, “cutaneous”, “derm” and “rash” were used without any language restriction (Table S2). Records were managed by the Endnote X9.0 software to exclude duplicates. To identify missing studies, we scanned the reference lists for each selected article. Additional articles were obtained from manual searching.

**Study selection**

We included published studies that reported cases of COVID-19 vaccine-related cutaneous manifestations with no limit to the duration of follow-up. The definition of adverse events following immunization (AEFI) by the World Health Organization (WHO) was employed. AEFI is regarded as any untoward medical occurrence, which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine.\(^5\)

Case reports, case series, case-control studies, retrospective/prospective cohort studies and randomized controlled trials were all eligible study designs. We excluded review articles and opinion articles that did not include original data and studies that reported on cases with insufficient information. Two authors (C.W. and J.T.) independently screened the title and abstract results from the initial search strategy. Comprehensive reviews of the full text of relevant articles were conducted using inclusion and exclusion criteria (Fig. 1). Disagreements were resolved by consensus or with the assistance of the third author (P.R.).

The quantitative synthesis (meta-analysis) included randomized controlled trials and observational studies that reported the prevalence of cutaneous manifestations following COVID-19 vaccination. Case reports, case series, observational studies and randomized controlled trials that could not be analysed in terms of prevalence and used descriptive statistics to summarize the findings were excluded from the meta-analysis.

**Data extraction**

Data extraction forms recorded details on the general information of studies (first author’s surname, year of publication), study characteristics (country, study design, study phase), participant characteristics (age, sex, underlying disease), details of intervention (name of the vaccine, type of vaccine, manufacturer and dose of administration) and skin manifestations after vaccination (prevalence, clinical morphology, onset, duration and treatment).

**Study quality assessment**

The quality of the RCT was evaluated using the Jadad scale,\(^6\) which ranges from 0 to 5, with a score of 3 or higher indicating a report of high quality. The risk of bias in observational studies was determined by the Newcastle–Ottawa quality assessment\(^7\) where the maximum score is 9 and a score of 7 is the threshold denoting high quality (low risk of bias). The Joanna Briggs Institute (JBI) critical appraisal checklist\(^8\) was used to assess the quality of case reports with a score of 0–8 and that of case series with a score of 0–10. Studies with a quality assessment score of 50% or higher (≥4 for case reports, ≥5 for case series) were included in the review. The level of evidence was assessed using the Oxford Centre for Evidence-Based Medicine criteria.\(^9\)

**Data synthesis and analysis**

**Quantitative synthesis** Odds ratios (ORs), pooled prevalence and 95% confidence intervals (95% CI) were used to summarize the weighted effect size for each study using the binary random-effects model. Heterogeneity was assessed using the \(I^2\) index and Q-test \(P\)-value. An \(I^2\) index of \(\geq50\%\) indicated medium to high heterogeneity. When heterogeneity was observed, it was investigated using subgroup analyses according to study design (randomized control trial versus observational study), type of skin manifestations (local injection site/near injection site reaction versus non-injection site/generalized skin reaction), type of vaccination (inactivated SARS-CoV-2 versus mRNA-based versus viral vector-based), type of placebo control (aluminium hydroxide solution versus normal saline) and dose administration (first dose versus the second dose). Publication bias was formally assessed using the Egger test. All analyses were performed using Comprehensive Meta-Analysis (version 2.0; Biostat, Englewood, NJ).

**Qualitative analysis** Descriptive, categorical variables were reported as frequency and percentage, while continuous data were
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**Results**

**Characteristics and quality of the studies**

A total of 2181 publications were identified and screened for COVID-19 vaccine-related cutaneous manifestations using a database search and article reference lists (Fig. 1). Of these studies, 300 met the systematic review’s inclusion criteria (15 randomized control trials, 34 observational studies, 75 case series, and 176 case reports), while 32 studies were included in the meta-analysis (nine randomized control trials and 23 observational studies). The characteristics of each study selected for the meta-analysis are summarized in Table S3–S4. All studies were judged as meeting a high standard of quality (Tables S5–S8).

**Prevalence of cutaneous adverse reactions following COVID-19 vaccination**

Thirty-two studies (23 observational studies and intervention arms of 9 randomized control trials) resulting in 946,366 participants were included in the meta-analysis for the pooled prevalence of overall cutaneous adverse reactions following COVID-19 vaccination. There were seven studies (21.9%) on inactivated SARS-CoV-2 vaccines, 17 (53.1%) on mRNA-based vaccines, 3 (9.4%) on viral vector-based vaccines and 5 (15.6%) covering more than one platform. The pooled prevalence of overall cutaneous adverse reactions following COVID-19 vaccination was 3.8% (95% CI, 2.7%–5.3%; $I^2 = 99.77$; Q-test $P < 0.001$). (Table S9 illustrates the prevalence of overall cutaneous adverse reactions following COVID-19 vaccination in each study.) The Egger test was not significant ($P = 0.750$), suggesting less publication bias.
Due to the substantial heterogeneity among studies, subgroup analyses by type of skin manifestations, dose administration, vaccine platforms and study design were performed. Skin reactions that were localized at the injection site or near the injection site were more common than non-injection site or generalized skin reactions, with a pooled prevalence of 2.5% (95% CI, 1.4%–4.5%; $I^2 = 99.85\%$; $Q$-test $P < 0.001$) vs. 1.6% (95% CI, 1.3%–2.0%; $I^2 = 99.85\%$; $Q$-test $P < 0.001$). The rate of cutaneous adverse events was similar after each dose of the vaccine, with a pooled prevalence of 4.2% (95% CI, 2.8%–6.4%; $I^2 = 99.85\%$; $Q$-test $P < 0.001$) for the first dose and 4.0% (95% CI, 2.1%–7.5%; $I^2 = 99.85\%$; $Q$-test $P < 0.001$) for the second dose. COVID-19 vaccines based on the mRNA platform had the highest prevalence of cutaneous adverse events at 6.9% (95% CI, 3.8%–12.3%; $I^2 = 99.85\%$; $Q$-test $P < 0.001$) followed by viral vector-based vaccines at 3.5% (95% CI, 0.2%–35.8%; $I^2 = 99.78\%$; $Q$-test $P < 0.001$), and inactivated SARS-CoV-2 vaccine at 0.9% (95% CI, 0.1%–9.0%; $I^2 = 99.32\%$; $Q$-test $P < 0.001$). The pooled prevalence from the 13 studies using multiple platforms was 2.4% (95% CI, 0.8%–6.7%; $I^2 = 99.75\%$; $Q$-test $P < 0.001$). Observational studies reported a greater number of cutaneous adverse events with a pooled prevalence of 5.9% (95% CI, 3.8%–8.8%; $I^2 = 99.83\%$; $Q$-test $P < 0.001$) compared to randomized control trials that reported a pooled prevalence of 1.1% (95% CI, 0.4%–3.4%; $I^2 = 99.19\%$; $Q$-test $P < 0.001$) (Fig. 2).

**Investigations of heterogeneity**  
Due to the substantial heterogeneity among studies, subgroup analyses by type of skin manifestations, dose administration, vaccine platforms and study design were performed. Skin reactions that were localized at the injection site or near the injection site were more common than non-injection site or generalized skin reactions, with a pooled prevalence of 2.5% (95% CI, 1.4%–4.5%; $I^2 = 99.85\%$; $Q$-test $P < 0.001$) vs. 1.6% (95% CI, 1.3%–2.0%; $I^2 = 99.85\%$; $Q$-test $P < 0.001$). The rate of cutaneous adverse events was similar after each dose of the vaccine, with a pooled prevalence of 4.2% (95% CI, 2.8%–6.4%; $I^2 = 99.85\%$; $Q$-test $P < 0.001$) for the first dose and 4.0% (95% CI, 2.1%–7.5%; $I^2 = 99.85\%$; $Q$-test $P < 0.001$) for the second dose. COVID-19 vaccines based on the mRNA platform had the highest prevalence of cutaneous adverse events at 6.9% (95% CI, 3.8%–12.3%; $I^2 = 99.85\%$; $Q$-test $P < 0.001$) followed by viral vector-based vaccines at 3.5% (95% CI, 0.2%–35.8%; $I^2 = 99.78\%$; $Q$-test $P < 0.001$), and inactivated SARS-CoV-2 vaccine at 0.9% (95% CI, 0.1%–9.0%; $I^2 = 99.32\%$; $Q$-test $P < 0.001$). The pooled prevalence from the 13 studies using multiple platforms was 2.4% (95% CI, 0.8%–6.7%; $I^2 = 99.75\%$; $Q$-test $P < 0.001$). Observational studies reported a greater number of cutaneous adverse events with a pooled prevalence of 5.9% (95% CI, 3.8%–8.8%; $I^2 = 99.83\%$; $Q$-test $P < 0.001$) compared to randomized control trials that reported a pooled prevalence of 1.1% (95% CI, 0.4%–3.4%; $I^2 = 99.19\%$; $Q$-test $P < 0.001$) (Fig. 2).
placebo (pooled OR 1.78; 95% CI, 0.57–5.57; $I^2 = 89.37$; Q-test $P < 0.001$) and those using normal saline (pooled OR 1.63; 95% CI, 0.19–14.29; $I^2 = 94.64$; Q-test $P < 0.001$). Interestingly, when a subgroup analysis was performed on different platforms of the COVID-19 vaccine, the mRNA-based vaccine again had the highest rate of associated cutaneous adverse effects. Individuals who received the mRNA-based vaccine were 7.2 times more likely to develop a cutaneous adverse event than those who received a placebo (95% CI, 6.35–8.19, $P < 0.001$; $I^2 = 0$; Q-test $P < 0.501$). Local skin reactions to the mRNA vaccine at the injection site were more common than non-injection site or generalized skin reactions (OR, 14.37; 95% CI, 11.97–17.25 vs. OR, 1.41; 95% CI 0.81–2.45). Second doses of mRNA caused injection site skin reactions 20.2 times more frequently than placebo (95% CI, 8.39–48.76, $P < 0.001$; $I^2 = 17.08$; Q-test $P < 0.299$).

In Fig. 3, the forest plot illustrates the cutaneous adverse events associated with each dose of the different types of vaccination.

**Clinical manifestations and therapeutic considerations**

From the systematic review, we identified 300 articles ($10–309$ (15 randomized control trials, $10–24$ 34 observational studies, $25–58$ 75 case series$^{18–133}$ and 176 case reports$^{134–309}$), resulting in a total of 44,582 cases that reported on COVID-19 vaccine-related cutaneous manifestations. The most frequent cutaneous manifestations were acute local injection site reactions ($n = 32,173$, 72.16%), followed by rash or unspecified skin eruption ($n = 6,518$, 13.81%), urticaria or angio-oedema ($n = 2,913$, 6.53%), pruritus without skin lesion ($n = 1,009$, 2.26%), delayed large local reactions ($n = 847$, 1.90%), maculopapular rash ($n = 221$, 0.50%), herpes zoster ($n = 182$, 0.41%), oral blister/ulcer/vesicle ($n = 162$, 0.36%), pityriasis rosea/pityriasis rosea-like lesion ($n = 108$, 0.24%), vesiculobullous lesion ($n = 86$, 0.19%), petechiae/purpura/ecchymosis ($n = 60$, 0.14%), chilblains/chilblains-like lesion ($n = 58$, 0.13%) and vasculitis/vasculitis-like lesion ($n = 46$, 0.10%). Additional less common cutaneous manifestations are included in Table 1.

A total of 23 cases of anaphylaxis were reported from the systematic review with 12 cases coming from one study.$^{123}$ This study covered data from Thailand for a three-month period during the initial rollout of the Sinovac inactivated vaccine that estimated a rate of one case of anaphylaxis per 2.2 million doses.$^{310}$

Demographic data, clinical presentations and therapeutic considerations of patients with COVID-19 vaccine-related cutaneous manifestations are summarized in Table 2.

**Discussion**

Results from our meta-analysis showed that cutaneous adverse reactions to COVID-19 vaccines are common with the pooled prevalence of global cutaneous adverse events following COVID-19 of 3.8% (95% CI, 2.7%–5.3%). This observed prevalence is close to previous estimates from vaccines.$^{311}$ A wide range of prevalence rates across studies, ranging from 0.04$^{35}$ to 25.4%$^{39}$ have been previously reported. We conducted a subgroup analysis and found that vaccine platform and study design may influence the prevalence of cutaneous adverse reactions, as cutaneous adverse events are much more prevalent in mRNA...
Table 1  Cutaneous manifestations following COVID-19 vaccination (n = number of cases)

| Cutaneous manifestations                  | Total (n = 44 582) | mRNA vaccine (n = 27 655) | Viral vector vaccine (n = 15 113) | Inactivated viral vaccine (n = 1112) | Protein subunit vaccine (n = 2) | Unidentified vaccine (n = 700) |
|-------------------------------------------|--------------------|---------------------------|-----------------------------------|-------------------------------------|-------------------------------|------------------------------|
|                                           | n                  | %                         | n                                 | %                                   | n                             | %                             |
| Acute injection site reaction             | 32 173             | 72.17                     | 19 106                            | 69.09                               | 12 110                        | 80.13                        |
| Viral vector vaccine                      |                    |                           |                                   |                                     |                               |                               |
| mRNA vaccine                              | 27 655             |                             |                                   |                                     |                               |                               |
| Viral vector                               | 15 113             |                             |                                   |                                     |                               |                               |
| Inactivated viral vaccine                 | 1112               |                             |                                   |                                     |                               |                               |
| Protein subunit vaccine                   | 2                  |                             |                                   |                                     |                               |                               |
| Unidentified vaccine                      | 700                |                             |                                   |                                     |                               |                               |
| Rash/unspecified skin eruption            | 6158               | 13.81                      | 3908                              | 14.13                               | 1803                          | 11.93                        |
| Urticaria and/or angio-oedema              | 2913               | 6.53                       | 1812                              | 6.55                                | 920                           | 6.09                         |
| Pruritus without skin lesion              | 1009               | 2.26                       | 986                               | 3.57                                | 6                             | 0.4                          |
| Delayed large local reactions             | 847                | 1.90                       | 820                               | 2.97                                | 24                            | 1.6                          |
| Maculopapular rash                        | 221                | 0.50                       | 162                               | 0.59                                | 36                            | 0.24                         |
| Herpes zoster                             | 182                | 0.41                       | 134                               | 0.49                                | 28                            | 0.19                         |
| Oral blister/ulcer/vesicle                | 162                | 0.36                       | 121                               | 0.44                                | 38                            | 0.25                         |
| PR/PR-like lesion                         | 108                | 0.24                       | 65                                | 0.24                                | 12                            | 0.8                          |
| Vesiculobullous lesion                    | 86                 | 0.19                       | 76                                | 0.28                                | 7                             | 0.05                         |
| Petechiae/purpura/ecthymosis              | 60                 | 0.14                       | 19                                | 0.07                                | 22                            | 0.15                         |
| Chilblains/chilblains-like lesion         | 58                 | 0.13                       | 43                                | 0.16                                | 7                             | 0.05                         |
| Vascilitis/vascular-like lesion           | 46                 | 0.10                       | 27                                | 0.10                                | 9                             | 0.06                         |
| CLE                                       | 42                 | 0.09                       | 40                                | 0.15                                | 2                             | 0.01                         |
| Eczema/eczematous lesion                  | 40                 | 0.09                       | 17                                | 0.06                                | 5                             | 0.03                         |
| Papulovesicular lesion                    | 35                 | 0.08                       | 19                                | 0.07                                | 9                             | 0.06                         |
| Erythema multiforme                       | 34                 | 0.08                       | 34                                | 0.12                                | 0                             | 0.00                         |
| DIR to dermal filler                      | 31                 | 0.07                       | 30                                | 0.11                                | 0                             | 0.00                         |
| Psoriasis                                 | 30                 | 0.07                       | 18                                | 0.07                                | 10                            | 0.07                         |
| Oral white/red plaque                     | 27                 | 0.06                       | 22                                | 0.08                                | 5                             | 0.03                         |
| Anaphylaxis                               | 23                 | 0.05                       | 3                                 | 0.01                                | 5                             | 0.03                         |
| Contact dermatitis                        | 18                 | 0.04                       | 17                                | 0.06                                | 0                             | 0.00                         |
| Herpes simplex virus infection            | 16                 | 0.04                       | 9                                 | 0.03                                | 7                             | 0.05                         |
| Residual skin discoloration               | 15                 | 0.03                       | 15                                | 0.05                                | 0                             | 0.00                         |
| Angular cheilitis                         | 14                 | 0.03                       | 13                                | 0.05                                | 1                             | 0.01                         |
| Lichen planus                             | 14                 | 0.03                       | 11                                | 0.04                                | 1                             | 0.01                         |
| Bullous pemphigoid                         | 13                 | 0.03                       | 11                                | 0.04                                | 1                             | 0.01                         |
| SCARs                                      | 12                 | 0.03                       | 4                                 | 0.01                                | 5                             | 0.03                         |
| Burning gingiva                           | 10                 | 0.02                       | 10                                | 0.04                                | 0                             | 0.00                         |
| Alopecia                                  | 11                 | 0.03                       | 5                                 | 0.02                                | 4                             | 0.03                         |
| ITP                                        | 8                  | 0.02                       | 6                                 | 0.02                                | 2                             | 0.01                         |
| Papulosquamous/pityriasiform lesion       | 8                  | 0.02                       | 0                                 | 0.00                                | 0                             | 0.00                         |
| Pemphigus Vulgaris                        | 7                  | 0.02                       | 5                                 | 0.02                                | 2                             | 0.01                         |
| Acne/acneiform lesion                     | 7                  | 0.02                       | 1                                 | <0.01                               | 1                             | 0.01                         |
| Sweet’s syndrome                          | 6                  | 0.01                       | 3                                 | 0.01                                | 3                             | 0.02                         |

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| Cutaneous manifestations                  | Total (n = 44 582) | mRNA vaccine (n = 27 655) | Viral vector vaccine (n = 15 113) | Inactivated viral vaccine (n = 1112) | Protein subunit vaccine (n = 2) | Unidentified vaccine (n = 700) |
|------------------------------------------|--------------------|----------------------------|-----------------------------------|-------------------------------------|-------------------------------|-------------------------------|
|                                          | n                  | %                          | n                                 | %                                  | n                             | n                             |
| Fixed drug eruption                      | 6                  | 0.01                       | 5                                 | 0.02                                | 0                             | 0                             |
| PRP/PRP-like lesion                      | 5                  | 0.01                       | 3                                 | 0.01                                | 2                             | 0.01                          |
| Hailey-Hailey                           | 5                  | 0.01                       | 5                                 | 0.02                                | 0                             | 0                             |
| SDRIFE                                   | 4                  | 0.01                       | 2                                 | 0.01                                | 1                             | 0.01                          |
| Vitiligo                                 | 4                  | 0.01                       | 3                                 | 0.01                                | 0                             | 1                             |
| Reaction to breast implant              | 4                  | 0.01                       | 3                                 | 0.01                                | 1                             | 0.01                          |
| Rust-like discoloration                  | 4                  | 0.01                       | 4                                 | 0.01                                | 0                             | 0                             |
| Alopecia areata                          | 4                  | 0.01                       | 1                                 | <0.01                               | 3                             | 0.02                          |
| Erythema nodosum                         | 4                  | 0.01                       | 0                                 | 0.00                                | 2                             | 0.01                          |
| Livedo reticularis                       | 4                  | 0.01                       | 3                                 | 0.01                                | 0                             | 0                             |
| Toxic erythema                           | 4                  | 0.01                       | 0                                 | 0.00                                | 0                             | 0                             |
| Granuloma annulare                       | 3                  | 0.01                       | 2                                 | 0.01                                | 0                             | 0                             |
| Skin necrosis                            | 3                  | 0.01                       | 2                                 | 0.01                                | 1                             | 0.01                          |
| Hay fever                                | 3                  | 0.01                       | 3                                 | 0.01                                | 0                             | 0                             |
| Still’s disease                          | 2                  | <0.01                      | 1                                 | <0.01                               | 1                             | 0.01                          |
| Nicolau syndrome                         | 2                  | <0.01                      | 2                                 | <0.01                               | 0                             | 0                             |
| Multisystem inflammatory syndrome        | 2                  | <0.01                      | 1                                 | <0.01                               | 1                             | 0.01                          |
| Radiation recall dermatitis              | 2                  | <0.01                      | 0                                 | <0.01                               | 1                             | 0.09                          |
| Exfoliation of the skin of the palms     | 2                  | <0.01                      | 2                                 | <0.01                               | 0                             | 0                             |
| Local skin reaction on BCG scar          | 2                  | <0.01                      | 2                                 | <0.01                               | 0                             | 0                             |
| Papulopustular lesion                    | 2                  | <0.01                      | 1                                 | <0.01                               | 1                             | 0.01                          |
| Lymphomatoid drug reaction               | 2                  | <0.01                      | 1                                 | <0.01                               | 0                             | 0                             |
| Palmar erythema                          | 2                  | <0.01                      | 0                                 | <0.01                               | 0                             | 2                             |
| Pityriasis lichenoides                   | 2                  | <0.01                      | 2                                 | <0.01                               | 0                             | 0                             |
| Eruptive cherry haemangiomatosis         | 1                  | <0.01                      | 1                                 | <0.01                               | 0                             | 0                             |
| Erythema annulare centrifugum            | 1                  | <0.01                      | 0                                 | 0.00                                | 1                             | 0.01                          |
| Livedo racemosa                          | 1                  | <0.01                      | 1                                 | <0.01                               | 0                             | 0                             |
| Pseudolymphoma                           | 1                  | <0.01                      | 1                                 | <0.01                               | 0                             | 0                             |
| Purpura annularis telangiectodes of Majocchi | 1                | <0.01                      | 1                                 | <0.01                               | 0                             | 0                             |
| Rowell’s syndrome                        | 1                  | <0.01                      | 1                                 | <0.01                               | 0                             | 0                             |
| Viral warts                              | 1                  | <0.01                      | 0                                 | 0.00                                | 1                             | 0.01                          |
| Psoriasiform eruption                    | 1                  | <0.01                      | 1                                 | <0.01                               | 0                             | 0                             |
| Danier’s disease                         | 1                  | <0.01                      | 0                                 | 0.00                                | 1                             | 0.01                          |
| Erythema migrans                         | 1                  | <0.01                      | 1                                 | <0.01                               | 0                             | 0                             |
| Cutaneous manifestations                                                                 | Total (n = 44 582) | mRNA vaccine (n = 27 655) | Viral vector vaccine (n = 15 113) | Inactivated viral vaccine (n = 1112) | Protein subunit vaccine (n = 2) | Unidentified vaccine (n = 700) |
|----------------------------------------------------------------------------------------|--------------------|---------------------------|-----------------------------------|-------------------------------------|-------------------------------|-------------------------------|
| Lichen striatus                                                                        | 1 (<0.01)          | 1 (<0.01)                 | 0 (0.00)                          | 0 (0.00)                           | 0 (0.00)                      | 0 (0.00)                      |
| Primary cutaneous CD30-positive lymphoproliferative disorder                          | 1 (<0.01)          | 1 (<0.01)                 | 0 (0.00)                          | 0 (0.00)                           | 0 (0.00)                      | 0 (0.00)                      |
| Eschar                                                                                | 1 (<0.01)          | 1 (<0.01)                 | 0 (0.00)                          | 0 (0.00)                           | 0 (0.00)                      | 0 (0.00)                      |
| Lipschütz ulcer                                                                        | 1 (<0.01)          | 0 (0.00)                  | 1 (0.01)                          | 0 (0.00)                           | 0 (0.00)                      | 0 (0.00)                      |
| Acute localized exanthematous pustulosis                                               | 1 (<0.01)          | 0 (0.00)                  | 1 (0.01)                          | 0 (0.00)                           | 0 (0.00)                      | 0 (0.00)                      |
| Superficial venous thrombosis                                                          | 1 (<0.01)          | 0 (0.00)                  | 1 (0.01)                          | 0 (0.00)                           | 0 (0.00)                      | 0 (0.00)                      |
| Eosinophilic cellulitis                                                                | 1 (<0.01)          | 1 (<0.01)                 | 0 (0.00)                          | 0 (0.00)                           | 0 (0.00)                      | 0 (0.00)                      |
| Pigmented purpuric dermatosis                                                          | 1 (<0.01)          | 1 (<0.01)                 | 0 (0.00)                          | 0 (0.00)                           | 0 (0.00)                      | 0 (0.00)                      |
| Serum sickness-like reaction                                                           | 1 (<0.01)          | 0 (0.00)                  | 0 (0.00)                          | 1 (0.09)                           | 0 (0.00)                      | 0 (0.00)                      |
| Eosinophilic dermatosis                                                                | 1 (<0.01)          | 0 (0.00)                  | 1 (0.01)                          | 0 (0.00)                           | 0 (0.00)                      | 0 (0.00)                      |
| Linear IgA bullous dermatosis                                                          | 1 (<0.01)          | 0 (0.00)                  | 1 (0.01)                          | 0 (0.00)                           | 0 (0.00)                      | 0 (0.00)                      |
| Exuberant lichenoid eruption                                                           | 1 (<0.01)          | 0 (0.00)                  | 1 (0.01)                          | 0 (0.00)                           | 0 (0.00)                      | 0 (0.00)                      |
| Multibacillary leprosy                                                                | 1 (<0.01)          | 1 (<0.01)                 | 0 (0.00)                          | 0 (0.00)                           | 0 (0.00)                      | 0 (0.00)                      |
| Subcutaneous nodule                                                                    | 1 (<0.01)          | 1 (<0.01)                 | 0 (0.00)                          | 0 (0.00)                           | 0 (0.00)                      | 0 (0.00)                      |
| Insect bite                                                                            | 1 (<0.01)          | 0 (0.00)                  | 1 (0.01)                          | 0 (0.00)                           | 0 (0.00)                      | 0 (0.00)                      |
| Morphoea                                                                              | 1 (<0.01)          | 1 (<0.01)                 | 0 (0.00)                          | 0 (0.00)                           | 0 (0.00)                      | 0 (0.00)                      |
| Raynaud                                                                                | 1 (<0.01)          | 1 (<0.01)                 | 0 (0.00)                          | 0 (0.00)                           | 0 (0.00)                      | 0 (0.00)                      |
| Sarcoidiosis                                                                           | 1 (<0.01)          | 0 (0.00)                  | 0 (0.00)                          | 0 (0.00)                           | 0 (0.00)                      | 1 (0.14)                      |
| Facial oedema                                                                          | 1 (<0.01)          | 1 (<0.01)                 | 0 (0.00)                          | 0 (0.00)                           | 0 (0.00)                      | 0 (0.00)                      |
| Folliculitis                                                                           | 1 (<0.01)          | 0 (0.00)                  | 0 (0.00)                          | 1 (0.09)                           | 0 (0.00)                      | 0 (0.00)                      |

CLE, cutaneous lupus erythematosus; DIR, delayed inflammatory reactions; ITP, idiopathic thrombocytopenic purpura; PR, pityriasis rosea; PRP, pityriasis rubra pilaris; SCARs, severe cutaneous adverse reactions; SDRIFE, systemic drug-related intertriginous and flexural exanthema.
### Table 2  Demographic data, clinical presentations and therapeutic considerations of patients with COVID-19 vaccine-related cutaneous manifestations ($n$ = number of cases)

| Cutaneous manifestations, $n$ | Age (years), Mean ($\pm$ SD) | Male/Female/ND ratio | Onset (days), Mean ($\pm$ SD) | Duration (days), Mean ($\pm$ SD) | Dose, $n$ (%) | Local symptoms, $n$ (%) | Systemic symptoms, $n$ (%) | Treatments, $n$ (%) |
|-----------------------------|-------------------------------|----------------------|------------------------------|----------------------------------|----------------|------------------------|--------------------------|----------------------|
| Injection site reaction ($n$ = 55) | 51.15 (15.10) | 4/23/28 | 2.50 (2.90) | 5.50 (2.12) | Dose 1: 36 (65.38), dose 2: 17 (30.77), both dose: 2 (3.85) | Pruritus 36 (65.45), pain 32 (58.18), burning 25 (45.45), no symptom 13 (23.6) | Fever 30 (54.55), headache 5 (9.09), myalgia 3 (5.45), no symptom 21 (38.18) | Topical corticosteroids 32 (58.18), antihistamine 30 (54.55), systemic corticosteroids 1 (1.82), spontaneous remission 30 (54.55) |
| Delayed injection site reaction ($n$ = 82) | 51.05 (13.86) | 10/72 | 6.72 (3.88) | 5.13 (4.64) | Dose 1: 40 (48.78), dose 2: 12 (14.63), dose 3: 1 (1.21), both dose 1 & 2: 28 (34.14), not report: 1 (1.21) | Pruritus 23 (28.05), pain 25 (30.49), burning 4 (4.88), no symptom 15 (18.29) | Fever 17 (20.73), myalgia 16 (19.51), headache 11 (13.41), fatigue 12 (14.63), lymphadenopathy 6 (7.32), no symptom 36 (43.90) | Topical corticosteroids 27 (32.93), antihistamine 20 (24.39), systemic corticosteroids 5 (6.09), antibiotics 4 (4.87), antipyretic drugs 3 (3.66), analgesic drugs 2 (2.44), spontaneous remission 18 (21.95) |
| Urticaria and/or angioedema ($n$ = 46) | 40.67 (12.92) | 10/36 | 6.46 (16.97) | 24.28 (34.38) | Dose 1: 22 (47.82), dose 2: 8 (17.39), both dose: 10 (21.74), not report: 6 (13.04) | Pruritus 45 (97.82), no symptom 1 (2.17) | Fever 2 (4.35), myalgia 2 (4.35), fatigue 1 (2.17), diarrhoea 1 (2.17), no symptom 34 (73.91) | Oral antihistamine 12 (26.09), intravenous antihistamine 9 (19.57), systemic corticosteroids 8 (17.39), topical corticosteroids 2 (4.35), anti-IgE monoclonal antibody 1 (2.17), spontaneous remission 20 (43.48) |
| Herpes zoster ($n$ = 72) | 56.25 (18.17) | 35/37 | 7.76 (6.38) | 12.46 (6.81) | Dose 1: 37 (51.39), dose 2: 24 (33.33), both dose: 2 (2.78), not report: 9 (12.50) | Pain 36 (50.00), pruritus 15 (20.83), burning 11 (15.28), dysaesthesia 3 (4.17), no symptom 13 (18.06) | Myalgia 4 (5.56), fatigue 3 (4.17), fever 2 (2.78), headache 1 (1.39), no symptom 38 (52.78) | Antiviral agents 57 (79.17), anticonvulsants 12 (16.67), analgesic drugs 9 (12.50), systemic corticosteroids 5 (6.94), antibiotics 3 (4.17), topical corticosteroids 1 (1.38), spontaneous remission 3 (4.17) |
| Cutaneous manifestations, n | Age (years), Mean (±SD) | Male/Female/ND ratio | Onset (days), Mean (±SD) | Duration (days), Mean (±SD) | Dose, n (%) | Local symptoms, n (%) | Systemic symptoms, n (%) | Treatments, n (%) |
|---------------------------|-------------------------|----------------------|-------------------------|-----------------------------|-------------|----------------------|----------------------|---------------------|
| PR/PR-like lesion (n = 58) | 42.98 (13.03)           | 26/32                | 9.64 (6.11)             | 49.00 (24.09)               | Dose 1: 32 (55.17), dose 2: 22 (37.93), both dose: 4 (6.90) | Pruritus 32 (55.17), no symptom 26 (44.83) | NA | Topical corticosteroids 7 (12.07), antihistamine 5 (8.62), systemic corticosteroids 1 (1.72), spontaneous remission 40 (68.97) |
| Psoriasis (n = 29) (new onset n = 5, flares of pre-existing n = 24) | 62.24 (13.80)           | 15/14                | 9.87 (8.03)             | 14.50 (11.96)               | Dose 1: 8 (27.59), dose 2: 19 (65.52), both dose: 2 (6.90) | Pruritus 18 (62.07), no symptom 11 (37.93) | Fever 4 (13.79), fatigue 3 (10.34), arthralgia 2 (6.89), 1 myalgia (3.44), no symptom 19 (65.51) | Vitamin D3 analogs 9 (31.03), topical corticosteroids 7 (24.13), biologics 5 (17.24), phototherapy 5 (17.24), antihistamine 4 (13.79), calcineurin inhibitors 2 (6.90), systemic corticosteroids 2 (6.90), vitamin A derivatives 1 (3.45) |
| Cutaneous vasculitis (n = 25) (new onset n = 24, flares of pre-existing n = 1) | 53.24 (22.75)           | 8/17                 | 6.35 (6.24)             | 15.21 (13.70)               | Dose 1: 11 (44.00), dose 2: 8 (32.00), both dose 1&2: 3 (12.00), both dose 1&2&3: 1 (4.00), not report: 2 (8.00) | Pruritus 6 (24.00), pain 4 (16.00), burning 3 (12.00), no symptom 5 (20.00) | Arthralgia 5 (20.00), fever 4 (16.00), myalgia 4 (16.00), fatigue 2 (8.00), diarrhoea 1 (4.00), abdominal pain 1 (4.00), haematuria 1 (4.00), no symptom 3 (12.00) | Systemic corticosteroids 12 (48.00), topical corticosteroids 9 (36.00), antihistamine 6 (24.00), analgesic drugs 3 (12.00), antibiotics 2 (8.00), spontaneous remission 5 (20.00) |
| Chilblains/chilblains-like lesion (n = 17) | 51.71 (14.11)           | 9/7/1                | 4.94 (3.99)             | 23.88 (13.93)               | Dose 1: 7 (41.17), dose 2: 3 (17.65), both dose: 5 (29.41), not report: 2 (11.76) | Pruritus 4 (23.53), pain 4 (23.53), oedema 2 (11.76), burning 1 (5.88), no symptom 4 (23.53) | Fatigue 1 (5.88), headache 1 (5.88), no symptom 3 (17.65) | Topical corticosteroids 7 (58.33), antihistamine 1 (5.88), spontaneous remission 8 (47.06) |
| BP (n = 13) (new onset n = 9, flares of pre-existing n = 4) | 77.77 (6.27)            | 6/6/1                | 11.47 (10.89)           | 55.50 (48.79)               | Dose 1: 7 (53.85), dose 2: 2 (15.38), both dose 4 (30.77) | Pruritus 4 (30.17), no symptom 9 (69.23) | NA | Systemic corticosteroids 11 (84.6), topical corticosteroids 5 (38.46), antihistamine 2 (15.38), spontaneous remission 1 (7.69) |
| PV (n = 7) (new onset n = 4, flares of pre-existing n = 3) | 57.71 (21.14)           | 5/1/1                | 8.29 (9.74)             | 117.00 (66.47)              | Dose 1: 2 (28.57), dose 2: 2 (28.57), both dose: 1 (14.29), not report: 2 (28.57) | Pain 3 (42.86), no symptom 4 (57.14) | NA | Systemic corticosteroids 7 (100.00), rituximab 2 (28.57), mycophenolate mofetil 1 (14.29), azathioprine 1 (14.29) |
| Cutaneous manifestations, n | Age (years), Mean (±SD) | Male/Female/ND ratio | Onset (days), Mean (±SD) | Duration (days), Mean (±SD) | Dose, n (%) | Local symptoms, n (%) | Systemic symptoms, n (%) | Treatments, n (%) |
|-----------------------------|--------------------------|----------------------|---------------------------|----------------------------|-------------|-----------------------|--------------------------|----------------------|
| Severe cutaneous adverse reactions (n = 11) | 49.55 (17.01) | 5/6 | 9.34 (15.38) | 20.83 (9.56) | Dose 1: 6 (54.54), dose 2: 2 (18.18), both dose: 1 (9.09), not report: 2 (18.18) | Pruritus 3 (27.27), pain 2 (18.18), burning 1 (9.09), no symptom 5 (45.45) | Fever 7 (63.63), myalgia 2 (18.18), fatigue 1 (9.09), lymphadenopathy 1 (9.09) | Topical corticosteroids 7 (63.63), systemic corticosteroid 5 (45.45), antihistamine 4 (36.36), analgesic drugs 2 (18.18), antipyretic drugs 2 (18.18), antibiotics 1 (9.09) |
| Erythema multiforme (n = 11) | 60.27 (19.31) | 3/7/1 | 5.00 (3.33) | 20.63 (19.31) | Dose 1: 7 (63.63), dose 2: 4 (36.36) | Pruritus 3 (27.27), pain 1 (9.09), no symptom 7 (63.63) | Fever 7 (63.63), myalgia 2 (18.18), fatigue 2 (18.18) | Topical corticosteroids 9 (81.81), systemic corticosteroid 5 (45.45), antihistamine 4 (36.36), spontaneous remission 4 (36.36) |
| Cutaneous lupus erythematosus (n = 8) | 47.88 (22.50) | 2/6 | 14.00 (12.96) | 15.75 (6.70) | Dose 1: 5 (62.50), dose 2: 2 (25.00), both dose: 1 (12.50) | Pruritus 3 (37.50), burning 2 (25.00), pain 1 (12.50), no symptom 2 (25.00) | Fatigue 5 (62.50), myalgia 2 (25.00), arthralgia 2 (25.00), lymphadenopathy 1 (12.50) | Systemic corticosteroids 6 (75.00), hydroxychloroquine 3 (37.50), topical corticosteroids 3 (37.50) |
| Delayed inflammatory reactions to dermal fillers (n = 7) | 42.00 (11.26) | 0/7 | 2.58 (2.69) | 11.14 (15.31) | Dose 1: 4 (57.14), dose 2: 2 (28.57), both dose: 1 (14.29) | Tender 4 (57.14), pain 2 (28.57), paraesthesia 1 (14.29) | Headache 2 (28.57), flu-like symptoms 2 (28.57), slurred speech 2 (28.57), no symptom 3 (42.86) | Systemic corticosteroids 4 (57.14), hyaluronidase 2 (28.57), antihistamine 2 (28.57), ACE inhibitor 1 (14.28), antibiotics 1 (14.28), intralesional 5-FU 1 (14.28) |
| Lichen planus (n = 6) (new onset n = 4, flares of pre-existing n = 2) | 58.53 (7.20) | 5/0/1 | 4.17 (3.50) | NA | Dose 1: 2 (33.33), dose 2: 1 (16.67), not report: 1 (16.67), no report: 2 (33.33) | Pruritus 3 (50.00), pain 1 (16.67), no symptom 2 (33.33) | NA | Topical corticosteroids 4 (66.67), systemic corticosteroids 1 (16.67), spontaneous remission 2 (33.33) |
| Sweet's syndrome (n = 6) | 57.50 (15.33) | 2/3/1 | 5.50 (3.62) | 29.88 (40.92) | Dose 1: 5 (83.33), not report: 1 (16.67) | Pain 2 (33.33), dysaesthesia 1 (16.67), no symptom 3 (50.00) | Fever 3 (50.00), headache 1 (16.67), dizziness 1 (16.67), arthralgia 1 (16.67), no symptom 2 (33.33) | Systemic corticosteroids 6 (100.00), topical corticosteroids 1 (16.7), antiviral agents 2 (33.33), antibiotics 2 (33.33) |
| Cutaneous manifestations, n | Age (years), Mean (±SD) | Male/Female/ND ratio | Onset (days), Mean (±SD) | Duration (days), Mean (±SD) | Dose, n (%) | Local symptoms, n (%) | Systemic symptoms, n (%) | Treatments, n (%) |
|-----------------------------|-------------------------|----------------------|--------------------------|------------------------------|-------------|----------------------|------------------------|---------------------|
| Pityriasis rubra pilaris (PRP) and PRP-like lesion (n = 5) | 66.00 (11.64) | 2/3 | 9.00 (7.07) | NA | Dose 1: 4 (80.00), both dose: 1 (20.00) | Pruritus 1 (20.00), no symptom 4 (80.00) | NA | Topical corticosteroids 3 (60.00), acitretin 2 (40.00), systemic corticosteroids 1 (20.00), methotrexate 1 (20.00) |
| Fixed drug eruption (n = 5) | 47.20 (23.18) | 0/5 | 11.67 (5.09) | 5.00<sup>a</sup> | Dose 2: 2 (40.00), both dose: 3 (60.00) | Pruritus 2 (40.00), no symptom 3 (60.00) | NA | Topical corticosteroids 5 (100.00), antihistamine 2 (40.00) |
| Symmetrical drug-related intertriginous and flexural exanthema (n = 4) | 52.25 (27.96) | 3/1 | 15.25 (18.68) | 27.00 (5.20) | Dose 2: 4 (100.00) | Pruritus 2 (50.00), pain 1 (50.00), burning 2 (50.00), no symptom 2 (50.00) | NA | Systemic corticosteroids 4 (100.00), topical corticosteroids 1 (25.00), antihistamine 1 (25.00) |
| Vitiligo (n = 4) (new onset n = 3, flares of pre-existing n = 1) | 41.25 (17.21) | 2/2 | 8.00 (5.57) | NA | Dose 1: 1 (25.00), dose 2: 2 (50.00), both dose: 1 (25.00) | NA | NA | Phototherapy 2 (50.00), topical calcineurin inhibitor 1 (25.00), topical tacrolimus 1 (25.00) |

BP = bullous pemphigoid; PV = pemphigus vulgaris; ND, not identified; NA, not available.

<sup>a</sup>This information was reported in only one case.
platforms than in other platforms, and observational studies reported a greater number of cutaneous adverse events than randomized control trials. A high degree of heterogeneity between studies was found to be present, which may be explained by different adverse event assessment methods, population and follow-up time. Some studies may have underreported minor adverse events. As a result, caution is needed when generalizing our global findings to different subpopulations.

From the systematic review, this report has described various cutaneous manifestations associated with the COVID-19 vaccine including injection site reactions, \(^{10, 18, 25–47}\) which were the most common cutaneous adverse reaction in almost all vaccines, uncommon adverse reactions such as delayed inflammatory reactions to tissue filler, \(^{73, 127, 228, 279}\) flares of pre-existing dermatoses (e.g. psoriasis, \(^{103, 133, 137, 141, 215, 239, 248, 252, 282, 312}\) bullous pemphigoid, \(^{63, 111}\) pemphigus vulgaris, \(^{111, 121}\) lichen planus, \(^{85, 164, 245}\) cutaneous vasculitis, \(^{163}\) vitiligo \(^{293}\) and cutaneous lupus erythematosus \(^{156, 188, 236}\) and viral reactivation (e.g. herpes zoster \(^{74, 81, 85, 92, 99, 100, 102, 107, 108, 113, 116, 131, 191, 260}\)). In addition, more severe but rare reactions such as anaphylaxis \(^{15, 37, 38, 40, 41, 44, 123}\) and severe cutaneous adverse reactions (SCARs) \(^{136, 185, 231, 271}\) have been reported as well. There is also some debate over whether some of the reported cutaneous adverse reactions following COVID-19 vaccination were causal or temporally coincidental. We hope that our study may pave the way for further research to confirm any causal relationship. In terms of practical implications, almost all of the cutaneous adverse reactions are mild and self-limiting or treatable with corticosteroids or antihistamines. Clinicians should emphasize to patients that the majority of cutaneous adverse reactions are not contraindications to subsequent vaccination. The only contraindication is severe allergic reactions to a previous dose of the COVID-19 vaccine including anaphylaxis. While an immediate allergic reaction such as acute-onset urticaria occurs within four hours of vaccine administration, clinicians should share decision-making with patients to determine whether to administer vaccinations in full dose or graded doses or change platforms. It has previously been suggested that vaccine centres prepare for any possibility of immediate severe adverse reactions. \(^{313}\)

The results of our meta-analysis showed that the prevalence of cutaneous adverse events following COVID-19 immunization was substantially different between vaccine platforms, with the mRNA-based vaccine exhibiting the highest prevalence of cutaneous adverse events. Previous research has indicated that cutaneous adverse reactions to the mRNA vaccines such as chills, erythromelalgia and ptyriasis-rosea-like exanthems may mimic dermatologic manifestations of natural SARS-CoV-2 infection. As a result, dermatologic manifestations are more likely to occur as a result of an immune response rather than direct viral effects. \(^{34, 314, 315}\) We therefore hypothesized that the observed differences in cutaneous adverse effects between different platforms of COVID-19 vaccines may be explained by the differences in their immune-mediated mechanisms. The mRNA-based vaccines may elicit more robust immune responses, resulting in a higher prevalence of cutaneous adverse events.

Although no current research has been conducted to shed light on the distinct immuno-dermatological mechanisms underlying each type of COVID-19 vaccine, numerous studies on the cutaneous manifestations of the COVID-19 vaccine support the pathophysiological hypothesis that the vaccine immunogenicity results in altered levels of chemokines and cytokines, which activate a variety of key players in the innate and adaptive immune systems. \(^{316}\) At least four distinct types of cutaneous reactions have been proposed. The first type of reaction is a classical antiviral response characterized by a predominantly cellular immune response pattern involving CD8+ T cells and macrophages with a Th1-polarized T-helper cell profile. Interferon-γ (IFN-γ), tumour necrosis factor-α (TNF-α) and various interleukins, such as IL-2 and IL-6, are key mediators, which cause skin reactions such as cutaneous lupus erythematosus, lichen planus, maculopapular rash, pityriasis rosea and erythema multiforme. Second, numerous vaccine components, including adjuvants such as aluminium, may act as haptens, inducing a predominantly Th2-polarized inflammatory response with high pro-inflammatory cytokines IL-4 and IL-13. The allergic reaction might be immediately due to an IgE hypersensitivity reaction or delayed onset since mast cell degranulation occurs in certain individuals. Classic manifestations of this reaction are urticaria, atopic dermatitis, acute injection site reactions and autoimmune bullous dermatoses, whereas delayed injection-site reactions (DIRs), also known as ‘COVID-arms’, and distant reactions involving cosmetic dermal fillers are possible manifestations of delayed hypersensitivity. \(^{317, 318}\) Third, in susceptible individuals, skin-resident memory T cells may be activated as a result of an active innate immune system, resulting in a Th17/ Th22-predominant environment, which causes skin reactions such as psoriasis, acute generalized exanthematous pustulosis and Sweet’s syndrome. \(^{319}\) Fourth, vaccine components may trigger inflammatory responses resulting in macrophages/histiocytes and granulomatous reactions. \(^{316, 319}\)

Our data synthesis has several strengths. To our knowledge, this is the first meta-analysis on the global prevalence of cutaneous adverse reactions following COVID-19 vaccination, which included all high-quality studies of randomized control trials and observational studies. The majority of these studies used a large sample size, ensuring that findings had adequate statistical power. Additionally, case reports and case series that could not be analysed in terms of prevalence were summarized using descriptive statistics in order to capture all characteristics of cutaneous manifestations, including uncommon reactions or flares of pre-existing chronic inflammatory dermatoses. The study does have several limitations. First, some reports lacked additional details about individual patients, resulting in insufficient characteristic descriptions of some cutaneous
manifestations. Second, although we performed subgroup analyses on the pooled prevalence of cutaneous adverse events, our meta-analysis still had a high degree of heterogeneity. Caution is needed when generalizing our global findings to different subpopulations. Finally, in most reports the causal relationship between the skin manifestations and the vaccination was not confirmed by in vivo or in vitro testing. The diagnosis was made based on the occurrence of the skin reactions following the vaccination and that other possible causes were ruled out. Therefore, it was very challenging to confirm that the skin reactions were, in fact, induced by the vaccines, not a coincidence.

Conclusions
Cutaneous adverse reactions to COVID-19 vaccines are common with a global prevalence rate of 3.8%. Various cutaneous manifestations have been reported with the mRNA-based vaccine showing a higher prevalence than other platforms. The majority of cutaneous adverse reactions are mild and self-limiting or treatable with corticosteroids or antihistamines. The only contraindication scheduled for filler injection should receive additional precoun-
ting of allergies, pre-existing inflammatory skin conditions, or history of reactions to tissue filler. It is recommended patients with a history of allergies, pre-existing inflammatory skin conditions, or scheduled for filler injection should receive additional precoun-
selling and monitoring and that vaccine centre be prepared for even rare adverse events. A better understanding of potential side-effects may strengthen public confidence among persons or communities reticent to receive new vaccine technologies.

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Conflict of Interest
None reported.

Data availability statement
The data that support the findings of this study are available in the supplementary material of this article.

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Supporting information
Additional Supporting Information may be found in the online version of this article:

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