communications medicine

Article

https://doi.org/10.1038/s43856-024-00656-y

Features of chronic urticaria after COVID-19 mRNA vaccine over time

Johan Schwab[1], Mathilde Foglierini[1,2], Eva Pescosolido[3], Ines Pacheco[1], Gustavo A. Ruiz Buendía[4,5,6], Natacha Madelon[4], Celine Pellaton[1], Véronique Banderet[1], Camillo Ribi[1], Marcel M. Bergmann[3,7,8], Arnaud M. Didierlaurent[4], Craig Fenwick[1], Olivier Duperrex[9] & Yannick D. Muller[1,10]

Abstract

Background New onsets of chronic urticaria (CU) have been reported after repeated immunizations, mainly with the Moderna mRNA-1273 vaccine (Spikevax). This study aims to evaluate patients with CU after COVID-19 mRNA vaccination. The contribution of SARS-Cov2 infection, atopy and IgE against the vaccine was analyzed.

Methods We monitored the features of patients who developed CU after vaccination through two surveys conducted in 2022 and 2023. Fifty individuals with CU underwent blood tests, and their results were compared with individuals without a history of urticaria ($N = 135$). The presence of anti-vaccine IgE was tested in 185 individuals with basophil activation tests (BAT). We assessed anti-SARS-Cov2 humoral response, and the presence of IgEs against common respiratory allergens (Phadiatop) as a surrogate for atopy.

Results Post-vaccination CU occurs after a median interval of 10 days and significantly more after the Spikevax booster, affecting middle-aged individuals (median 41, 66% females). In 2023, CU was still active in 53% of the cases. Inducible forms of CU, primarily dermographism, are reported in 54% (2022) and 61% (2023) of the cases. BAT positivity is not specific to CU, anti-nucleocapsid positivity, or atopy but is significantly associated with higher anti-spike neutralizing activities and younger age. Four CU patients tolerate an additional dose of mRNA vaccine with no disease exacerbation/recurrence.

Conclusions The spikevax booster induces anti-vaccine IgE independently of CU, the latter being not directly associated with COVID-19 infection nor atopy. The tolerance to a new booster in 4/4 patients suggests that the Spikevax vaccine indirectly triggers CU in predisposed individuals.

Plain language summary

Urticaria is an itchy transient skin rash which can become in some cases recurrent and chronic. Repeated immunizations with COVID-19 mRNA vaccines can rarely lead to the development of chronic urticaria (CU), on average 10 days after vaccination. Here, we monitored people who developed CU after vaccination. One year following vaccination 53% of people still had CU. CU after vaccination was not directly associated with COVID infection, allergic predisposition or other effects of vaccination. Re-exposure to the vaccine was safe and well tolerated in four patients with vaccine-related CU suggesting an absence of a direct causality between the vaccine and CU. Therefore, managing CU post-vaccination should follow previously established guidelines as for other forms of CU.

A major contribution to reducing the burden of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) pandemic was the rapid development of an efficient vaccination strategy[1]. The two mRNA vaccines, the mRNA-1273 (Spikevax®) from Moderna and BNT 162b2 (Comirnaty®) from Pfizer-BioNTech were authorized in January 2021[2] and December 2020[3] and were the most commonly given vaccines in Switzerland[4–6]. Yet, these COVID-19 vaccines were associated with several adverse effects with up to 17,000 reports of suspected adverse drug reactions collected in Switzerland by February 2023[7,8]. In particular, new onsets of chronic urticaria (CU) have been

[1]Division of Immunology and Allergy, Lausanne University Hospital (CHUV) and University of Lausanne, Lausanne, Switzerland. [2]Biomedical Data Science Centre (BDSC) Lausanne University Hospital (CHUV) and University of Lausanne, Lausanne, Switzerland. [3]Centro Pediatrico del Mendrisiotto, Mendrisio, Switzerland. [4]Centre of Vaccinology, University of Geneva, Geneva, Switzerland. [5]Translational Data Science Facility, AGORA Cancer Research Center, Lausanne, Switzerland. [6]Swiss Institute of Bioinformatics, Lausanne, Switzerland. [7]Faculty of Biomedical Science, Università della Svizzera Italiana (USI), Lugano, Switzerland. [8]Pediatric Allergy Unit, Department of Women, Children and Adolescents, University Hospitals of Geneva, Geneva, Switzerland. [9]Center for Primary Care and Public Health (Unisanté) and University of Lausanne, Lausanne, Switzerland. [10]Centre for Human Immunology Lausanne, Lausanne, Switzerland.
e-mail: Yannick.muller@chuv.ch

reported after repeated immunizations, mainly with the Spikevax vaccine[9–11].

CU is defined by the European Academy of Allergology and Clinical Immunology (EAACI) as the development of wheals (hives), angioedema, or both for more than six weeks[12]. It can be classified as spontaneous, inducible, or both. Chronic inducible urticaria is triggered by external factors such as pressure, contact, vibration, temperatures, sun, or cholinergic activity. In Switzerland, we observed an outbreak of CU starting in December 2021[9,11]. In the first analysis, we collected pharmacovigilance data from the Swiss Agency for Therapeutic Products (Swissmedic), and we estimated the overall crude incidence rate of CU after a COVID-19 booster at 19/100,000 from 2021-01-21 to 2022-08-31. The relative risk of new-onset CU after Spikevax compared to Comirnaty was 16.1 (95%CI, 10.8-24.0)[11]. Immunological data in seven patients revealed a systematic sensitization against the mRNA lipid nanoparticles but not against the linear polyethylene glycol-2000 nor the tromethamine[9]. The contribution of this IgE dependent sensitization to the pathogenesis and persistence of CU remains undetermined[13]. Notably, the contribution of infections with the omicron variant could also have been a confounding factor.

In the present study, our primary objectives were (1) to analyze patient's clinical features and evolution of patients who developed CU through two separate surveys sent in 2022 and 2023, (2) to better define the contribution of COVID-19 infection to the onset of CU, (3) to compare the high sensitization rate against the vaccine in CU patients with control populations without CU. In this perspective, we recruited 50 CU patients for blood tests. We compared the results to 135 individuals not suffering from CU but either infected with COVID-19 (cohort COSED) or vaccinated with the COVID-19 mRNA booster (cohort ImmunoVax). As our study was not designed to address the pathomechanistic pathways of CU, mainly subgrouped as auto-allergic (type I) and autoimmune (IIb)[14], we did not include a control population with CU unrelated to the vaccination status.

In this study, we show that post-vaccination CU most commonly occurs after the Spikevax booster, primarily affecting middle-aged women, with over half of the cases remaining active in 2023. We also observe that inducible CU forms, such as dermographism, are frequently present. Chronic urticaria after vaccination is not directly associated with COVID infection nor atopy and it initiates independently of vaccine sensitization. Re-exposure to the vaccine is safe in all four patients studied.

Methods

Ethical approval

This retrospective observational study was approved by the local ethical committee ("Commission cantonale d'éthique de la recherche sur l'être humain" CER-VD, BASEC 2021-00735 (COVURT), https://swissethics.ch/en/basec). All patients received a study information form. Written informed consent was not required for completing the two surveys, as local allergists were not allowed the enroll directly the patients. Written informed consent was obtained for all cases involving a blood test. This study followed the STROBE reporting guideline.

Study population

We assembled the COVURT cohort with the help of local allergists, contacted trough their association ("Groupement Vaudois des allergologues et immunologues"). Sixteen allergists contributed in identifying eligible patients with CU after receiving a dose of COVID-19 mRNA vaccine. The University Hospital of Lausanne (CHUV) contacted patients who gave their consent and sent them a link to an online questionnaire and included cases which were previously reported[11]. Study data of the first survey were collected by participants between April 14th and January 5th 2023 and managed using REDCap electronic data capture tools hosted at Unisanté (Lausanne, Switzerland). All patients received a link to a second online questionnaire in 2023. Study data of the second survey were collected by participants between June 12th and September 4th 2023. Blood tests were performed from May 16th until January 23rd 2023. We arbitrary chose to perform blood tests in 50 patients.

As controls for the blood testing, we included patients from two observational cohorts without CU. The first study cohort regrouped patients with a formal diagnosis of COVID infection and who developed persistent symptoms in 56% (59/105) of the cases. Median age was 45 (IQR 35.5-54). 78/105 (74%) were females. Blood testing was performed between May 20, 2022 and January 13, 2023. The second group consisted of healthy collaborators from our hospital who systematically received a primary vaccination and a booster. Median age was 41 (IQR 35-48). 21/30 (70%) were females. Blood testing was performed between August 30th and October 4th 2022.

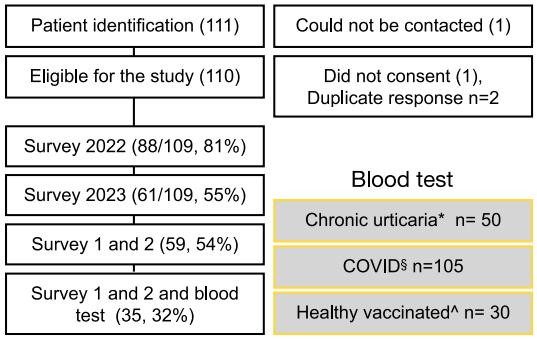
The third group consisted of heathy volunteers ($n = 17$) recruited at the Geneva University Hospitals between Dec 2021 and Feb 2022 willing to receive their dose of mRNA COVID-19 vaccine (Comirnaty or Spikevax). Blood samples were collected before the third vaccine dose. Nine out of 17 (53%) were females and median age was 44.

Whole blood RNA sequencing. Blood samples were collected in PAXgene Blood RNA Tube (BD Biosciences). RNA extraction was performed using the PAXgene Blood miRNA Kit (BD) on the QIAcube instrument (QIAGEN) following the manufacturer's instructions. RNA concentration and quality were assessed by using the Qubit instrument (Invitrogen) and the Agilent 2100 Bioanalyzer, respectively. The Stranded Total RNA Ribo-Zero Plus kit from Illumina was used for the library preparation with 100 ng of total RNA as input. Library molarity and quality were assessed with the Qubit and Tapestation using a DNA High sensitivity chip (Agilent Technologies). Libraries were pooled at 2 nM for clustering and sequenced on an Illumina HiSeq4000 sequencer for aminimum of 30 million single-end 100 reads per sample. The RNA-sequencing libraries were aligned to the human genome (GRCh38.96) using STAR ([15]. Only uniquely mapped reads were kept for downstream steps. Gene expression quantification was performed with featureCounts[16] for reads overlapping protein-coding genes. Low-count genes were filtered out with the filtered.data() function from the NOISeq R package [17]using the following parameters: method = 1, norm = FALSE, cv.cutoff = 100, cpm = 1.

Basophil activation test

As previously reported vaccine-sensitization could be assessed by means of CD63 upregulation with Spikevax or Comirnaty in an interchangeable way, as a surrogate of intra-dermal skin test[18]. Briefly, blood samples were collected in 3 ml EDTA tubes and were used up to 24 h of blood collection using the Flow CAST® from Bühlmann Labs (Basel, Switzerland) according to manufacturer's instructions (FK-CCR). Briefly, 50 µL whole blood from a 2.5ml K-EDTA venipuncture tube was added into a ready-to-use 1 ml vial pre-coated with an anti-CD63 FITC and anti-CCR3-PE antibodies (clones not disclosed by Bühlmann Labs). 50 µL of (a) stimulation buffer background, (b) 1-3 vaccine stimulations condition with Spikevax (1% 0.5% and/or 0.1%) and (c) a stimulation control (anti-FcεRI mAb and/or fMLP) was mixed with 100 µL of stimulation buffer containing calcium, heparin and IL-3 (concentration non disclosed by Bühlmann Labs) and mixed with 50 µL of whole blood (from a 2.5 ml K-EDTA venipuncture) in a ready-to-use 1 ml vial pre-coated with an anti-CD63 FITC and anti-CCR3-PE antibodies (clones/concentration not disclosed by Bühlmann Labs). After blood lysis, acquisition was performed by flow cytometry (BD LSRFortessa™ Cell Analyzer, BD Biosciences). A threshold of 10% in the αFcεRI-stimulated or FMLP condition was used to define non-responders (=areactivity). The same threshold was applied to the stimulated condition with mRNA vaccine to defined positivity (in any of the 3 different concentrations). For this study, 185 BAT were performed, 177 were interpretable, four subjects were classified as non-responder (all from the cohort CU), four subjects were excluded because of lack of basophils (two from the cohort CU). Results were analyzed using the FlowJo software (FLowJo LLC, Becton Dickinson, Ashland, OR).

a



b

	Chronic Urticaria	COVID	Healthy vaccinated
Gender			
F	37 (74%)	78 (74%)	21 (70%)
M	13 (26%)	27 (26%)	9 (30%)
Age, years (median)	42 (IQR 37-48)	45 (IQR 36-54)	41 (IQR 35-48)
Vaccine received			
Yes	50 (100%)	80 (76%)	30 (100%)
No	0	25 (24%)	0
Vaccine Type			
Spikevax	46 (92%)	34 (43%)	16 (53%)
Cominraty	4 (8%)	45 (56%)	14 /47%)
Janssen	0	1 (1%)	0
Number of Dose			
1	2	14 (13%)	0
2	3	35 (33%)	0
booster	45 (90%)	31 (39%)	30 (100%)

Fig. 1 | Flowchart of the study and patients' characteristics. a Flowchart of the patients included in the COVURT study. **b** Patients characteristics across the three groups. Foot note *cohort COVURT, §cohort COSED, ^cohort Immunovax.

Phadiatop assay

All analyses were performed retrospectively on frozen serum samples. ImmunoCAP Phadiatop (Réf. Article 14-4405-35, Thermo Fischer Scientific, Waltham, MA) is a ready to use qualitative and semi-quantitative in vitro test for the determination of aeroallergen-specific IgE antibodies in human plasma or serum. This test detected IgEs against a mixture of common respiratory allergens, including grass, birch, olive, mugwort, parietaria, dog, cat, horse, house dust mite, flour mite, and *Cladosporium*. The test was measured on a Phadia 250 instrument, Thermo Fischer Scientific). The lower detection limit was 0.35 kU/L for the Phadiatop assay. Patients with a positive Phadiatop (≥ 0.35 kU/L) were considered atopic as previously reported[19].

Neutralization assay

Serum IgG anti-S and anti-nucleocapsid antibody levels and neutralizing antibody levels were determined using two Luminex bead-based binding assays recently developed in our laboratory[20,21]. Briefly, Spike protein-coupled beads (50 µg of homemade proteins derived from SARS-Cov2, wild type or the BA.1, BA.2, BA4, BQ.1, BQ.1.1 and XBB variants coupled to 1 ml of activated MagPlex-C Microsphere beads) were diluted in 1:100 PBS with 50 µl added to each well of a Bio-Plex Pro 96-well flat-bottom plates (Biorad, CA). 80 µl of individual serum samples at different dilutions (1:10, 1:30, 1:90, 1:300, 1:2700, and 1:8100) in PBS was added to the plate wells and incubated for 60 min on a plate shaker at 500 RPM. An ACE2 mouse Fc fusion protein (Creative Biomart or produced by École polytechnique fédérale de Lausanne (EPFL) Protein Production and Structure Core Facility) was then added to each well at a final concentration of 1 µg/ml. Following a 60 min incubation on a plate shaker, beads were washed and an anti-mouse IgG-PE secondary antibody (PE labeled (F(ab')2-Goat anti-Human IgG (H + L) Antibody, Invitrogen) was added at a 1:100 dilution with 50 µl per well. Neutralizing activity was assessed by monitoring the ability of anti-S antibodies to prevent S-trimer protein binding to the angiotensin-converting enzyme 2 (ACE2) entry receptor, which is essential for the viral infection of a target cell. Half maximal inhibitory concentration (IC_{50}) dilution values in the Spike-ACE2 surrogate neutralization assay and binding IgG anti-S antibody ratios were $\log_{10}$ transformed for visualization and statistical modeling as previously described[22].

Statistics

The neutralization assay was analyzed with a two-way ANOVA test using the software package GraphPad PRISM v9. Two-tailed unpaired *T* tests were performed for comparing group with a positive versus negative BAT. Mean and standard deviation are shown. A value of $P < 0.05$ was considered statistically significant. Using a Fisher exact test, statistical analysis evaluated associations between vaccination parameters (type and doses), cohorts, gender, and BAT or PhadiatTop results. Unvaccinated donors served as the reference group for each specific vaccine dose. Analyses were conducted using R Statistical Software (v4.2.1). Patients with missing data were not excluded from the dataset.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Results

Initial survey

Among the 111 identified CU patients, we were able to contact 110, and 88 responded to our 2022 survey. One patient did not consent, one response was duplicated and excluded (Fig. 1a). Of these 88 patients, 66% were middle-aged female (median age 41, IQR 35-48, Fig. 1b). In 89% of cases, CU started after the booster shot and not after primary vaccination, predominantly with Spikevax (93%). The median interval time between vaccination and CU onset was 10 days. As of June 2022, CU remained active in 81% of these cases. Only 14% of the patients reported a previous history of urticaria, with the majority being cases of acute urticaria (92%). Inducible factors, mainly dermographism, were reported in 55% of the cases. The Urticaria Control Test (UCT) score, the number of lesions, and the severity of pruritus at disease onset indicated poor disease control. Although disease activity improved over time, control remained largely insufficient, possibly due to suboptimal antihistamine therapy (Table 1). Notably, only one-third of the patients reported pollinosis, and a mere 2% reported asthma, suggesting that the disease is unrelated to atopy.

Follow-up survey

A year later, we contacted the same patients for a follow-up survey, to which 61 patients responded (Table 2). Similar to the previous survey, 64% were middle-aged females (median age 41.5); 92% developed CU after the booster shot with Spikevax. CU was still active in 53% of these cases. In 41% (13/32) of cases (compared to 42% in 2022), patients reported inducible factors, primarily dermographism (68% compared to 77% in 2022). Of note, we could confirm the high prevalence of dermographism in patients who volunteered to come for a blood test. Of 40 patients analyzed, 19 had a negative FricTest, 12 had a strongly positive test (3 or 4), and in 10 patients, the test was only slightly positive (1/4, 2/4). When further analyzing the 2023 survey, the UCT score, number of lesions, and pruritus severity showed clear improvement compared to 2022. Yet the disease was still insufficiently controlled in 50% of the patients. Only four patients received omalizumab, which was discontinued in three cases. Worsening of CU by non-steroidal anti-inflammatory drugs was reported by 10% of cases (Tables 1 and 2). Importantly, mRNA vaccine was readministered in four CU patients—two in remission and two with persistent symptoms (Comirnaty in 3 and Spikevax in one) (Table 3). Subsequent immunization was not associated with CU re-occurrence or worsening.

Table 1 | 2022 survey of patients with chronic urticaria of the COVURT cohort

Survey 2022 (n = 88)			
Gender		**Pruritus severity (last week)**	
Female	58 (66%)	None	10 (11%)
Male	30 (34%)	mild (bearable)	34 (39%)
Age, (median IDR) * missing data (n = 4)	41 (35-47)	medium	29 (33%)
UC after booster		severe (interfere with sleep and/or daily activities)	15 (17%)
yes	78 (89%)	**Onging anti-histamine therapy**	
no	10 (11%)	yes	67 (75%)
Delays between last dose and CU (days)	10 (8,12)	no	16 (19%)
Vaccine received		missing	5 (6%)
Spikevax	82 (93%)	**Anti-histamine therapy (maximum)**	
Cominraty	6 (7%)	not taken	1 (1%)
CU active by June 2022		1 pill/day	22 (25%)
yes	71 (81%)	2 pills/day	23 (26%)
no	17 (19%)	3 pills/day	10 (11%)
Inducible urticaria		4 pills/day	27 (31%)
yes	48 (55%)	unknown	5 (6%)
no	40 (45%)	**Urticaria in the past**	
Inducible factors		yes	12 (14%)
dermographism	37 (77%)	no	76 (86%)
sun	12 (25%)	**Duration of previous urticaria**	
water	14 (29%)	<6 weeks	11 (92%)
cold	10 (20%)	> 6 weeks	1 (8%)
sport	7 (15%)	**NSAIDs exacerbating CU**	
UCT score (first month of activity)		yes	4 (5%)
<12	86 (98%)	no	84 (95%)
> 12	2 (2%)	**COVID infection**	
UCT score (last month of activity)		yes	30 (34%)
<12	83 (94%)	no	58 (66%)
> 12	4 (5%)	**Did CU get worse after COVID**	
Unknown	1 (1%)	yes	11 (12%)
Mean number of lesion (first week of activity)		no	20 (22%)
None	2 (2%)	**Asthma**	
<20	20 (24%)	yes	2 (2%)
20-50	38 (43%)	no	86 (98%)
> 50	28 (31%)	**Pollinosis**	
Mean number of lesion (last week of activity)		yes	25 (28%)
None	11 (13%)	no	63 (72%)
<20	61 (69%)	**Drug allergies**	
20–50	11 (13%)	yes	9 (10%)
>50	5 (6%)	no	79 (90%)
Pruritus severity (first week)			
None	1 (1%)		
Mild (bearable)	0		
Medium	11 (13%)		
Severe (interfere with sleep and/or daily activities)	76 (86%)		

Missing data for age n = 4
UCT urticaria control test, *NSAID* Nonsteroidal Anti-Inflammatory Drug-Induced

COVID-19 and chronic urticaria

We further explored the potential association between COVID infection and CU. Based on our surveys, only 34% and 44% of patients reported a formal SARS-CoV-2 infection in 2022 and 2023, respectively. When analyzing the time to CU comparing COVID infection and vaccination, we observed that COVID infection was rarely detected before CU onset (Fig. 2a). Interestingly, CU exacerbation after infection occurred in one-third of the cases in 2022 and 15% in 2023. We also compared the CU onset dates with official COVID infection reports and vaccination dates in the population of the canton of Vaud. Interestingly, the peak of booster vaccinations preceded the peak of CU cases, which in turn preceded the peak of COVID cases (Fig. 2b). Antibodies against the nucleocapsid were negative in 21/50 (42%) of subjects tested. Importantly, seropositivity to the nucleocapsid as a surrogate for past COVID infection did not influence the UCT in 2022 nor disease duration (Supplementary Fig. 1A, B). These findings suggest that, in contrast to the vaccine, there is not association between COVID infection and CU.

Vaccine sensitization and chronic urticaria

We then explored the potential link between vaccine sensitization and CU. To do this, we conducted basophil activation tests (BAT) using a cryopreserved batch of the Spikevax vaccine, which we previously validated[18]. Out of 50 blood samples tested, two patients had no basophils, and four were excluded due to basophil areactivity. BAT was positive in 64% of the cases. To further understand the relevance of this sensitization, we included patients without a history of CU from two separate cohorts monitored by our division. The first cohort (n = 105) consisted of 59 patients with long COVID and 46 patients with an acute COVID infection yet without persistent symptoms. The second cohort comprised 30 healthy vaccinated volunteers. We were able to subgroup these patients according to the type of vaccine received (Spikevax versus BNT 162b2) and the number of doses (0-1-2-booster) (Fig. 3a). Notably, sensitized patients were predominantly those vaccinated with the Spikevax booster, regardless of their CU status. Females were sensitized in 60% compared to 44% of males. Younger age was associated with a higher rate of sensitization (Fig. 3b). Sensitization didn't predict the duration of CU (Fig. 3c). No significant difference in CD63 levels on basophils, an activation marker, was observed in sensitized patients when comparing the two vaccines (Fig. 3d).

It was previously suggested that control patients who recovered from COVID infection are more likely sensitized against the vaccine[23]. Thus, we wanted to evaluate the frequency and level of anti-nucleocapsid antibodies in patients with positive and negative BAT against the vaccine. Anti-nucleocapsid antibodies did not correlate with higher CD63 expression. In fact, sensitized patients exhibited significantly lower level of nucleocapsid antibodies arguing against a direct link between COVID infection and vaccine sensitization (Fig. 3e, f). On the other hand, we found that sensitized patients had higher levels of anti-Spike antibodies, which correlated with a better neutralization against the wild-type but not the Omicron variant (Fig. 3h). Intriguingly, CU patients also had significantly higher anti-Spike neutralizing activity against the wild-type compared to patients from the two control cohorts (Immunovax, COSEDH) (Fig. 3i). Thus, our results suggest that younger females with good vaccine immuno-reactivity are at a higher risk of developing CU and getting sensitized against the vaccine. However, vaccine sensitization does not appear to be associated with the onset of CU.

Atopy and chronic urticaria

To understand whether new-onset CU following mRNA vaccination was associated with atopy, i.e., a genetic predisposition to produce IgE against common respiratory allergens, we performed a Phadiatop analysis. This test quantifies the presence of IgE against various allergens including grass, birch, olive, mugwort, parietaria, dog, cat, horse, house dust mite, flour mite, and Cladosporium. Patients with CU were not more frequently atopic compared to those in the two control cohorts (Fig. 3j). In addition, IgE sensitization to the vaccine was not associated with atopy, nor was it

Table 2 | 2023 survey of patients with chronic urticaria of the COVURT cohort

Survey 2023 (*n* = 61)			
Gender		**Antihistamine therapy**	
Female	39 (64%)	<3 times a week	13 (42%)
Male	22 (36%)	>3 times a week	6 (19%)
Age (median, IDR) (missing data *n* = 1)	41.5 (35-50)	1 pill/day	8 (26%)
Vaccine received		2 pills/day	1 (3%)
Spikevax	56 (92%)	3 pills/day	0
Cominraty	3 (5%)	4 pills/day	2 (6%)
missing data	2 (3%)	missing data	1 (3%)
CU after booster		**Omalizumab**	
yes	56 (92%)	yes ongoing	1 (2%)
no	4 (7%)	yes stopped	3 (5%)
unknown	1 (2%)	no	54 (89%)
CU active by June 2023		missing data	3 (5%)
yes	32 (52.5%)	**Corticosteroids (anytime)**	
no	29 (47.5%)	yes	14 (23%)
Active CU is		no	47 (77%)
inductible	7 (22%)	**NSAIDs exacerbating CU**	
spontaneous	13 (42%)	yes	6 (10%)
both	12 (39%)	no	53 (87%)
If inducible, triggered by		missing data	2 (3%)
dermographism	13 (68%)	**New booster after CU onset**	
sun	7 (37%)	yes	3 (5%)
water	2 (11%)	no	58 (95%)
cold	5 (26%)	**Did CU get worse after the booster**	
sport	8 (42%)	yes	0
vibration	2 (11%)	no	3/ 3 (100%)
UCT score		**Which vaccine was recevied?**	
<12	16 (50%)	Cominraty	3/ 3 (100%)
> 12	16 (50%)	**COVID infection after CU onset**	
Unknown	0	yes	27 (44%)
Mean number of lesion during the past week		no	31 (56%)
None	6 (19%)	**Did CU get worse after COVID**	
<20	22 (69%)	yes	4/ 27 (15%)
20-50	4 (13%)	no	23/ 27 (85%)
> 50	0		
Prurit severity			
None	1 (3%)		
Mild (bearable)	15 (47%)		
Medium	10 (31%)		
Severe (interfere with sleep and/or daily activities)	6 (19%)		

NSAID Nonsteroidal Anti-Inflammatory Drug-Induced

Table 3 | Characteristics of patients with chronic urticaria who tolerate a new dose of mRNA vaccines after chronic urticaria onset

	patient 1	patient 2	patient 3	patient 4
Cohort	VD	VD	VD	TI
gender	female	male	male	female
age	80-84	40-44	50-54	50-54
CU still active	no	yes	yes	no
CU after	dose 1	booster	booster	booster
Vaccine received	Cominraty	Spikevax	Spikevax	Spikevax
Timing between vaccine and CU	8 days	7 days	12 days	10 days
BAT against mRNA (>10%)	neg	pos	neg	pos
Inducible?	no	no	yes (sun)	yes (dermog)
NSAID and CU	no	no	no	no
History of urticaria	yes	no	no	no
COVID infection	no	no	yes (no impact on CU)	no
Asthma	no	no	no	no
Hay fever	no	no	yes	no
Drug allergy	no	no	no	no
Vaccine received after CU onset	Comirnaty	Comirnaty	Comirnaty	Spikevax
Did the vaccine worsened CU?	no	no	no	no
Antihistamine	no	3x/week	1 anti histamine/ days	on demand
Treated with omalizumab	no	no	no	no

NSAID Nonsteroidal Anti-Inflammatory Drug, *CU* chronic urticaria

correlated with the level of IgE against common respiratory allergens (Fig. 3k, l). Finally, we did not find any specific signature for CU based on a pilot bulk RNA study comparing the transcriptional profile of 15 patients with CU and 17 vaccinated heathy volunteers recruited at the university hospital of Geneva (Supplemental Fig. 2).

Discussion

This study represents the first comprehensive analysis of a large cohort of patients who developed CU following mRNA vaccination, mostly the Moderna vaccines, an observation also made by others[24]. The majority of patients were middle-aged individuals with in overall 54-61% suffering from an inducible form of CU. We demonstrated that CU was unrelated to the Omicron Wave, atopic predisposition, and vaccine sensitization. Importantly, 4/4 CU patients re-exposed to the mRNA vaccine did not exacerbate CU and tolerated the vaccine well. These results expand a series cases of another four patients with CU who received a subsequent COVID-19 booster vaccine without disease exacerbation at a military academy[25]. They also corroborate the low frequency (9%) of vaccine-induced exacerbation of CU as recently reported by the UCARE COVAC-CU study[26]. Altogether, these results may help reinsuring patients and possible reduce vaccine hesitancy, a feeling highly prevalent in patients who develop acute urticaria after COVID-19 vaccine[27]. In all cases, it is recommended to have CU under control before considering a re-vaccination[28,29].

The primary objective of this study was to understand the contribution of COVID-19 infection in the onset of CU after vaccination. Thus, in acute urticaria, there is undoubtedly a causal relationship with infection, notably viral upper airway infection (mainly in children)[30]. In chronic urticaria, viral

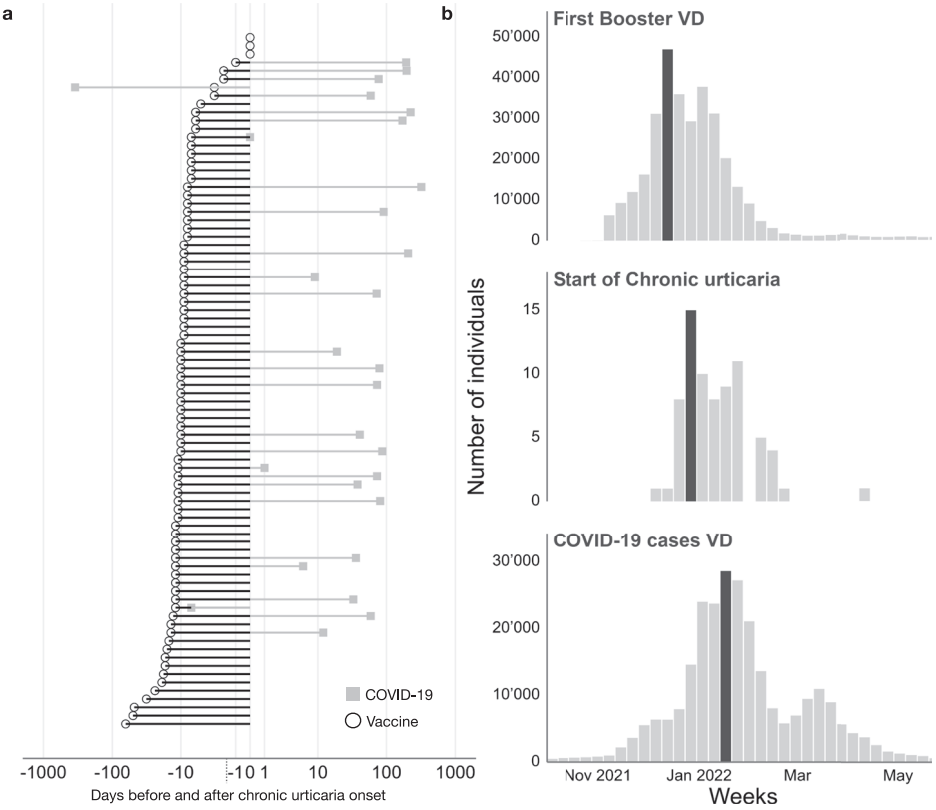


Fig. 2 | Timing between the vaccine, COVID-19 and chronic urticaria onset. a Distribution per participant of the days before (negative values) and after (positive values) the onset of chronic urticaria for the latest SARS-Cov-2 vaccination (black circles) and COVID-19 infection (gray squares) ($n = 84$, 4 missing values for onset date). **b** Peak incidence of the first booster ($n = 312{,}723$), new-onset chronic urticaria after booster ($n = 74$), and COVID-19 cases over time ($n = 260{,}802$). Only patients who developed CU after November 1st, 2021 without missing values were included in the analysis. VD, canton of Vaud.

hepatitis, HIV, and herpes viruses are also discussed as possible triggers of CU[30]. For COVID-19, the relationship to CU remains scarce in the literature. A case series from five Urticaria Centers of Reference and Excellence (UCARE) reported only 14 cases with a mean of 18 days after infection[31]. While, we cannot exclude a contribution of the Omicron wave in the onset and/or exacerbation of CU after vaccination, our survey revealed only rare cases of COVID-19 infection prior to CU and was reported by only 34% of the patients. Importantly, a positive titer against the nucleocapsid did not correlated with disease duration nor with disease severity. Finally, even if caution should be made when comparing the results of a case series cohort to the general statics of the Canton, we did not find a temporal relationship with peak of COVID cases.

Interestingly too, the incidence of CU reported to the Swiss national pharmacovigilance database was significantly higher than in other countries. This could be related to the notably higher proportion of Spikevax administered in Switzerland as compared to other European countries (Fig. 4). Whether this explains the higher number of CU cases remains still speculative. Finally, reinfection with SARS-CoV-2 only led to CU exacerbation in a minority of cases (15%). This is less than initially reported by a cross-sectional, international study that found that one third of the patients had CU exacerbation upon SARS-CoV2 infection[32]. Since this study was performed before the Omicron wave, it is tempting to speculate that the variants and disease severity may influence the mast-cell degranulation sensitivity in CU patients.

In our study, we observed a substantial number of patients who were sensitized to mRNA vaccines independently of known allergies nor active CU. These findings are consistent with the higher prevalence of positive skin tests in patients vaccinated with Spikevax[13]. This sensitization is mediated through specific IgE against the spherical polyethylene glycol (PEG) conformation of the lipid nanoparticle[33]. The clinical relevance of those IgE remains undefined. On the one hand, they could contribute to protective immunity as previously suggested in the context of flu vaccines[34] corroborating the positive association we observed between the anti-spike titer and anti-vaccine IgE. On the other hand, they could predispose individuals to developing allergic reactions[35]. At this stage, this remains speculative as it has been repeatedly shown that the majority of sensitized patients can tolerate the vaccine[33]. Thus, there is growing evidence showing that immediate reactions are primarily non-IgE dependent, due to complement activation[36], and that C5a could be a relevant biomarker of anaphylaxis[37]. In conclusion, IgE against PEG molecules on lipid nanoparticles (LNP) are frequently produced after multiple exposures to mRNA-based vaccines independently of CU. Their clinical relevance requires further investigation and careful monitoring.

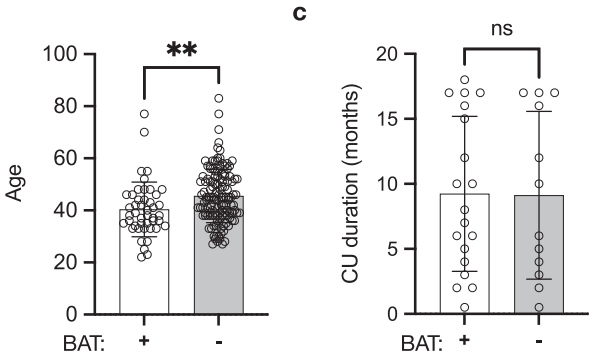
We did not observe a direct link between CU and atopy. This is corroborated by the rate of allergic rhinitis (28%) in CU patients which is comparable to the general population and confirmed by the Phadiatop analysis, which was positive in one-third of CU patients, a rate not higher than that observed in controls. Thus, the relationship between atopy and CU, while frequently discussed, is currently recognized as a co-occurring condition without a clear pathogenetic link[12,38]. Even in cases of autoallergic or type 1 CU, conditions associated with self-antigen IgEs like anti-TPO or anti-IL24[39,40], atopic disease affects less than half of the patients[39].

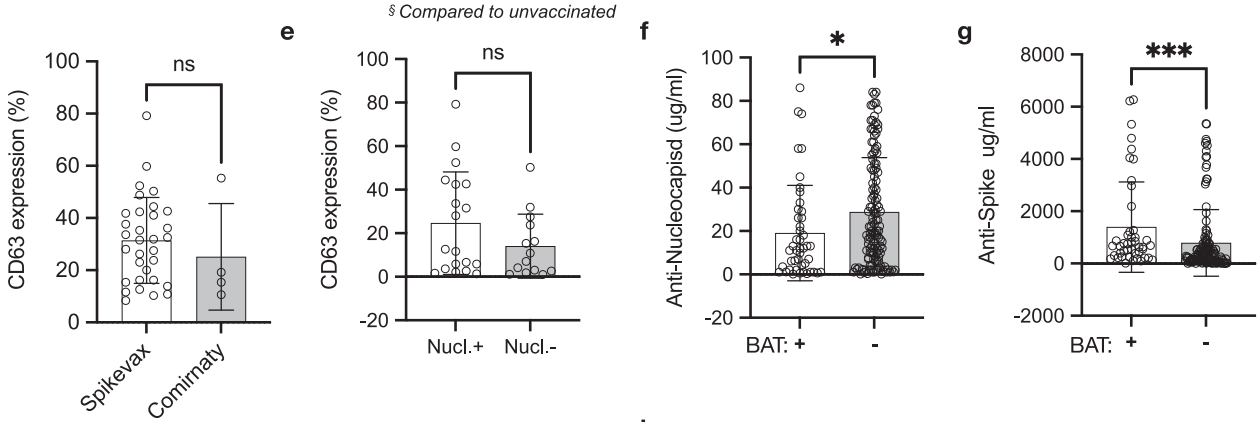
As of June 1st 2022, in Switzerland, 44% and 26 % of the population were fully vaccinated with Spikevax and Comirnaty, respectively[41]. Yet, over 90% of CU occurred after the Spikevax booster. Several hypotheses might explain this observation. Firstly, the mRNA content in the Spikevax vaccine is higher (100 µg) compared to Comirnaty (30 µg). Secondly, the Spikevax vaccine seems more stable in solution than Comirnaty after reconstitution[18]. Thus, we recently demonstrated that cell lines become spike protein positive in culture when exposed to Spikevax but not to Comirnaty[18]. Apart from the dosage differences, the Pfizer and Moderna platforms have few distinctions, with some variations in the structures of LNP carriers. Both contain PEG-2000, albeit in different forms and quantities (ALC-0519 and ALC-0315 in Comirnaty, PEG2006-DMG in Spikevax (8,20,52,53)) potentially also contributing to the immunogenicity of the vaccine. Thus, it has been repeatedly shown that the mRNA-1273 vaccine elicits higher and more persistent antibody production[22,42,43]. Future research should explore the

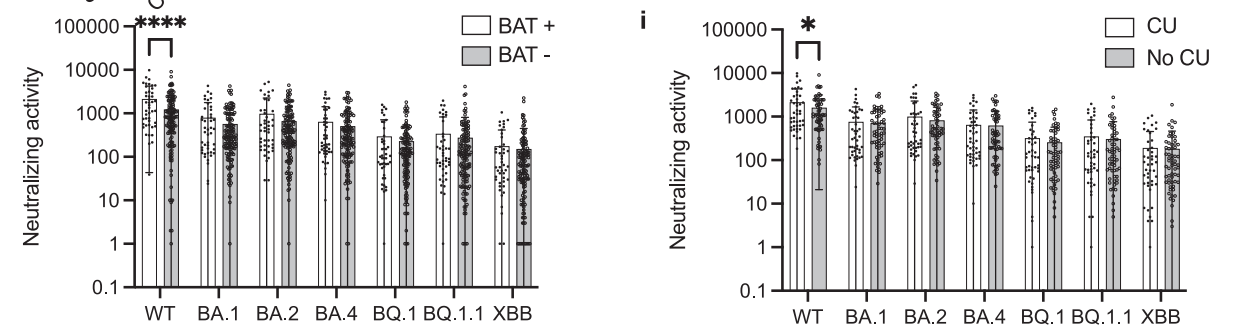
a

	BAT **Neg**	BAT **Pos**	P value
Unvaccinated	24 (96%)	1 (4%)	-
Comirnaty			
1 dose	7 (100%)	0	1§
2 dose	17 (94%)	1 (6%)	1§
3 dose	31 (91%)	3 (9%)	0.6§
Spikevax			
1 dose	7 (87.5%)	1 (12,5%)	0.4§
2 dose	16 (84%)	3 (16%)	0.3§
3 dose	29 (45%)	36 (55%)	<0.001§
Spikevax booster			
Cohort			0.3
Chronic urticaria	14 (37%)	24 (63%)	
COVID	6 (55%)	5 (45%)	
Healthy Vaccinated	9 (56%)	7 (44%)	
Gender			0.4
Female	19 (40%)	28 (60%)	
Male	10 (56%)	8 (44%)	

§ Compared to unvaccinated

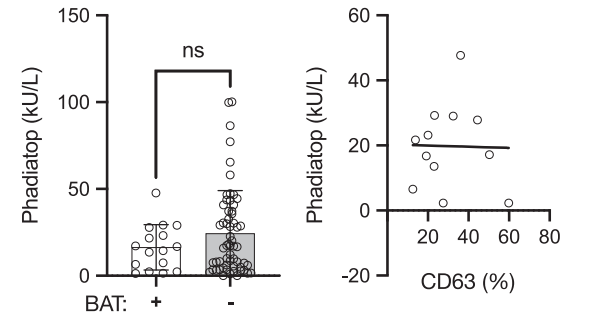






j

	Phadiatop **Neg**	Phadiatop **Pos**	P value
Cohort			
Chronic urticaria	27 (64%)	15 (36%)	0.3
COVID	56 (54%)	48 (46%)	0.3
Healthy Vaccinated	11 (58%)	8 (42%)	1
Unvaccinated	12 (48%)	13 (52%)	0.4
Vaccination type			0.7
Spikevax	50 (59%)	35 (41%)	
Comirnaty	32 (59%)	22 (41%)	
Janssen	0	1 (100%)	
Vaccination			0.6
1 dose	11 (69%)	5 (31%)	
2 dose	21 (55%)	17 (45%)	
3 dose	51 (59%)	36 (41%)	
BAT			1
Positive	22 (58%)	16 (42%)	
Negative	72 (57%)	55 (43%)	



contribution of vaccine intervals and prior COVID-19 infection as risk factors for the development of new-onset CU.

This study has several limitations. First, this study only recruited patients who developed CU with a temporal relationship to the vaccination. Thus, we did not include CU patients unrelated to the vaccine as a control group. As the study started after the booster doses, there could also be a selection bias towards patients who received multiple doses. Yet, the data from the Swissmedic showed that CU occurred in 81% of the cases after the booster[11]. Secondly, we did not investigate the presence of type IIb autoimmune mechanisms by performing autologous serum skin tests, immunoassays for IgG autoantibodies, or indirect basophil activation tests[14]. Thirdly, several measures, such as total IgE, IgG anti-thyroid peroxidase, and complete blood count, were not available for all patients in this study. Indeed, CU is associated with an increased odds ratio for antithyroid antibodies and a higher incidence of autoimmune diseases including rheumatoid arthritis, Sjögren's syndrome, celiac disease, type I diabetes mellitus, and systemic lupus erythematosus[44]. Given that only 4 out of 58 required omalizumab, of which 75% were able to discontinue the treatment, one

Fig. 3 | Contribution of vaccine sensitization and atopy to chronic urticaria. **a** Table summarizing the percentage of patients across the different cohort studies with positive versus negative basophil activation tests (BAT). Associations between the different variables were assessed using a Fisher exact test. **b** Age (mean and SD) of patients with a positive (+) ($n = 45$) or negative (−) BAT ($n = 132$). **c** CU duration in patients with a positive (+) ($n = 19$) or negative (−) BAT ($n = 12$). **d** CD63 expression (BAT condition shown 0.1%, missing data $n = 8$) in patients with a positive BAT who received the Spikevax ($n = 32$) and the BNT 16b2 ($n = 4$). **e** CD63 expression in CU patients with a positive (≥10 µg/ml) ($n = 19$) versus negative ($n = 14$) serology for the nucleocapsid (BAT condition shown 0.1%, missing data $n = 11$). Anti-nucleocapsid (**f**) and anti-spike (**g**) titers in patients with positive (+) ($n = 45$) or negative (−) BAT ($n = 132$). **h** Neutralizing activities against the different SARS-COV2 variants in patients with a positive (+) ($n = 45$) or negative (−) BAT ($n = 132$), or (**i**) with ($n = 45$) /without CU ($n = 61$) among patients who received the booster. **j** Table summarizing the percentages of patients across the different cohort studies with positive or negative Phadiatop results. For 13 patients, not sufficient material to perform the analysis. **k** Phadiatop titer in patients with a negative (−) ($n = 55$) or positive (+) ($n = 16$) BAT. **l** Phadiatop titer correlated to CD63 expression in patients with a positive BAT and phadiatop result ($n = 12$, BAT condition shown 0.1%, missing data $n = 4$). BAT, basophil activation tests; Nucl, nucleocapsid, CU chronic urticaria; ns non-significant. *Statistics*. Mean and SD are shown. Unpaired two-sided *T* tests or two-way ANOVAs were used for statistical analysis. For the tables, Fisher's exact test was performed for each vaccine on a contingency table comparing the number of donors who received one, two, or three doses with the number of unvaccinated donors in the BAT-negative and BAT-positive groups (as a reference). In (**a**), Fisher's exact test was performed on a contingency table comparing the number of donors who received the mRNA-1273 booster in the BAT-negative and BAT-positive groups, along with their cohort or gender.

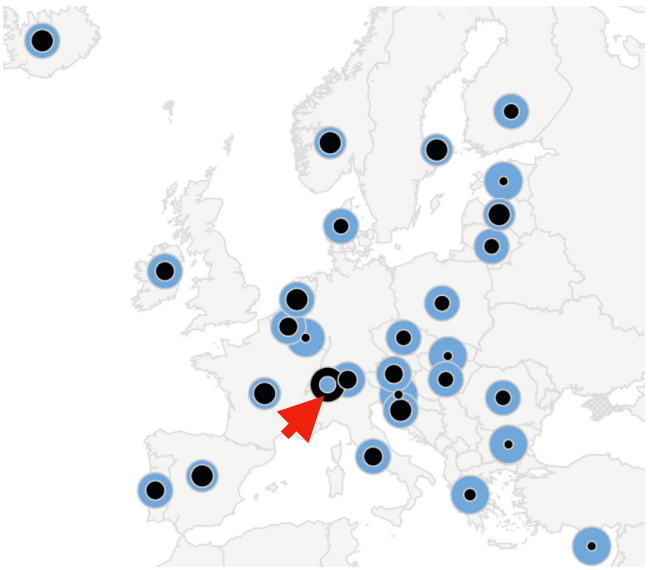


Fig. 4 | Spikevax to Comirnaty administration ratios across Europe compared to Switzerland. The map of Europe shows the proportion of individuals who received Spikevax (black) and the Comirnaty (blue circles) vaccines for each country. The larger the circle is, the larger the frequency is. The red arrow indicates Switzerland. Data were downloaded from the European Centre for Disease Prevention and Control (ECDC) and Federal Office of Public health (FOPH) of Switzerland on November 27th. Bivalent vaccines were not included in the analysis.

might speculate that type IIb autoimmune CU, which is typically more refractory to anti-IgE therapies[14], is less frequently present in our CU population. Thus, future metanalysis should compare the phenotype of our population to other CU cases which are unrelated to vaccination.

In conclusion, our one-year survey revealed that CU remained active in about 50% of the cases, with the inducible form of CU being quite common. There was no direct correlation between the onset of CU, PEG sensitization, atopy, and the concurrent Omicron virus infection. The fact that several individuals were able to tolerate an additional dose of the COVID mRNA vaccine without disease exacerbation, and considering that new onset CU remains a relatively rare event following vaccination, strongly suggests that the mRNA vaccine is not an inducer for CU but rather a facilitator in predisposed individuals. Yet, repeated exposure to the vaccine appears to be necessary in most cases to reveal this predisposition, indicating that a vaccine-specific pre-existing immunity may provide a favorable condition and environment for recruitment of a CU-specific B cell repertoire. Therefore, future research should focus on characterizing the nature of the auto-antibody response and comparing it to CU cases that are temporally unrelated to mRNA vaccines. Finally, the results of this study should not prevent nor restrain any vulnerable patients from getting vaccinated or boosted for COVID-19.

Data availability

The clinical data are not publicly available due to ethical restrictions. The raw sequencing data files for RNA sequencing generated in this study have been deposited in the GEO database: GSE272645. The source data for Figs. 2a-b, 3b-l and 4 are provided in Supplementary Data 1. All other data supporting the findings of this study are available from the corresponding author on reasonable request.

Code availability

The associated R scripts are available on https://github.com/MathildeFogPerez/manuscript-CU-schwab/ Foglierini Perez, M.[45]. R script used in the manuscript 'Features of chronic urticaria after COVID-19 mRNA vaccine'. Zenodo. https://doi.org/10.5281/zenodo.13939668[45], and on Duperrex, O.[46]. R script for Fig. 2A and B of manuscript 'Features of chronic urticaria after COVID-19 mRNA vaccine' by Schwab et al. Zenodo. https://doi.org/10.5281/zenodo.13970955[46].

Abbreviations

BAT	basophil activation test
CIU	chronic inducible urticaria
COVID-19	coronavirus disease
CSU	chronic spontaneous urticaria
CU	chronic urticaria
EAACI	European Academy of Allergology and Clinical Immunology
FcεRI	high-affinity IgE receptor
Spikevax	The mRNA-1273 Moderna vaccine
NSAID	non-steroidal anti-inflammatory drugs
PEG	polyethylene glycol
Comirnaty	BNT 162b2 vaccine from BioNtech/Pfizer
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
UCT	urticaria control test

Received: 16 March 2024; Accepted: 24 October 2024;
Published online: 30 November 2024

References

1. Zhang, Z., Shen, Q. & Chang, H. Vaccines for COVID-19: a systematic review of immunogenicity, current development, and future prospects. *Front. Immunol* **13**, 843928 (2022).
2. Public Summary SwissPAR—Spikevax® [Internet]. Available from https://www.swissmedic.ch/swissmedic/fr/home/ueber (2023).
3. Comirnaty®, Concentré pour reconstitution d'une dispersion injectable (Tozinameranum) [Internet]. Available from https://www.

swissmedic.ch/swissmedic/fr/home/humanarzneimittel/authorisations/new-medicines/comiraty-tozinameranum.html (2023).
4. Swissmedic octroie une autorisation de durée limitée au vaccin Nuvaxovid de Novavax contre le Covid-19 [Internet]. [cited 2023 Aug 10]. Available from https://www.swissmedic.ch/swissmedic/fr/home/news/coronavirus-covid-19/zl-nuvaxovid-novovax.html.
5. Contrats d'acquisition des vaccins COVID-19 [Internet]. Available from https://www.bag.admin.ch/bag/fr/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov/impfen/beschaffungsvertraege-covid-19-impfstoffe.html (2023).
6. OFSP Office fédéral de la santé publique. Coronavirus: Vaccination contre le COVID-19 [Internet]. Available from https://www.bag.admin.ch/bag/fr/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov/information-fuer-die-aerzteschaft/covid-19-impfung.html (2023).
7. Reports of suspected adverse reactions to COVID-19 vaccines in Switzerland—update 29 [Internet]. Available from https://www.swissmedic.ch/swissmedic/en/home/news/coronavirus-covid-19/covid-19-vaccines-safety-update-19.html (2023).
8. Klein, N. P. et al. Surveillance for adverse events after COVID-19 mRNA vaccination. *JAMA* **326**, 1390–1399 (2021).
9. Pescosolido, E. et al. Clinical and immunological data from chronic urticaria onset after mRNA SARS-CoV-2 vaccines. *Clin. Exp. Allergy* **52**, 1343–1346 (2022).
10. Wolfson, A. R., Freeman, E. E. & Blumenthal, K. G. Urticaria 12 days after COVID-19 mRNA booster vaccination. *JAMA* **327**, 1702–1703 (2022).
11. Duperrex, O., Tommasini, F. & Muller, Y. D. Incidence of chronic spontaneous urticaria following receipt of the COVID-19 vaccine booster in Switzerland. *JAMA Netw Open* **6**, e2254298 (2023).
12. Zuberbier, T. et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy* **77**, 734–766 (2022).
13. Stehlin, F. et al. Intradermal testing with COVID-19 mRNA vaccines predicts tolerance. *Front. Allergy* **3**, 818049 (2022).
14. Kolkhir, P. et al. Autoimmune chronic spontaneous urticaria. *J. Allergy Clin. Immunol.* **149**, 1819–1831 (2022).
15. Dobin, A. et al. STAR: ultrafast universal RNA-seq aligner. *Bioinformatics* **29**, 15–21 (2013).
16. Liao, Y., Smyth, G. K. & Shi, W. featureCounts: an efficient general purpose program for assigning sequence reads to genomic features. *Bioinformatics* **30**, 923–930 (2014).
17. Tarazona, S. et al. Data quality aware analysis of differential expression in RNA-seq with NOISeq R/Bioc package. *Nucleic Acids Res.* **43**, e140 (2015).
18. Alcaraz-Serna, A. et al. Basophil activation tests with cryopreserved mRNA-based COVID-19 vaccines. *Allergol. Int.* **72**, 600–603 (2023).
19. Porret, R. et al. Atopy as an independent predictor for long-term patient and graft survival after kidney transplantation. *Front. Immunol* **13**, 997364 (2022).
20. Fenwick, C. et al. Changes in SARS-CoV-2 spike versus nucleoprotein antibody responses impact the estimates of infections in population-based seroprevalence studies. *J Virol* **95**, e01828–20 (2021).
21. Fenwick, C. et al. A high-throughput cell- and virus-free assay shows reduced neutralization of SARS-CoV-2 variants by COVID-19 convalescent plasma. *Sci. Transl. Med.* **13**, eabi8452 (2021).
22. Obeid, M. et al. Humoral responses against variants of concern by COVID-19 mRNA vaccines in immunocompromised patients. *JAMA Oncol* **8**, e220446 (2022).
23. Labella, M. et al. The value of the basophil activation test in the evaluation of patients reporting allergic reactions to the BNT162b2 mRNA COVID-19 vaccine. *Allergy* **77**, 2067–2079 (2022).
24. Nickels, A. et al. Case series of patients with acute and chronic urticaria after COVID-19 vaccination. *Ann Allergy Asthma Immunol.* **132**, 395–397 (2024).
25. Miller, M. A., Raffetto, E. R. & Lee, R. U. Chronic spontaneous urticaria following mRNA COVID-19 booster vaccination at a military academy. *Mil Med.* **189**, e911–e914 (2024).
26. Kocatürk, E. et al. Urticaria exacerbations and adverse reactions in patients with chronic urticaria receiving COVID-19 vaccination: Results of the UCARE COVAC-CU study. *J Allergy Clin Immunol* **152**, 1095–1106 (2023).
27. Judd, A. et al. Urticaria after COVID-19 vaccination and vaccine hesitancy. *J. Allergy Clin. Immunol. Pract.* **11**, 958–960 (2023).
28. Picard, M., Stone, C. A. & Greenhawt, M. Management of patients with immediate reactions to COVID-19 vaccines. *J. Allergy Clin. Immunol.* **151**, 413–415 (2023).
29. Banerji, A., Norton, A. E., Blumenthal, K. G., Stone, C. A. & Phillips, E. Rapid progress in our understanding of COVID-19 vaccine allergy: a cause for optimism, not hesitancy. *J. Allergy Clin. Immunol.* **150**, 12–16 (2022).
30. Kocatürk, E. et al. How infection and vaccination are linked to acute and chronic urticaria: a special focus on COVID-19. *Viruses* **15**, 1585 (2023).
31. Öztaş Kara, R. et al. Features of chronic spontaneous urticaria induced by COVID-19. *Int. Arch. Allergy Immunol.* **184**, 792–796 (2023).
32. Kocatürk, E. et al. The global impact of the COVID-19 pandemic on the management and course of chronic urticaria. *Allergy* **76**, 816–830 (2021).
33. Ieven, T. et al. Endotyping of IgE-mediated polyethylene glycol and/or polysorbate 80 allergy. *J. Allergy Clin. Immunol. Pract.* **11**, 3146–3160 (2023).
34. Smith-Norowitz, T. A. et al. Long term persistence of IgE anti-influenza virus antibodies in pediatric and adult serum post vaccination with influenza virus vaccine. *Int. J. Med. Sci.* **8**, 239–244 (2011).
35. Nagao, M., Fujisawa, T., Ihara, T. & Kino, Y. Highly increased levels of IgE antibodies to vaccine components in children with influenza vaccine-associated anaphylaxis. *J. Allergy Clin. Immunol.* **137**, 861–867 (2016).
36. Stehlin, F. et al. Graded-dosing immunization in adults at risk for immediate-type reactions to mRNA SARS-CoV-2 vaccines. *Allergol. Int.* **72**, 332–334 (2023).
37. Lim, X. R. et al. Anaphylatoxin complement 5a in Pfizer BNT162b2-induced immediate-type vaccine hypersensitivity reactions. *Vaccines (Basel)* **11**, 1020 (2023).
38. Chen Q., Y. X., Ni B., Song Z. Atopy in chronic urticaria: an important yet overlooked issue. *Authorea* **15** (2023).
39. Sánchez, J., Sánchez, A. & Cardona, R. Causal relationship between anti-TPO IgE and chronic urticaria by in vitro and in vivo tests. *Allergy Asthma Immunol. Res.* **11**, 29–42 (2019).
40. Schmetzer, O. et al. IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria. *J. Allergy Clin. Immunol.* **142**, 876–882 (2018).
41. FOPH, F. O. O. P. H. https://www.covid19.admin.ch/en/vaccination/status?vaccZoomVaccine=2021-01-27_2022-08-26&vaccZoomDev=2021-04-19_2022-09-04.
42. Steensels, D., Pierlet, N., Penders, J., Mesotten, D. & Heylen, L. Comparison of SARS-CoV-2 antibody response following vaccination with BNT162b2 and mRNA-1273. *JAMA* **326**, 1533–1535 (2021).
43. Collier, A. Y. et al. Differential kinetics of immune responses elicited by Covid-19 vaccines. *N. Engl. J. Med.* **385**, 2010–2012 (2021).
44. Confino-Cohen, R. et al. Chronic urticaria and autoimmunity: associations found in a large population study. *J. Allergy Clin. Immunol.* **129**, 1307–1313 (2012).
45. Foglierini Perez, M. R script used in the manuscript 'Features of chronic urticaria after COVID-19 mRNA vaccine'. *Zenodo* https://doi.org/10.5281/zenodo.13939668 (2024).

46. Duperrex, O. R script for Figs. 2A and 2B of manuscript 'Features of chronic urticaria after COVID-19 mRNA vaccine' by Schwab et al. *Zenodo* https://doi.org/10.5281/zenodo.13970955 (2024).

Acknowledgements

This work was supported by the Giorgi-Cavaglieri Foundation (to Y.D.M.). The authors are indebted to the patients who participated in the study, to Silvia Sabatino and Claudia Lima de Paiva Campos from the Vaccine and Immunology Center as well as to the Immunology and Allergy Department staff the for their most valuable efforts. The authors thank all the local allergists from the GVAIC who contributed to identifying patients and Giuseppe Pantaleo (Lausanne University Hospital and University of Lausanne) for critical reading and helpful comments.

AI-assisted technologies were used only to improve the grammar and readability of the text. YDM reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Author contributions

Conceptualization: Y.D.M. Supervision: Y.D.M. Designed experiments: A.D, C.F, O.D, Y.D.M. Contributed in data collection/analysis: J.S., M.F., E.V., I.P., G.A.R.B., N.M., C.P., V.M., Y.D.M. Provided reagents and advice: C.F., C.R., M.B., A.D., O.D. Wrote the original draft: J.S. Y.D.M. Reviewed and edited the manuscript: all. All authors approved the manuscript.

Competing interests

The authors declare the following competing interests: Dr Fenwick report having a patent pending (application No. EP20205298.1) for a SARS-Cov2 neutralization assay. Prof. Muller has received grant support/consulting income from AstraZeneca, Viatris, Blueprint Medicine, Sanofi and GSK. Prof. Didierlaurent received research grants from Moderna, GSK and Sanofi outside the scope of this study. The research was conducted without any other commercial or financial relationships that could be construed as a potential conflict of interest to this study. Authors J. Schwab, M. Foglierini, E. Pescosolido, I. Pacheco, G. A. Ruiz Buendía, N. Madelon, C. Pellaton, V. Banderet, C. Ribi, M. M. Bergmann, and O. Duperrex declare no competing interests relevant to this study.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s43856-024-00656-y.

Correspondence and requests for materials should be addressed to Yannick D. Muller.

Peer review information *Communications Medicine* thanks Emek Kocatürk Göncü and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available.