











Cutaneous reactions after SARS-CoV-2 vaccination: a cross-sectional Spanish nationwide study of 405 cases*

A. Català,¹ C. Muñoz-Santos ,² C. Galván-Casas ,³ M. Roncero Riesco,⁴ D. Revilla Nebreda,⁴ A. Solá-Truyols,⁵ P. Giavedoni,¹ M. Llamas-Velasco,⁶ C. González-Cruz ,⁷ X. Cubiró,⁸ R. Ruíz-Villaverde ,⁹ S. Gómez-Armayones,¹ M.P. Gil Mateo,¹⁰ D. Pesqué,¹¹ O. Marcantonio ,¹¹ D. Fernández-Nieto ,¹² J. Román ,¹³ N. Iglesias Pena,¹⁴ L. Carnero Gonzalez,¹⁵ J. Tercedor-Sanchez,¹⁶ G. Carretero,¹⁷ T. Masat-Ticó,¹⁸ P. Rodríguez-Jiménez ,⁶ A.M. Gimenez-Arnau,¹¹ M. Utrera-Busquets,¹⁹ E. Vargas Laguna,²⁰ A.G. Angulo Menéndez,²¹ E. San Juan Lasser,²² M. Iglesias-Sancho,²³ L. Alonso Naranjo,²⁴ I. Hiltun ,²⁵ E. Cutillas Marco,²⁶ I. Polimon Olabarrieta ,³ S. Marinero Escobedo,³ X. García-Navarro,²⁷ M.J. Calderón Gutiérrez,²⁸ G. Baeza-Hernández,²⁹ L. Bou Camps,³⁰ T. Toledo-Pastrana³¹ and A. Guilabert²

¹Servicio de Dermatología, Hospital Clínic, Barcelona, Spain

²Servicio de Dermatología, Hospital General de Granollers, Barcelona, Spain

³Servicio de Dermatología, Hospital Universitario de Móstoles, Madrid, Spain

⁴Servicio de Dermatología, Complejo Asistencial Universitario de Salamanca, Salamanca, Spain

⁵Servicio de Dermatología, Hospital Universitario Son Llatzer, Mallorca, Spain

⁶Servicio de Dermatología, Hospital Universitario de La Princesa, Madrid, Spain

⁷Servicio de Dermatología, Hospital Universitari Vall D'Hebron, Barcelona, Spain

⁸Servicio de Dermatología, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

⁹Servicio de Dermatología, Hospital Universitario San Cecilio, Granada, Spain

¹⁰Servicio de Dermatología, Hospital General de La Palma, Santa Cruz de Tenerife, Spain

¹¹Servicio de Dermatología, Hospital del Mar, IMIM, Universitat Autònoma, Barcelona, Spain

¹²Servicio de Dermatología, Hospital Ramón y Cajal, Madrid, Spain

¹³Servicio de Dermatología, Parc Taulí Hospital Universitari, Sabadell, Barcelona, Spain

¹⁴Servicio de Dermatología, Hospital Universitario Lucus Augusti, Lugo, Spain

¹⁵Servicio de Dermatología, Hospital Universitario Araba, Vitoria, Spain

¹⁶Servicio de Dermatología, Hospital Virgen de las Nieves, Granada, Spain

¹⁷Servicio de Dermatología, Hospital Universitario Gran Canaria Doctor Negrín, Las Palmas Gran Canaria, Spain

¹⁸CAP Cardedeu, Institut Català de la Salut, Barcelona, Spain

¹⁹Servicio de Dermatología, Hospital Comarcal Infanta Elena, Huelva, Spain

²⁰Servicio de Dermatología, Hospital Universitario Severo Ochoa, Madrid, Spain

²¹Servicio de Dermatología, Serveis Medics Penedés Vilanova i la Geltrú, Barcelona, Spain

²²Consulta privada, Dra Eliana San Juan Lasser, Madrid, Spain

²³Servicio de Dermatología, Hospital Universitari Sagrat Cor, Barcelona, Spain

²⁴Servicio de Dermatología, Hospital Universitario de Toledo, Toledo, Spain

²⁵Servicio de Dermatología, Complejo Hospitalario de Navarra, Navarra, Spain

²⁶Servicio de Dermatología, Hospital General Universitario Reina Sofía, Murcia, Spain

²⁷Servicio de Dermatología, Consorci Sanitari Alt Penedès-Garraf, Barcelona, Spain

²⁸Consulta Privada María José Calderón, Bilbao, Spain

²⁹Servicio de Dermatología, Hospital Universitario de Fuenlabrada, Madrid, Spain

³⁰Consulta Dr Lola Bou, Barcelona, Spain

³¹Hospital Quirónsalud Infanta Luisa, Sevilla, Spain

Linked Comment: V. Bataille and S. Puig. *Br J Dermatol* 2022; **186**:15.

Summary

Correspondence

Carlos Muñoz-Santos.

Email: carlosmunozsantos@gmail.com

Accepted for publication

10 July 2021

Background Cutaneous reactions after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines are poorly characterized.

Objective To describe and classify cutaneous reactions after SARS-CoV-2 vaccination.

Methods A nationwide Spanish cross-sectional study was conducted. We included patients with cutaneous reactions within 21 days of any dose of the approved vaccines at the time of the study. After a face-to-face visit with a dermatologist, information on cutaneous reactions was collected via an online professional

Funding sources

None.

Conflicts of interest

The authors declare they have no conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon request. The data are not publicly available for privacy/ethical reasons.

A.C, C. M.-S. and C.G.-C. contributed equally as first authors.

*Plain language summary available online

DOI 10.1111/bjd.20639

survey and clinical photographs were sent by email. Investigators searched for consensus on clinical patterns and classification.

Results From 16 February to 15 May 2021, we collected 405 reactions after vaccination with the BNT162b2 (Pfizer-BioNTech; 40.2%), mRNA-1273 (Moderna; 36.3%) and AZD1222 (AstraZeneca; 23.5%) vaccines. Mean patient age was 50.7 years and 80.2% were female. Cutaneous reactions were classified as injection site ('COVID arm', 32.1%), urticaria (14.6%), morbilliform (8.9%), papulovesicular (6.4%), pityriasis rosea-like (4.9%) and purpuric (4%) reactions. Varicella zoster and herpes simplex virus reactivations accounted for 13.8% of reactions. The COVID arm was almost exclusive to women (95.4%). The most reported reactions in each vaccine group were COVID arm (mRNA-1273, Moderna, 61.9%), varicella zoster virus reactivation (BNT162b2, Pfizer-BioNTech, 17.2%) and urticaria (AZD1222, AstraZeneca, 21.1%). Most reactions to the mRNA-1273 (Moderna) vaccine were described in women (90.5%). Eighty reactions (21%) were classified as severe/very severe and 81% required treatment.

Conclusions Cutaneous reactions after SARS-CoV-2 vaccination are heterogeneous. Most are mild-to-moderate and self-limiting, although severe/very severe reactions are reported. Knowledge of these reactions during mass vaccination may help healthcare professionals and reassure patients.

What is already known about this topic?

- In clinical trials, COVID-19 vaccines were associated with cutaneous adverse events, especially local injection site reactions.
- Previous descriptions of cutaneous reactions beyond the injection site were case reports or mostly reported by non-dermatologists and lacked clinical images.

What does this study add?

- We describe and classify a large, representative sample of patients with unexplained skin manifestations after COVID-19 vaccination, using consensus to define associated morphological patterns.
- We describe six morphological reaction patterns and herpesvirus reactivations, and their association with demographic factors and the medical record, and provide illustrations to allow for easy recognition.

The search for an effective vaccine has been unrelenting since 31 December 2019, when the first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported in China.¹ As of 4 June 2021, COVID-NMA, an international World Health Organization-supported research initiative that live-maps and reviews SARS-CoV-2 trials, had compiled 256 vaccine trials (<https://covid-nma.com/vaccines/mapping/>).

Vaccine development can take more than 15 years.² SARS-CoV-2 vaccines have had an accelerated timeline and were approved in record time,³ showing good safety and immunogenicity profiles in randomized controlled trials (RCTs).⁴⁻⁷ Currently, the European Medicines Agency (EMA) has authorized four vaccines: BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), AZD1222 (AstraZeneca) and Ad26.COV2.S (Janssen).

SARS-CoV-2 is associated with a wide spectrum of skin manifestations.⁸⁻¹¹ Some may appear after immunization with vaccines expressing the SARS-CoV-2 spike (S) protein. The

Spanish Agency for Medicines and Health Products (AEMPS) pharmacovigilance report found that, as of 25 April 2021, of 14 290 507 vaccine doses administered in Spain (70% BNT162b2, 24% AZD1222 and 6% mRNA-1273), 1468 non-specified cutaneous adverse events (AEs; 0.01%) had been notified.¹² Cutaneous AEs reported in clinical and postauthorization trials include local injection site reactions and local or generalized reactions beyond the injection site. Local injection site reactions, both immediate or delayed (≥ 4 days after vaccination), were the most frequent manifestation.^{4-6,13-16} Apart from anaphylactic rashes,¹⁷ less frequent cutaneous reactions have been described in case reports and small case series: urticaria, maculopapular or morbilliform rash, pityriasis rosea-like rash, chilblain-like lesions, facial dermal filler reactions, reactivation of varicella zoster virus (VZV), lichen planus, erythema multiforme and nonspecific hypersensitivity eruptions.^{4,5,7,13,15,18-27} An American registry-based study

analysed 414 cases after mRNA vaccination.²⁸ Most reactions were reported by nondermatologists and a small number of clinical images were shown.

Since the beginning of mass vaccination in Spain, dermatologists have treated skin rashes in vaccinees. The reactions were poorly characterized and some observers considered them more frequent than previously reported and mimicking some reactions described after SARS-CoV-2 infection.^{8–11}

The primary objective of our study was to characterize and classify the clinical features of cutaneous reactions after SARS-CoV-2 vaccination. Secondary objectives were to identify the timing of reactions, associations with other dermatological or allergic conditions, and possible relationships with diagnoses of SARS-CoV-2 or SARS-CoV-2-associated cutaneous reactions.

Materials and methods

We conducted a nationwide, multicentre, cross-sectional observational study. The study was endorsed by the Spanish Academy of Dermatology and all Spanish dermatologists were invited to participate.

The planned recruitment period lasted 3 months (16 February–15 May 2021). Inclusion criteria were people of any age vaccinated against SARS-CoV-2 with any skin manifestation within 21 days after any dose of a vaccine approved by the EMA and AEMPS. Exclusion criteria were explainable causes other than SARS-CoV-2 vaccination and injection site reactions lasting ≤ 3 days, as this reaction was very common in SARS-CoV-2 vaccine RCTs.^{4–7}

Data were collected and managed using an electronic case report form (e-CRF) and a questionnaire administered using an online professional survey company (LimeSurvey GmbH, Hamburg, Germany). Data treatment complied with the European Commission General Data Protection Regulation and Information Security regulations. After a face-to-face visit, patient data were recorded and clinical pictures, if available, were sent by email. Data were encrypted, patient and investigator anonymity were assured, and no external servers were used. Case entry was restricted to dermatologists, to provide a more accurate description and classification of the morphology of the lesions. As in a previous study of SARS-CoV-2 skin manifestations,⁸ reporting dermatologists preclassified skin rashes in a predefined cutaneous reaction pattern, with an option for a free clinical description. Only the three principal investigators had access to the clinical image dataset and independently reviewed the photographs and clinical data, and sought consensus on the cutaneous patterns. If clinical images were not available, the case was considered as missing data, unless the clinical pattern described was unequivocal. If consensus was not initially reached but histopathology was available, the case was classified according to an agreed clinicopathological correlation. If consensus was not reached and histopathology was not available or not diagnostic, the reporting dermatologist was consulted, and if clinical consensus was not reached, the case was not classified.

Variables collected through the e-CRF included patient characteristics (geographical area, age, sex, history of allergy, atopic dermatitis, urticaria and/or cutaneous reactions to other vaccines before SARS-CoV-2 diagnosis, previous SARS-CoV-2-associated cutaneous manifestations and new drugs prescribed in the 5 weeks before the reaction). Vaccine reaction data included type of vaccine, dose at the time of the cutaneous reaction and days between doses. Cutaneous reaction data included day of onset, duration, injection site involvement (local or generalized beyond the injection site), location, clinical pattern of the reaction (predefined or free description), cutaneous and systemic symptoms, treatment, photographs and histopathological findings, if available.

The severity of reactions was classified as grade 1 or mild (local macular or papular erythematous rash without associated systemic symptoms); grade 2 or moderate (the same as grade 1 plus systemic symptoms); grade 3 or severe (generalized erythematous macular or papular or vesicular rash); and grade 4 or very severe (generalized erythrodermic or exfoliative or ulcerative or bullous rash).

The study was authorized by the ethics committees of the three principal investigation centres and the regional drug regulatory agency for postauthorization of observational studies (Generalitat de Catalunya, registry number: 9015-363592/2021). All patients gave written informed consent to participate and explicit consent to publish images.

The sample size could not be determined a priori because of the uncertain number of reported reactions and participating dermatologists. We planned for 3 months of recruitment to include the AstraZeneca vaccine (approved in Spain after the RNA-based vaccines) and to cover populations other than healthcare workers and older people. The analysis included description of the data and distribution tests (χ^2 -test for qualitative variables and ANOVA for quantitative variables). Patients with missing data for a specific mandatory parameter were excluded. A P-value < 0.05 was considered to be statistically significant in univariate analyses. The analysis was done with SPSS (version 22.0; IBM, Armonk, NY, USA).

Results

We collected 419 cases of cutaneous reactions from 31 public hospitals and private clinics. Fourteen cases not meeting the inclusion criteria and/or with missing data were excluded. The final sample included 405 reactions in 391 patients after BNT162b2 [$n = 163$ (40.2%)], mRNA-1273 [$n = 147$ (36.3%)] and AZD1222 [$n = 95$ (23.5%)] vaccination. Owing to delayed authorization, only one reaction after Janssen vaccination was reported, which was excluded from the final analysis. A flowchart of patient inclusion is shown in Figure 1. Skin biopsies were performed in 50 cases (12.3%).

Baseline patient characteristics are shown in Table 1. All patients were white, with a mean (SD) age of 50.7 (17.6) years and 80.2% were female. Regarding the mRNA vaccines, 165 reactions (53.2%) appeared after the first dose and 145 (46.8%) after the second. We could not evaluate the

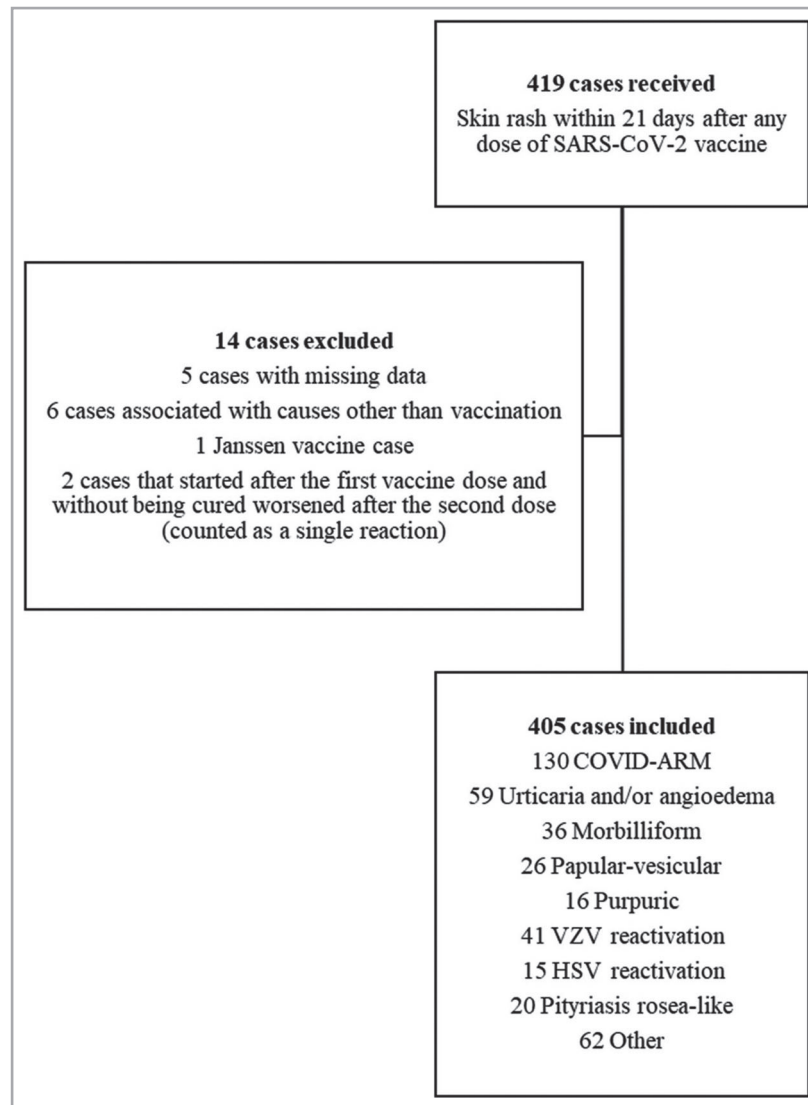


Figure 1 Study flowchart of the inclusion and exclusion of reported reactions. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; HSV, herpes simplex virus; VZV, varicella zoster virus.

AZD1222 vaccine as second doses were not administered during the study period. Fourteen patients with first-dose reactions [$n = 14/165$ (8.5%)] after mRNA vaccines developed a second-dose reaction, of whom seven had the same reaction and seven had different reactions.

Reactions were located at the injection site in 131 cases (32.3%) and beyond the injection site in 274 (67.7%) (138 local and 136 generalized). The mean (SD) time to onset was 5.1 (4.4) days after vaccination and the mean (SD) duration was 12.2 (13.1) days.

Clinical images were available for 293 reactions (72.3%). Six major clinical morphological reaction patterns were described in 287 reactions (70.9%). Other miscellaneous cutaneous reactions were reported after vaccination. Photographic examples and the main features of each pattern are shown in Figure 2 and Table 2, and Appendix S1 (Photographic atlas, see Supporting Information). The six major patterns described

were (in order of frequency): (i) local injection site reactions [commonly known as 'COVID arm'; $n = 130$ (32.1%)] – erythematous patches or swollen plaque at the injection site, of which 53.8% were delayed (≥ 4 days after vaccination); (ii) urticaria and/or angioedema [$n = 59$ (14.6%)] – hives mostly distributed on the trunk, or generalized, and usually appearing > 24 h postvaccination (93.2%); (iii) morbilliform [$n = 36$ (8.9%)] – an erythematous, maculopapular rash reminiscent of measles, mostly generalized affecting the trunk and limbs; (iv) papulovesicular or pseudovesicular [$n = 26$ (6.4%)] – small papules/vesicles with surrounding erythema, without herpetiform arrangement; (v) pityriasis rosea-like [$n = 20$ (4.9%)] – erythematous, scaly oval-shaped plaques in a 'Christmas tree' distribution on the trunk; and (vi) purpuric rashes [$n = 16$ (4.0%)] – mostly located in the limbs. According to the histopathology, four reactions were consistent with small-vessel vasculitis.

Table 1 Baseline patient characteristics

No. of patients	391
No. of reactions	405
No. of patients with reported reactions after both doses	14
Mean (SD) age (years)	50.7 (17.6)
Range	20–95
Sex	
Female	325 (80.2)
Male	80 (19.8)
Medical history	
Atopic dermatitis	28 (6.9)
Allergic asthma	24 (5.9)
Allergic rhinitis	42 (10.4)
Urticaria	26 (6.4)
History of allergy to drugs or excipients	
Yes	47 (11.6)
No	358 (88.4)
Any antibiotic	23 (5.7)
ASA and/or NSAIDs	16 (4.0)
Iodine	4 (1.0)
History of cutaneous reactions to other vaccines	9 (2.2)
Previous diagnosis of SARS-CoV-2 infection ^a	
Yes	45 (11.1)
No	360 (88.9)
Clinical suspicion only	2 (4.4)
PCR+	33 (73.3)
Antibody+	11 (24.4)
Rapid antigen test+	3 (6.7)
Cutaneous manifestations after SARS-CoV-2 infection	
Yes	7/45
Maculopapular rash	3/7
Urticaria	2/7
Morbilliform rash	1/7
Pseudovesicular rash	1/7

Data are n (%) unless otherwise indicated. ASA, acetylsalicylic acid; NSAID, nonsteroidal anti-inflammatory drugs; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. ^aSome patients were diagnosed by one or more methods.

Cutaneous findings not included in this classification were grouped as: (i) flare/reactivation of latent pre-existing cutaneous infection or condition [VZV, n = 41 (10.1%); herpes simplex virus (HSV), n = 15 (3.7%); psoriasis (n = 6); lichen planus (n = 3)]; (ii) new-onset condition [n = 31 (7.6%)], listed in Table 3; and (iii) nonclassifiable [n = 22 (5.4%)].

The most frequently reported reactions were injection site reactions in women [n = 124/325 (38.1%)] and VZV reactivation in men [n = 16/80 (20%)]. Systemic symptoms associated with the skin rash were present in 207 patients (51.1%), particularly in those with the COVID arm pattern (64.6%), with low fever/fever being the most frequent symptom in this group (45.3%). The earliest pattern that appeared was the morbilliform pattern (mean 4 days), the last was VZV reactivation (mean 6.9 days) and the longest lasting was pityriasis rosea-like (mean 25.2 days).

Thirty-one patients (7.7%) were taking new drugs at the time of the cutaneous reaction, of which acetaminophen was the most frequent [n = 9/31 (29%)].

Forty-five patients (11.1%) had been diagnosed with mild or asymptomatic SARS-CoV-2 infection. Seven (15.5%) had cutaneous reactions after both infection and vaccination. Cutaneous reactions after vaccination and their severity in this group are shown in Table S1 (see Supporting Information). There were no significant differences in the severity of cutaneous reactions between this group and patients with no prior SARS-CoV-2 infection (22.1% vs. 21% of severe/very severe reactions).

Dermatological findings and systemic symptoms according to type of vaccine are shown in Table 3. There were more reactions in men who received the BNT162b2 [n = 49 (30.1%)] vaccine than with the mRNA-1273 [n = 14 (9.5%)] and AZD1222 [n = 17 (17.9%)] vaccines. Nearly all patients with a reaction to the Moderna vaccine were women (90.5%). The most frequently reported patterns in each vaccine group were VZV infection (BNT162b2, 17.2%), COVID arm (mRNA-1273, 61.9%) and urticaria (AZD1222, 21.1%).

In total, 166 reactions (41.0%) were classified as grade 1 (mild), 154 (38.0%) as grade 2 (moderate), 80 (19.8%) as grade 3 (severe) and five (1.2%) as grade 4 (very severe). Very severe reactions included one case each of morbilliform rash progressing to erythroderma, bullous pemphigoid, acute generalized exanthematous pustulosis, vasculitis and urticaria. Fifty-eight patients (14.3%) took sick leave, mostly due to herpes zoster [n = 15/58 (25.9%)] and urticaria [n = 10/58 (17.2%)]. Severe/very severe cases were reported more frequently with the BNT162b2 (25.2% and 2.4%, respectively) and AZD1222 (25.3% and 1.0%, respectively) vaccines. No patient died. Treatment was required in 328 cases (81%) and is detailed in Table 2.

Discussion

We described dermatological reactions after vaccination with three SARS-CoV-2 vaccines (two mRNA and one adenovirus-vectored vaccines) and classified them into six well-defined morphological reactions patterns and new-onset or reactivation of dermatosis.

Initial reports mostly described local injection site reactions and, subsequently, other miscellaneous skin reactions after mRNA vaccination.^{4,5,7,13,15,18–27} In 2021, McMahon *et al.* published a large registry-based study (mostly with the mRNA-1273 vaccine) in healthcare workers and older people, describing not only injection site reactions, but also urticarial and morbilliform rashes.²⁸

Unlike the study of McMahon *et al.*,²⁸ our data entry, description and assignment of clinical patterns were made by dermatologists and were mostly supported by photographs. Case collection throughout Spain and the 3-month recruitment period permitted a more representative sample beyond healthcare workers and older people.

Reactions were more frequent in women (80.2%), which may reflect a real difference or reporting bias, although

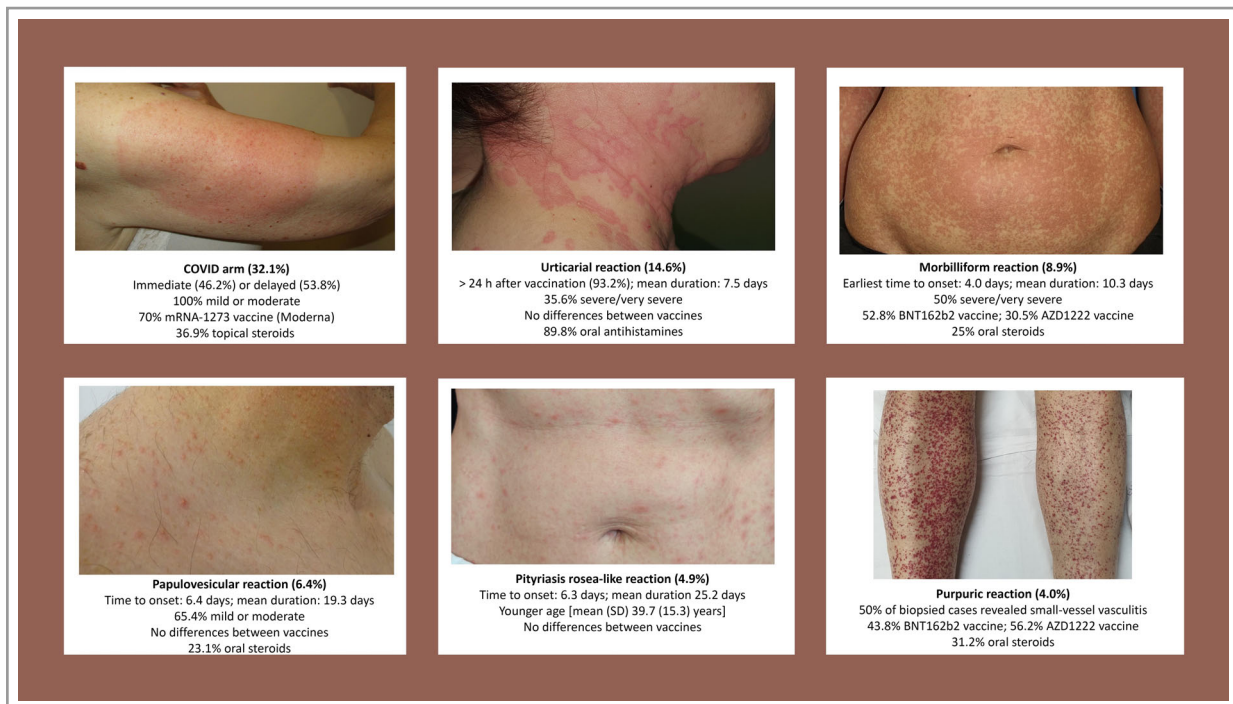


Figure 2 Summary of the main features of the six reaction patterns.

women are known to have greater reactivity to vaccines,²⁹ and 60% of vaccinated people in Spain were women at the time of the study.¹² Therefore, women's immune systems may be more reactive to SARS-CoV-2 proteins, which would result in lower susceptibility to the disease and greater reactivity to vaccines.

Few people had previous atopic dermatitis (6.9%) or urticaria (6.4%). In the general population, the prevalence of atopic dermatitis is around 10%,^{30,31} and the lifetime prevalence of acute urticaria is approximately 20%,³² so it cannot be concluded that previous atopy or acute urticaria predisposes to SARS-CoV-2 vaccine cutaneous reactions. However, 18.6% of patients with acute urticarial reactions to vaccines in our study had a history of urticaria. Case-control studies are needed to clarify this association. Only 7.7% of people were receiving new drugs (mainly acetaminophen) at the time of the reaction, and this factor was therefore unlikely to be related to cutaneous reactions.

There was a previous diagnosis of SARS-CoV-2 in 11.1% of cases, similar to the seroprevalence in Spain at the time of writing (9.9%).³³ The severity of cutaneous reactions in this group did not differ from the rest of the sample. Thus, prior SARS-CoV-2 infection does not seem to predispose to cutaneous reactions or more severe reactions, after vaccination.

The COVID arm, the most reported pattern was described after vaccination with all three vaccines, particularly mRNA-1273 (70.0%), and almost exclusively in women (95.4%). This pattern had the closest association with systemic symptoms (64.6%).

Two-thirds of reported reactions were beyond the injection site. Each morphological pattern seems to correspond to a

different spectrum of delayed hypersensitivity reaction, with most of the few skin biopsies that were performed showing nonspecific changes consistent with this reaction. In contrast to previous series,²⁸ some reactions were scarce (chilblain-like/periostitis) or unrepresented (erythromelalgia), while other reactions were more frequently reported (pityriasis rosea-like, VZV reactivations and papulovesicular rashes). The morbilliform and purpuric patterns were reported mostly after BNT162b2 and AZD1222 vaccination, and were associated with more severe reactions. VZV reactivation was more frequent after BNT162b2 vaccination and in men.

UK spontaneous AE reports are the main information source on AZD1222 vaccine cutaneous reactions,³⁴ which, in our series, were mainly acute urticaria (21.1%), injection site reactions (16.8%) and morbilliform rash (11.6%). Owing to the precautionary suspension of the vaccine in the initial target population, we could not study the second dose.

We found a large number of herpes reactivations (VZV and HSV, 13.8%). For VZV, the number [$n = 41$ (10.1%)], severity (36.6% took sick leave) and the percentage in healthy people aged < 50 years (29.2%) were particularly striking.^{35,36} There were fewer HSV than VZV reactivations, probably because patients with HSV do not usually seek medical care. We also found pityriasis rosea-like eruptions, which might have been due to human herpesvirus 6 and 7 reactivation. These herpetic reactivations were also described after SARS-CoV-2 infection and other vaccinations.^{8,9,37,38} Taken together, these data strengthen a causal link between herpesvirus reactivation and the SARS-CoV-2 vaccine. A plausible mechanism is that a strong specific immune response against

Table 2 Characteristics of patients with cutaneous reactions (n = 405) after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination

Characteristics	COVID arm	HSV reactivation	VZV reactivation	Papular vesicular	Pityriasis rosea-like	Morbiliform	Urticaria and/or angioedema	Purpuric	P-value
No. of cases	130 (32.1)	15 (3.7)	41 (10.1)	26 (6.4)	20 (4.9)	36 (8.9)	59 (14.6)	16 (4.0)	–
Mean (SD) age (years)	48.8 (15.7)	44.0 (14.6)	60.6 (17.4)	43.5 (15.4)	39.7 (15.3)	50.4 (20.8)	47.9 (15.5)	55.9 (20.5)	< 0.001
Sex									< 0.001
Female	124 (95.4)	12 (80.0)	25 (61.0)	22 (84.6)	15 (75.0)	27 (75.0)	46 (78.0)	11 (68.8)	
Male	6 (4.6)	3 (20.0)	16 (39.0)	4 (15.4)	5 (25.0)	9 (25.0)	13 (22.0)	5 (31.2)	0.0
Medical history									
Atopic dermatitis	12 (9.2)	0 (0.0)	1 (2.4)	1 (3.8)	2 (10.0)	4 (11.1)	6 (10.2)	1 (6.3)	0.714
Allergic asthma	6 (4.6)	2 (13.3)	1 (2.4)	4 (15.4)	0 (0.0)	5 (13.9)	1 (1.7)	0 (0.0)	0.030
Allergic rhinitis	13 (10.0)	2 (13.3)	2 (4.9)	2 (7.7)	5 (25.0)	8 (22.2)	5 (8.5)	1 (6.3)	0.147
Urticaria	6 (4.6)	0 (0.0)	2 (4.9)	1 (3.8)	2 (10.0)	2 (5.6)	11 (18.6)	0 (0.0)	0.053
History of allergy to drugs or excipients	19 (14.6)	0 (0.0)	2 (4.9)	1 (3.8)	0 (0.0)	8 (22.2)	5 (8.5)	4 (25.0)	0.023
History of cutaneous reactions to other vaccines	5 (3.8)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	0.835
Vaccine									< 0.001
BNT162b2 (Pfizer)	23 (17.7)	5 (33.3)	28 (68.3)	11 (42.3)	11 (55.0)	19 (52.8)	24 (40.7)	7 (43.8)	
mRNA-1273 (Moderna)	91 (70.0)	4 (26.7)	6 (14.6)	7 (26.9)	5 (25.0)	6 (16.7)	15 (25.4)	0 (0.0)	
AZD1222 (AstraZeneca)	16 (12.3)	6 (40.0)	7 (17.1)	8 (30.8)	4 (20.0)	11 (30.5)	20 (33.9)	9 (56.2)	0.969
Vaccination dose at the time of cutaneous reaction									
First	85 (65.4)	9 (60.0)	26 (63.4)	18 (69.2)	12 (60.0)	25 (69.4)	35 (59.3)	11 (68.8)	
Second	45 (34.6)	6 (40.0)	15 (36.6)	8 (30.8)	8 (40.0)	11 (30.6)	24 (40.7)	5 (31.2)	
Mean (SD) time to onset after vaccination (days)	4.9 (3.7)	4.4 (4.0)	6.9 (6.4)	6.4 (5.2)	6.3 (3.6)	4.0 (3.9)	4.9 (3.4)	7.6 (5.4)	0.002
Mean (SD) duration of the reaction (days) ^a	7.4 (4.1)	9.3 (5.9)	12.1 (6.8)	19.3 (17.2)	25.2 (14.5)	10.3 (12.0)	7.5 (10.0)	15.7 (11.9)	< 0.001
Photograph availability	83 (63.8)	10 (66.7)	30 (73.2)	26 (100)	19 (95)	29 (80.5)	35 (59.3)	15 (93.8)	< 0.001
Associated skin symptoms									
Yes	118 (90.8)	14 (93.3)	38 (92.7)	24 (92.3)	11 (55.0)	30 (83.3)	54 (91.5)	9 (56.2)	< 0.001
No	12 (9.2)	1 (6.7)	3 (7.3)	2 (7.7)	9 (45.0)	5 (13.9)	5 (8.5)	7 (43.8)	
Itch	74 (56.9)	3 (20.0)	14 (34.1)	23 (88.5)	10 (50.0)	28 (77.8)	49 (83.1)	5 (31.2)	< 0.001
Pain	62 (47.7)	4 (26.7)	34 (82.9)	2 (7.7)	0 (0.0)	0 (0.0)	6 (10.2)	4 (25.0)	< 0.001
Stinging	25 (19.2)	8 (53.3)	14 (34.1)	2 (7.7)	0 (0.0)	6 (16.7)	8 (13.6)	0 (0.0)	< 0.001
Burning	19 (14.6)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	< 0.001
Dysaesthesia	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	1 (2.8)	1 (1.7)	0 (0.0)	0.354
Painful lymph node	8 (6.2)	1 (6.7)	4 (9.8)	0 (0.0)	0 (0.0)	1 (2.8)	0 (0.0)	0 (0.0)	0.175
Systemic symptoms									
Yes	84 (64.6)	8 (53.3)	20 (48.8)	11 (42.3)	8 (40.0)	16 (44.4)	29 (49.2)	5 (31.2)	0.046
No	46 (35.4)	7 (46.7)	21 (51.2)	15 (57.7)	12 (60.0)	20 (55.6)	30 (50.8)	11 (68.8)	
Cough	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.1)	0 (0.0)	0.377
Dyspnoea	1 (0.8)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (2.8)	2 (3.4)	0 (0.0)	0.520
Low fever (37.1–38 °C)	31 (23.8)	1 (6.7)	10 (24.4)	5 (19.2)	4 (20.0)	5 (13.9)	8 (13.6)	1 (6.3)	0.416
Fever (> 38 °C)	28 (21.5)	4 (26.7)	1 (2.4)	1 (3.8)	0 (0.0)	5 (13.9)	6 (10.2)	0 (0.0)	0.002
Myalgia	37 (28.5)	4 (26.7)	2 (4.9)	4 (15.4)	3 (15.0)	8 (22.2)	10 (16.9)	2 (12.5)	0.060

(continued)

Table 2 (continued)

Characteristics	COVID arm	HSV reactivation	VZV reactivation	Papular vesicular	Pityriasis rosea-like	Morbiliform	Urticaria and/or angioedema	Purpuric	P-value
Asthenia	38 (29.2)	5 (33.3)	8 (19.5)	5 (19.2)	1 (5.0)	11 (30.6)	15 (25.4)	5 (31.2)	0.342
Headache	29 (22.3)	3 (20.0)	6 (14.6)	3 (11.5)	3 (15.0)	8 (22.2)	13 (22.0)	3 (18.8)	0.891
Nausea/vomiting/diarrhoea	17 (13.1)	1 (6.7)	0 (0.0)	1 (3.8)	1 (5.0)	4 (11.1)	6 (10.2)	1 (6.3)	0.236
Anosmia/ageusia	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.224
Severity of cutaneous reaction									< 0.001
Mild (grade 1)	66 (50.8)	9 (60.0)	13 (31.7)	10 (38.5)	5 (25.0)	10 (27.8)	21 (35.6)	9 (56.3)	
Moderate (grade 2)	64 (49.2)	6 (40.0)	23 (56.1)	7 (26.9)	2 (10.0)	8 (22.2)	17 (28.8)	4 (25.0)	
Severe (grade 3)	0 (0.0)	0 (0.0)	5 (12.2)	9 (34.6)	13 (65.0)	17 (47.2)	20 (33.9)	2 (12.5)	
Very severe (grade 4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.8)	1 (1.7)	1 (6.3)	
Medical sick leave									< 0.001
Yes	10 (7.7)	1 (6.7)	15 (36.6)	3 (11.5)	0 (0.0)	8 (22.2)	10 (16.9)	5 (31.2)	
No	120 (92.3)	14 (93.3)	26 (63.4)	23 (88.5)	20 (100)	28 (77.8)	49 (83.1)	11 (68.8)	
Treatment of cutaneous reactions									
Yes	93 (71.5)	12 (80.0)	40 (97.6)	22 (84.6)	13 (65.0)	30 (83.3)	57 (96.6)	8 (50.0)	< 0.001
No	37 (28.5)	3 (20.0)	1 (2.4)	4 (15.4)	7 (35.0)	6 (16.7)	2 (3.4)	8 (50.0)	
Topical corticosteroids	48 (36.9)	1 (6.7)	1 (2.4)	12 (46.2)	9 (45.0)	12 (33.3)	16 (27.1)	4 (25.0)	< 0.001
Systemic corticosteroids	3 (2.3)	0 (0.0)	0 (0.0)	6 (23.1)	1 (5.0)	9 (25.0)	15 (25.4)	5 (31.2)	< 0.001
Topical antibiotics	5 (3.8)	1 (6.7)	7 (17.1)	5 (19.2)	1 (5.0)	1 (2.8)	3 (5.1)	0 (0.0)	0.024
Oral antibiotics	4 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (2.8)	0 (0.0)	0 (0.0)	0.601
Paracetamol	42 (32.3)	0 (0.0)	6 (14.6)	2 (7.7)	1 (5.0)	3 (8.3)	3 (5.1)	1 (6.3)	< 0.001
NSAIDs	12 (9.2)	0 (0.0)	7 (17.1)	1 (3.8)	0 (0.0)	1 (2.8)	1 (1.7)	0 (0.0)	0.057
Oral antihistamines	33 (25.4)	0 (0.0)	3 (7.3)	17 (65.4)	7 (35.0)	22 (61.1)	53 (89.8)	2 (12.5)	< 0.001
Adrenaline	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	0.621
Systemic antiviral	0 (0.0)	10 (66.7)	38 (92.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	< 0.001
New drugs (last 5 weeks) before the onset of cutaneous reaction	9 (6.9)	0 (0.0)	4 (9.8)	3 (11.5)	1 (5.0)	3 (8.3)	4 (6.8)	4 (25.0)	0.370
Prior diagnosis of SARS-CoV-2 infection	19 (14.6)	2 (13.3)	3 (7.3)	1 (3.8)	2 (10.0)	5 (13.9)	6 (10.2)	1 (6.3)	0.808

Data are presented as n (%), unless otherwise stated. P-values are from χ^2 -tests for qualitative variables and ANOVA for quantitative variables. HSV, herpes simplex virus; NSAID, nonsteroidal anti-inflammatory drug; VZV, varicella zoster virus. *Missing data for 12 patients; the percentages were calculated using the available data.

Table 3 Characteristics of patients with cutaneous reactions (n = 405) according to vaccine

Characteristics	BNT162b2 (Pfizer-BioNTech)	mRNA-1273 (Moderna)	AZD1222 (AstraZeneca)	P-value
No. of cases	163 (40.2)	147 (36.3)	95 (23.5)	
Mean (SD) age (years)	55.3 (20.7)	46.1 (13.8)	50.0 (15.2)	< 0.001
Sex				
Female	114 (69.9)	133 (90.5)	78 (82.1)	< 0.001
Male	49 (30.1)	14 (9.5)	17 (17.9)	
Medical history				
Atopic dermatitis	9 (5.5)	9 (6.1)	10 (10.5)	0.278
Allergic asthma	11 (6.7)	10 (6.8)	3 (3.2)	0.426
Allergic rhinitis	19 (11.6)	14 (9.5)	9 (9.5)	0.784
Urticaria	9 (5.5)	11 (7.5)	6 (6.3)	0.780
History of allergy to drugs or excipients				
Yes	20 (12.2)	18 (12.2)	9 (9.5)	0.760
No	143 (87.7)	129 (87.8)	86 (90.5)	
History of cutaneous reactions to other vaccines				
Yes	5 (3.1)	4 (2.7)	0 (0.0)	0.261
No	158 (96.9)	143 (97.3)	95 (100)	
Cutaneous reaction				
COVID arm	23 (14.1)	91 (61.9)	16 (16.8)	< 0.001
HSV reactivation	5 (3.1)	4 (2.7)	6 (6.3)	0.301
VZV reactivation	28 (17.2)	6 (4.1)	7 (7.4)	< 0.001
Papulovesicular	11 (6.7)	7 (4.8)	8 (8.4)	0.371
Pityriasis rosea-like	11 (6.7)	5 (3.4)	4 (4.2)	0.419
Morbilliform	19 (11.7)	6 (4.1)	11 (11.6)	0.037
Urticaria and/or angioedema	24 (14.7)	15 (10.2)	20 (21.1)	0.065
Purpuric	7 (4.3)	0 (0.0)	9 (9.5)	0.001
Other ^a	35 (21.5)	13 (8.8)	14 (14.7)	0.008
Vaccination dose at the time of cutaneous reaction				
First	82 (50.3)	83 (56.5)	95 (100)	< 0.001
Second	81 (49.7)	64 (43.5)	0 (0.0)	
Systemic symptoms				
No	104 (63.8)	54 (36.7)	40 (42.1)	
Cough	2 (1.2)	3 (2.0)	0 (0.0)	0.374
Dyspnoea	3 (1.8)	4 (2.7)	0 (0.0)	0.309
Low fever (37.1–38 °C)	21 (12.9)	33 (22.4)	16 (16.8)	0.084
Fever (> 38°C)	6 (3.7)	30 (20.4)	16 (16.8)	< 0.001
Myalgia	20 (12.3)	37 (25.2)	22 (23.2)	0.010
Asthenia	27 (16.6)	44 (29.9)	32 (33.7)	0.003
Headache	17 (10.4)	34 (23.1)	25 (26.3)	0.002
Nausea/vomiting/diarrhoea	8 (4.9)	18 (12.2)	10 (10.5)	0.062
Anosmia/ageusia	0 (0.0)	1 (0.7)	0 (0.0)	0.598
Severity of cutaneous reaction				
Mild (grade 1)	66 (40.5)	64 (43.5)	36 (37.9)	0.002
Moderate (grade 2)	52 (31.9)	68 (46.3)	34 (35.8)	
Severe (grade 3)	41 (25.2)	15 (10.2)	24 (25.3)	
Very severe (grade 4)	4 (2.4)	0 (0.0)	1 (1.0)	
Medical sick leave				
Yes	30 (18.4)	10 (6.8)	18 (18.9)	0.005
No	133 (81.6)	137 (93.2)	77 (81.1)	

Data are presented as n (%) unless stated otherwise. P-values are derived from χ^2 -tests for qualitative variables and ANOVA for quantitative variables. HSV, herpes simplex virus; VZV, varicella zoster virus. ^aOther' includes: (i) flare/reactivation of latent pre-existing cutaneous infection or condition [VZV, n = 41 (10.1%); HSV, n = 15 (3.7%); psoriasis, n = 6; lichen planus, n = 3]; (ii) new-onset condition (psoriasis, n = 3; eczema, n = 7; chilblain-like/pernio, n = 3; acute generalized exanthematous pustulosis, n = 2; Raynaud syndrome, n = 2; bullous pemphigoid, n = 2; erythema multiforme, n = 2; generalized morphea, n = 1; cutaneous B lymphoma, n = 1; livedo reticularis, n = 1; symmetrical drug-related intertriginous and flexural exanthema-like eruption, n = 1; erythema nodosum, n = 1; reaction to facial dermal fillers, n = 1; scrotal tongue, n = 1; xanthochia (n = 1), staphylococcal skin infection, n = 1; ankle oedema secondary to deep vein thrombosis, n = 1); and (iii) nonclassifiable.

SARS-CoV-2 or the S protein from vaccines may distract the cell-mediated control of another, latent virus.

New-onset or worsening of inflammatory conditions were also reported, including psoriasis, lichen planus and bullous pemphigoid. These conditions were previously described after SARS-CoV-2 and other vaccinations.^{20,28,39–43} As previously stated,⁴³ vaccines may exacerbate skin manifestations in patients with immune-mediated skin diseases, but further investigation is necessary.

The patterns found in this and previous studies are heterogeneous and similar to those described in association with SARS-CoV-2 infection.^{8,9,28} One case repeated the same papulovesicular rash after SARS-CoV-2 infection and vaccination. Therefore, the host immune response to the infection, and not direct viral damage, may cause these skin manifestations. However, a delayed hypersensitivity reaction against vaccine excipients cannot be ruled out.

Although most reactions were classified as mild/moderate, 21% were considered severe/very severe. This degree of severity was not reported in the study by McMahon *et al.*²⁸ This percentage is most likely over-represented (reporting bias) but should not be ignored, as some reactions may be life threatening.

The study has some limitations. Firstly, the design did not permit causal associations or the measurement of risks or incidence. We could not compare the incidence or severity of cutaneous reactions by vaccine type, as vaccine distribution depended on availability during the study period. Secondly, the data collection period was short, which might limit study of the comprehensive data and evolution, especially after the second doses and AZD1222 vaccination. Thirdly, only 12.3% of cases were biopsied and histopathology might have prevented misclassification. Fourthly, there was a possible reporting bias towards previously reported or more serious reactions. Fifthly, SARS-CoV-2 infection after vaccination cannot be excluded as a plausible cause of cutaneous reactions. Finally, the lack of ethnic diversity in our sample does not permit generalization of the results.

In conclusion, we have described and classified cutaneous reactions reported after SARS-CoV-2 vaccination in a large Spanish case series. Most reactions were mild/moderate and self-limiting, but some were severe/very severe and required treatment. Better knowledge of these reactions may aid physicians during mass vaccination and reassure patients seeking advice.

Acknowledgments

We thank the following Spanish dermatologists for their generous contributions: I. García-Doval, J. Sola-Ortigosa, S. Mateo Suárez, M. Elosua González, D. Ruiz Sanchez, B. Roque Quintana, M. Sidro Sarto, C.F. Vázquez Chinchay, J.F. Millán Calletano, A. Rodríguez-Villa Lario, E. Amores Martín, A. Suarez Valle, J. Fernández Vazquez, J. Riera Monroig, L. Armillas-Llitas, M. Corral Forteza, J. Arandes Marcocci, J. Jimenez Cauhe, G. Selda Enriquez, L. Haya Martinez, A. Frías Sanchez, A. Pérez Pérez, M. Salleras Redonnet, A. Tuneu Valls, I. Fuertes

De la Vega, M. Alegre Fernández, E. Baselga Torres, I. Escandel Gonzalez, A. Fernández Orland, A. Lopez Valle, V. García-Patos Briones, M.C. Juárez Dobjanschi, G. Aparicio Español, C. Ferrándiz Pulido, A. Castany Pich, V. Cabezas Calderón and C. Plà Ferrer. We also thank primary care physicians from the Granollers-Valles Oriental area, Spain (J. Alonso, M. Vilageliu, A. Estefanell, M. Manzano, M. Martín-Gil), Dr M. Ribell (Internal Medicine Department, Hospital General de Granollers), and the Pharmacovigilance and Occupational Health departments and technical committee of the Hospital Clinic of Barcelona, Maria Angeles Diaz Sotero (Hospital de Móstoles) and Joana Guerrero (Hospital General de Granollers), Spain. This study formed part of the PhD degree of Alba Català, Department of Medicine, Dermatology, Universidad Autónoma de Barcelona, Spain.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Appendix S1 Photographic atlas: Cutaneous reactions after severe acute respiratory syndrome coronavirus 2 vaccination.

Table S1 Cutaneous reactions and their severity after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines in people who had previous SARS-CoV-2 infection.

Powerpoint S1 Journal Club Slide Set.

Video S1 Author video.