Freeman Esther (Orcid ID: 0000-0001-7751-9466)
Falchi Mario (Orcid ID: 0000-0002-5646-1004)
Visconti Alessia (Orcid ID: 0000-0003-4144-2019)
Bataille V (Orcid ID: 0000-0002-8750-4150)



# Cutaneous Manifestations of SARS-CoV-2 infection during the Delta and Omicron waves in 348,691 UK users of the UK ZOE COVID Study App

Alessia Visconti,[1] Benjamin Murray,[2] Niccolò Rossi,[1] Jonathan Wolf,[3] Sebastien Ourselin,[2] Tim D. Spector,[1] Esther E. Freeman,[4] Veronique Bataille[1,5] and Mario Falchi[1]

[1] Department of Twin Research & Genetic Epidemiology, King's College London, London, UK
[2] School of Biomedical Engineering & Imaging Sciences, King's College London, London, UK
[3] Zoe Ltd, London, UK
[4] Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts
[5] Department of Dermatology, Mount Vernon Cancer Centre, Northwood, UK

**Corresponding author:** Veronique Bataille

**Email:** bataille@doctors.org.uk

**Funding:** Zoe Ltd provided in-kind support for all aspects of building, running, and supporting the app and service to all users worldwide. Investigators received support from the Wellcome Trust, the MRC/BHF, Alzheimer's Society, EU, NIHR, Chronic Disease Research Foundation (CDRF), and the NIHR-funded BioResource, Clinical Research Facility and BRC based at GSTT NHS Foundation Trust in partnership with King's College London. This work was also supported by the UK Research and Innovation London Medical Imaging & Artificial Intelligence Centre for Value Based Healthcare.

**Conflicts of interest:** JW is an employee of Zoe Ltd. TDS is co-founder and shareholder of Zoe Ltd. EEF is an author for UpToDate on COVID-19 Dermatology. EEF is the Principal Investigator of the COVID-19 Dermatology Registry and serves on the AAD COVID-19 Task Force. The other authors have no conflict of interest to declare.

A.V. and B.M. contributed equally.
V.B. and M.F. jointly supervised this work.

**Data availability:** Data collected in the app are being shared with other health researchers through the NHS-funded Health Data Research UK (HDRUK)/SAIL consortium, housed in the UK Secure e-Research Platform (UKSeRP) in Swansea. Anonymized data collected by the symptom tracker app can be shared with researchers who provide a methodologically sound proposal via HDRUK, provided the request is made according to their protocols and is in the public interest (see https://healthdatagateway.org/detail/9b604483-9cdc-41b2-b82c-14ee3dd705f6). Data updates can be found at https://covid.joinzoe.com.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.21784

**Ethics statement:** The study has been approved by the King's College London Research Ethics Committee REMAS ID 18210, review reference LRS-19/20-18210. All app users provided informed consent, either themselves or by proxy.

**What's already known about this topic?**

Several studies during the wild-type COVID-19 wave reported that patients presented with common skin-related symptoms. Additionally, it has been observed that COVID-19 symptoms differ among variants. However, no study has focused on how skin-related symptoms have changed across different variants.

**What does this study add?**

We showed, in a community-based retrospective study including over 348,000 individuals, that the presence of cutaneous symptoms is predictive of SARS-CoV-2 infection during the Delta and Omicron waves, and that this diagnostic value, along with symptom frequency and duration, differs between variants. Furthermore, we showed that infected vaccinated and unvaccinated individuals reported similar skin-related symptoms during the Delta and Omicron waves, with only burning rashes being less common after vaccination.

**Plain language summary**

Individuals infected with COVID-19 experienced unusual skin rashes such as urticaria, chickenpox-type rash, and reddish and purplish bumps on the fingers or toes (COVID toes) as well as rarer skin manifestations.

Using data from over 348,000 UK users of the ZOE COVID Study app collected during the Delta and Omicron waves, we observed that self-reported skin-related symptoms were associated with COVID-19 infection and that their frequency and duration differ between the Delta and Omicron waves. Additionally, we observed that there was no difference in skin-related symptoms between infected vaccinated and unvaccinated users apart from burning rashes, which were less common after vaccination. Taking these observations together, we suggest that skin-related symptoms should be tracked both to identify individuals infected with COVID-19 and help recognise new variants.

**Abstract**

**Background.** Symptoms of SARS-CoV-2 infection have differed during the different waves of the pandemic, but little is known about how cutaneous manifestations have changed.

**Objectives.** Investigate the diagnostic value, frequency, and duration of cutaneous manifestations of SARS-CoV-2 infection and explore their variations between the Delta and Omicron waves of the pandemic.

**Methods.** In this retrospective study, we used self-reported data from 348,691 UK users of the ZOE COVID Study app, matched 1:1 for age, sex, vaccination status, and self-reported eczema diagnosis between the Delta and Omicron wave, to assess the diagnostic value, frequency, and duration of five cutaneous manifestations of SARS-CoV-2 infection (*i.e.,* acral, burning, erythematopapular, and urticarial rash and unusual hair loss), and how these changed between waves. We also investigated whether vaccination had any effect on symptom frequency.

**Results.** We show a significant association between any cutaneous manifestations and a positive SARS-CoV-2 test result, with a diagnostic value that was higher in the Delta compared to the Omicron wave (OR=2.29, 95% CI=2.22-2.36, $P<1.0x10^{-300}$ and OR=1.29, 95% CI=1.26-1.33, $P=6.6x10^{-64}$, respectively), when cutaneous manifestations were also more common (17.6% vs 11.4%, respectively) and had a longer duration. During both waves, cutaneous symptoms clustered with other frequent symptoms and only rarely (in less than 2% of the users) were the first or only clinical sign of SARS-CoV-2 infection. Finally, we observed that vaccinated and unvaccinated users showed similar odds of presenting a cutaneous manifestation, apart from burning rash, whose odds were lower in vaccinated users.

**Conclusions.** Cutaneous manifestations are predictive of SARS-CoV-2 infection, and their frequency and duration have changed with different variants. Therefore, we advocate for their inclusion in the list of clinically relevant COVID-19 symptoms and suggest that their monitoring could help identify new variants.

## Introduction

Skin-related symptoms of SARS-CoV-2 infection were reported in the wild-type wave in 2020 and were notable both for their variety, spanning more than thirty different cutaneous manifestations[1,2], and for their utility as a presenting symptom of COVID-19 that could lead to testing and diagnosis[3]. Data from our group[3] evaluating the prevalence of cutaneous manifestations in the UK between May and June 2020, found that 9% of users with a PCR-confirmed SARS-CoV-2 infection reported a skin rash. Moreover, using an independent retrospective survey, we showed that, for 21% of participants, the rash was the first symptom to appear, and in 17% was the only sign of the infection[3].

To date, the WHO has identified five variants of concern that have been globally dominant[4]. The Alpha variant (B.1.1.7) became dominant in September 2020, followed by the Beta variant (B.1.351) in May 2020 and the Gamma variant (P.1) in November 2020. Currently, circulating variants of concern are Delta (B.1.617.2) and Omicron (B.1.1.529), whose earliest documented samples were detected in October 2020 and November 2021, respectively. Variants are associated with different clinical presentations of the disease, as shown by a study comparing symptoms' prevalence between the Delta and Omicron waves in the UK[5]. For instance, during the Omicron wave, users were more likely to report sore throat and hoarse voice and less likely to report at least one of the three classic COVID-19 symptoms (*i.e.,* those included in the UK National Health Service guidelines: anosmia, fever, and persistent cough) compared to the Delta wave[5]. However, changes in COVID-19 symptoms across variants have not been evaluated specifically for cutaneous manifestations. Anecdotally, dermatologists have noted fewer consultations for rashes during the Delta and even less during the Omicron wave[6], but data are needed to formally assess how cutaneous manifestations of SARS-CoV-2 infection have changed with the different variants.

In this retrospective study, we report on the diagnostic value, frequency, and duration of five cutaneous manifestations (*i.e.,* acral, burning, erythematopapular, and urticarial rash and unusual hair loss) for SARS-CoV-2 by leveraging longitudinal self-reported information collected *via* the ZOE COVID Study app[7] during Delta and Omicron waves. Additionally, we investigated whether vaccination influenced the frequency of skin-related symptoms.

## Materials and Methods

### The ZOE COVID Study app

Users of the ZOE COVID Study app[7] were recruited through social media outreach and included anyone able to download and use the app, either themselves or by proxy. The app collects on sign up, among the others, data on sex, age, ethnicity (*i.e.,* Asian, Black, Chinese, Middle East, Mixed, Other, or White), height, weight, common disease status (*e.g.,* eczema), and the use of medications (*e.g.,* corticosteroids and immunosuppressants). Users could provide daily updates on the presence of 33 COVID-19-related symptoms (**Supplementary Table S1**), including five cutaneous manifestations: red/purple sores or blisters on the feet or toes (acral rash), strange, unpleasant sensations like pins & needles or burning (burning rash), rash on arm or torso (erythematopapular rash), red, itchy welts on the face or body or sudden swelling of the face or lips (urticarial rash), and unusual hair loss. When a symptom was not

reported we assumed that the user was not experiencing that symptom (passive reporting). Users could self-report if/when they had a SARS-CoV-2 test, how it was performed (*e.g.,* PCR swab, lateral flow test [LFT], antibody testing), and the result. From December 11th, 2020, users could also log information on vaccination, including the date of each administered dose.

**Ethical statement**

The study has been approved by the King's College London Research Ethics Committee REMAS ID 18210, review reference LRS-19/20-18210. All app users provided informed consent, either themselves or by proxy.

**Data curation**

The data curation workflow was performed using ExeTera[8] (v0.6.0b), a software specifically developed for handling the large volumes of data present in the dataset, followed by *ad hoc* R scripts to perform further data cleaning and the specific statistical analyses.

This study included UK residents, reporting a numeric plausible range between 1 and 90 years, and who entered data during the Delta (June 27th and November 27th, 2021) and/or the Omicron (December 20th, 2021 to the day of the last data dump before the presented analysis, February 23rd, 2022) wave[5], either themselves or by proxy (data snapshot: 2022-02-24).

Since the app does not perform any validation of user-inputted data at the time of logging, as done in our previous study[3], we used the following criteria to exclude users reporting unreliable and extreme observations: for users 16 years old or older, height, weight, or body mass index (BMI) outside the range of 1.1 to 2.2 m, 40 to 200 kg, and 15 to 55 kg/m$^2$, respectively; for users younger than 16 years old, height, weight or BMI outside two standard deviations from the sample's mean for each age group. We further excluded: users who did not report their sex, users younger than 12 years old reporting being vaccinated (these individuals were not eligible for vaccination at the time of the study), and users younger than 16 years old reporting as being healthcare workers. Details on the data selection protocol are shown in **Supplementary Figure S1**.

A SARS-CoV-2 positive illness was defined as the period starting 14 days before a positive PCR or LFT SARS-CoV-2 test result, as done previously[9], and ending on the day the first negative test result was logged, provided there were no additional positive tests within a 45-day window from the negative test date. Positive test results within 45 days of each other were considered part of an ongoing illness. When no negative test result was logged within 45 days of a positive test, the end of the illness was fixed to 45 days after the last recorded positive test. We used a shorter window size compared to the 90 days used with earlier variants as there is mounting evidence that the Omicron reinfection window is considerably shorter than for Delta and prior variants[10]. Due to this choice, during the Delta wave, we observed 66 users (0.1%) that logged a SARS-CoV-2 positive illness twice, with the first two positive test results no more than 134 days apart (median=69 days). Since we could not confirm these were actual reinfections, only the first SARS-CoV-2 positive illness was retained. No double log of SARS-CoV-2 positive illnesses, and therefore of suspected reinfection, was recorded during the Omicron wave. Only symptomatic SARS-CoV-2 positive illnesses were used in this study.

Due to the wide free testing availability in the UK during the study period, distinct periods of symptomatic logging not accompanied by a positive PCR or LFT COVID-19 test (*i.e.,* when the result was negative, or no result was logged) were considered non-SARS-CoV-2-related illnesses. A non-SARS-CoV-2-related illness started 14 days before the logging of the first symptom and ended with the

first asymptomatic report, provided there were no further symptomatic assessments within a 14-day window.

To avoid biases due to users being able to log both SARS-CoV-2 positive illnesses and unrelated illnesses within the same wave, and to maximize the number of users with positive test results, we considered only the data entry for confirmed SARS-CoV-2 infections. When users logged multiple non-SARS-CoV-2-related illnesses during the same wave, one was selected at random.

For each illness, the date of the last vaccination and the number of doses administered before the illness started were recorded. Users were considered vaccinated when they had at least two doses of vaccine, and the start of the recorded illness was at least 14 days but no more than 240 days (8 months) after the last dose, that is when vaccine effectiveness decreases for all three vaccines used in the UK[11].

**Statistical analyses**

Statistical analyses were carried out using R (v4.1.0). Comparisons between categorical values were carried out using Pearson's $\chi^2$ test or Fisher's exact test, as reported in the text. Comparisons between continuous values were carried out using Wilcoxon's test or, for BMI, using linear regression after correction for age and sex.

Due to the observational nature of our study, differences in users who logged during the Delta and Omicron waves were present. Therefore, to increase the robustness of our results, users logging during the Omicron wave were matched 1:1 to randomly selected users logging during the Delta wave on age, sex, vaccination status, and self-reporting a diagnosis of eczema. Overall, 72,269 and 3,049 users who logged during the Delta and Omicron wave were discarded because no 1:1 match could be identified. Of the matched users, 1,273 (0.3%) logged a SARS-CoV-2 positive illness both during the Delta and the Omicron wave.

Associations between the presence/absence of self-reported cutaneous symptoms and SARS-CoV-2 test results were carried out through multivariate logistic regression and sex, age, BMI, ethnicity, self-reported diagnosis of eczema, vaccination status, and whether corticosteroids and/or immunosuppressants were administered were included as covariates. Associations passing a Bonferroni-derived threshold of 0.05/5=0.01 were considered statistically significant.

The duration of each symptom was calculated as the difference between the date on which the symptom was last and first logged. Symptoms' durations between waves were compared using the Wilcoxon's test and those passing a Bonferroni-derived threshold of 0.05/5=0.01 were considered statistically significant.

The association between the presence/absence of self-reported cutaneous symptoms and vaccination status was carried out using Fisher's exact test on a subset of SARS-CoV-2 positive users matched 1:1 for age, sex, and self-reported diagnosis of eczema.

Plots were generated with the following R packages: forest plots with the ggplot2 (v3.3.5), heatmaps with pheatmap (v1.0.12), and the plot showing duration of the skin-related symptoms with gghalves (v0.1.1). P values in the plots were calculated using rstatix (v0.7.0) and displayed with ggprism (v1.0.3).

**Results**

**Cutaneous symptoms' diagnostic value, frequency, and duration**

Longitudinal self-reported data were collected from 348,691 UK users matched 1:1 for age, sex, vaccination status, and self-reported eczema diagnosis between the Delta and Omicron wave. They included 42,299 SARS-CoV-2 infections confirmed *via* PCR or LFT and 156,835 unrelated illnesses

during the Delta wave, and 75,580 confirmed infections and 123,554 unrelated illnesses during the Omicron wave (**Table 1**).

Cutaneous symptoms were reported by 7,430 (17.6%) and 8,632 (11.4%) infected and 14,041 (9.0%) and 11,805 (9.6%) non-infected users during the Delta and Omicron waves, respectively. We investigated their overall diagnostic value, confirming a significantly higher prevalence among users who tested positive compared to those who tested negative both during Delta (odds ratio [OR]=2.29, 95% confidence interval [CI]=2.22-2.36, $P<1.0x10^{-300}$) and Omicron (OR=1.29, 95% CI=1.26-1.33, $P=6.6x10^{-64}$) waves, with burning rash having the highest odds ratio (OR=2.61, 95% CI=2.52-2.72, $P<1.0x10^{-300}$ and OR=1.46, 95% CI=1.40-1.51, $P=7.7x10^{-86}$, for the Delta and Omicron waves, respectively; **Table 2**). In comparison, the odds ratios for fever and cough, well-known SARS-CoV-2 manifestations, were 3.17 (95% CI=3.09-3.24, $P<1.0x10^{-300}$) and 2.53 (95% CI=2.47-2.59, $P<1.0x10^{-300}$), respectively, for Delta wave and 1.93 (95% CI=1.89-1.97, $P<1.0x10^{-300}$) and 2.04 (95% CI=2.00-2.08, $P<1.0x10^{-300}$), for the Omicron wave, suggesting a similar diagnostic value compared to skin, especially during Delta (**Figure 1a**).

The diagnostic value of all cutaneous symptoms was higher in the Delta compared to the Omicron wave (**Table 2**), in line with a change of cutaneous symptoms' frequency across variants, as cutaneous manifestations were more common in the Delta compared to the Omicron wave (17.6% and 11.4%, Fisher's $P=6.1x10^{-186}$; **Figure 1b, Table 1**). For instance, acral rashes were the most common in confirmed SARS-CoV-2 cases during the wild-type wave[3] and decreased thereafter. They were reported by 3.1%, 1.1%, and 0.7% of the infected users in the wild-type[3], Delta, and Omicron wave respectively (Fisher's $P=3.7x10^{-25}$), and were diagnostic in the wild-type[3] (OR=1.74; 95% CI=1.33-2.28, $P=5.9\times10^{-5}$) and in the Delta (OR=1.79, 95% CI=1.60-2.01, $P=2.6\times10^{-24}$) but not in the Omicron wave.

Additionally, all cutaneous manifestations (apart from acral rash) showed an average longer duration during the Delta than the Omicron wave (Wilcoxon's $P<2.0\times10^{-3}$; **Supplementary Figure S2)**.

**Timing of cutaneous symptoms in relation to other COVID-19 symptoms**

In infected users, cutaneous symptoms clustered with other frequent symptoms, such as headache, runny nose, sore throat, and sneezing (**Supplementary Figure S3**). They were most often reported after (61.5% and 55.8% for Delta and Omicron waves, respectively; Fisher's $P=3.9x10^{-13}$), on average after 6 and 5 days for Delta and Omicron waves, respectively (Wilcoxon's $P=2.6x10^{-5}$), or at the same time as other symptoms (37.8% and 43.0%, for Delta and Omicron waves, respectively; Fisher's $P=4.9x10^{-11}$). Only 0.5% and 0.8% of the infected users reported cutaneous manifestation as the first presentation in the Delta and Omicron waves, respectively (Fisher's P=0.01), an average 5 days before the next logged symptom in both waves. Similarly, only 0.2% and 0.4% of the infected users in the Delta and Omicron waves, respectively, logged a skin-related symptom as the only clinical sign of infection (Fisher's $P=6.0x10^{-3}$).

**Cutaneous symptoms in vaccinated and unvaccinated users**

We compared the odds of developing a cutaneous symptom in vaccinated versus unvaccinated users who tested positive for SARS-CoV-2 infection. The two groups were matched 1:1 for age, sex, and self-reported eczema diagnosis, as vaccinated users were more likely to be female (OR=1.14, 95% CI=1.09-1.19, $P=8.2x10^{-9}$ and OR=1.15, 95% CI=1.11-1.19, for the Delta and Omicron wave, respectively), older (median age: 51 vs 21 years old, Wilcoxon's test $P<1.0x10^{-300}$ and median age: 50 vs 22 years old, Wilcoxon's test $P<1.0x10^{-300}$, for the Delta and Omicron wave, respectively), and more

likely to self-report eczema (OR=1.22, 95% CI=1.14-1.30, P=1.4x10$^{-8}$ and OR=1.29, 95% CI=1.23-1.35, for the Delta and Omicron wave, respectively) than unvaccinated users. We observed that cutaneous symptoms were similar in the two groups, apart the odds of burning rash which were lower in vaccinated users (**Figure 1c, Supplementary Table S2**).

**Discussion**

In this study we observed that the frequency of cutaneous manifestations and their diagnostic power were higher in the Delta than in the Omicron wave. While possible unmeasured confounders might be present, we believe that they are unlikely differently distributed between the populations in the two waves, and that cutaneous manifestations were genuinely more common in the Delta than in the Omicron wave. Indeed, changes in cutaneous manifestations across variants are expected as these were observed for other non-skin-related symptoms[5]. Monitoring these changes may help identifying the emergence of new variants and it is particularly important now that several national surveillance studies, including those involving genomic sequencing, have been scaled back or terminated. Our findings also back up anecdotal clinical observations that rashes such as chilblains have presented less frequently to dermatologists during the Omicron relative to prior waves[6]. While this could be due to a true biologic decrease based on variants' characteristics or to a previous exposure to the virus, an increasing familiarity with rashes as a part of COVID-19 presentation by both primary care physicians and the public, who found them less concerning and less worth of a referral to a specialist, cannot be ruled out. We could not directly compare the frequency of the currently collected skin-related symptoms with those collected during the wild-type wave[3], apart from acral rash which was progressively less common in the Delta and Omicron waves. In the previous study[3], indeed, erythematopapular and urticarial rash were collected together, and neither burning rash nor unusual hair loss were included in the list of symptoms.

Despite the observed decrease in frequency from the Delta to the Omicron wave, the odds ratio for skin-related symptoms remained comparable, in both waves, to that of more well-known COVID-19 symptoms, such as fever and cough. In contrast, the WHO has not yet included cutaneous manifestations in its COVID-19 Case Definition of symptoms suspicious for SARS-CoV-2 infection[12], possibly leading to delayed or missed diagnoses.

We also observed that cutaneous symptoms clustered with other frequent symptoms and that less than 2% of the users infected with SARS-CoV-2 reported them as the first or the only clinical. In our previous study[3], using a retrospective survey on COVID-19-related skin rashes during the wild-type wave, we observed that 21% of positive cases reported a skin-related symptom as the only clinical presentation and 17% as the first presenting symptom. This difference may be explained by the survey specifically targeting individuals aware of the link between skin-related symptoms and COVID-19, and who were asked to describe their symptoms in more detail.

Analogously, we observed a much shorter symptom duration during the Delta and Omicron waves compared to the wild-type wave[3]. However, our current data suggest that users may interrupt logging after the acute phase of the infection, while the survey presented in our previous study[3], due to its retrospective nature, was able to record the entire duration of skin-related symptoms. Thus, the durations reported here may be an underestimation of a longer course of symptoms, which was correctly captured by ours and other studies[3,2,13].

The mechanism of why symptoms differ between waves is still an area of active investigation, with tissue tropism and viral replication possibly contributing to this variation[14]. For example, the Delta and

Omicron waves show less tropism for the lung compared to the wild-type and instead, upper respiratory symptoms such as sore throat and sneezing are common[5]. In addition, many users may have experienced COVID-19 more than once, and their prior exposure and immunity may have altered the presentation of symptoms in further waves. While we have historical data for a subset of users, it is likely that many presented with an asymptomatic SARS-CoV-2 infection or one which did not present any of the classic symptoms and was therefore never documented on the app, especially during the early waves when access to testing was very limited, making the comparison of symptoms between subsequent infections impossible.

Vaccination status has also been proposed to play a role in differences in symptoms over time, with infected vaccinated individuals reporting almost all COVID-19 symptoms less frequently than unvaccinated ones[15]. However, we observed, on a large scale, that there was no difference in skin-related symptoms between vaccinated and unvaccinated users with confirmed infection apart from burning rash, which was less common after vaccination.

A major limitation of this study is that our sample represents a self-selected group of individuals, and, therefore, is not fully representative of the general population. A second limitation of this study is the self-reported nature of the data. However, in our previous study[3], using a reasonably large number of photographs (N=260) blindly assessed by four dermatologists, we showed that a large majority of individuals (86%) were able to self-identify cutaneous manifestation likely to be related to COVID-19 infection. Additionally, assigning infection to a specific variant based on the variance prevalence at the time in the UK population rather than using individual sequencing information may introduce misclassifications. However, individual sequencing was not feasible due to the size of this study, and data from the UK Health Security Agency confirmed that, within the reported periods, more than 70% of SARS-CoV-2 sequenced cases were either Delta or Omicron[16].

In summary, this study suggests changes in cutaneous manifestations may help identify new variants and provide additional evidence to support their inclusion in the list of clinically relevant COVID-19 symptoms.

**References**


1. Daneshgaran, G., Dubin, D. P. & Gould, D. J. Cutaneous Manifestations of COVID-19: An Evidence-Based Review. *Am J Clin Dermatol* **21**, 627–639 (2020).
2. Freeman, E. E. *et al.* The spectrum of COVID-19–associated dermatologic manifestations: An international registry of 716 patients from 31 countries. *Journal of the American Academy of Dermatology* **83**, 1118–1129 (2020).
3. Visconti, A. *et al.* Diagnostic value of cutaneous manifestation of SARS-CoV-2 infection*. *Br J Dermatol* **184**, 880–887 (2021).

4. World Health Organization. Tracking SARS-CoV-2 variants. https://www.who.int/activities/tracking-SARS-CoV-2-variants.
5. Menni, C. *et al.* Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: a prospective observational study from the ZOE COVID Study. *The Lancet* S0140673622003270 (2022) doi:10.1016/S0140-6736(22)00327-0.
6. Willyard, C. Are 'COVID toes' actually caused by the coronavirus? *Nature* **603**, 779–779 (2022).
7. Drew, D. A. *et al.* Rapid implementation of mobile technology for real-time epidemiology of COVID-19. *Science* **368**, 1362–1367 (2020).
8. Murray, B. *et al.* Accessible data curation and analytics for international-scale citizen science datasets. *Sci Data* **8**, 297 (2021).
9. Sudre, C. H. *et al.* Attributes and predictors of long COVID. *Nat Med* **27**, 626–631 (2021).
10. Pulliam, J. R. C. *et al.* Increased risk of SARS-CoV-2 reinfection associated with emergence of Omicron in South Africa. *Science* eabn4947 (2022) doi:10.1126/science.abn4947.
11. Menni, C. *et al.* COVID-19 Vaccine Waning and Effectiveness and Side Effects of Boosters: A Prospective Community Study From the ZOE COVID Study. *SSRN Journal* (2021) doi:10.2139/ssrn.3980542.
12. World Health Organization. WHO COVID-19 Case definition. https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2.
13. McMahon, D. E. *et al.* Long COVID in the skin: a registry analysis of COVID-19 dermatological duration. *The Lancet Infectious Diseases* **21**, 313–314 (2021).
14. Hui, K. P. Y. *et al.* SARS-CoV-2 Omicron variant replication in human bronchus and lung ex vivo. *Nature* **603**, 715–720 (2022).
15. Antonelli, M. *et al.* Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. *The Lancet Infectious Diseases* **22**, 43–55 (2022).

16. UK Health Security Agency. Omicron daily overview. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1043098/20211221_OS_Daily_Omicron_Overview.pdf.

**Table 1. Sample characteristics.** Categorical variables are reported as number (percentage). Continuous variables are reported as mean ± standard deviation. Within each wave, differences between positive and negative users were assessed using: for cutaneous manifestation, multivariate logistic regression adjusting for age, sex, body mass index (BMI), self-reported diagnosis of eczema, and whether the users were taking corticosteroids and/or immunosuppressants; for other binary values, $\chi^2$ test; for age, Wilcoxon's test; for BMI, linear regression adjusting for the age and sex.

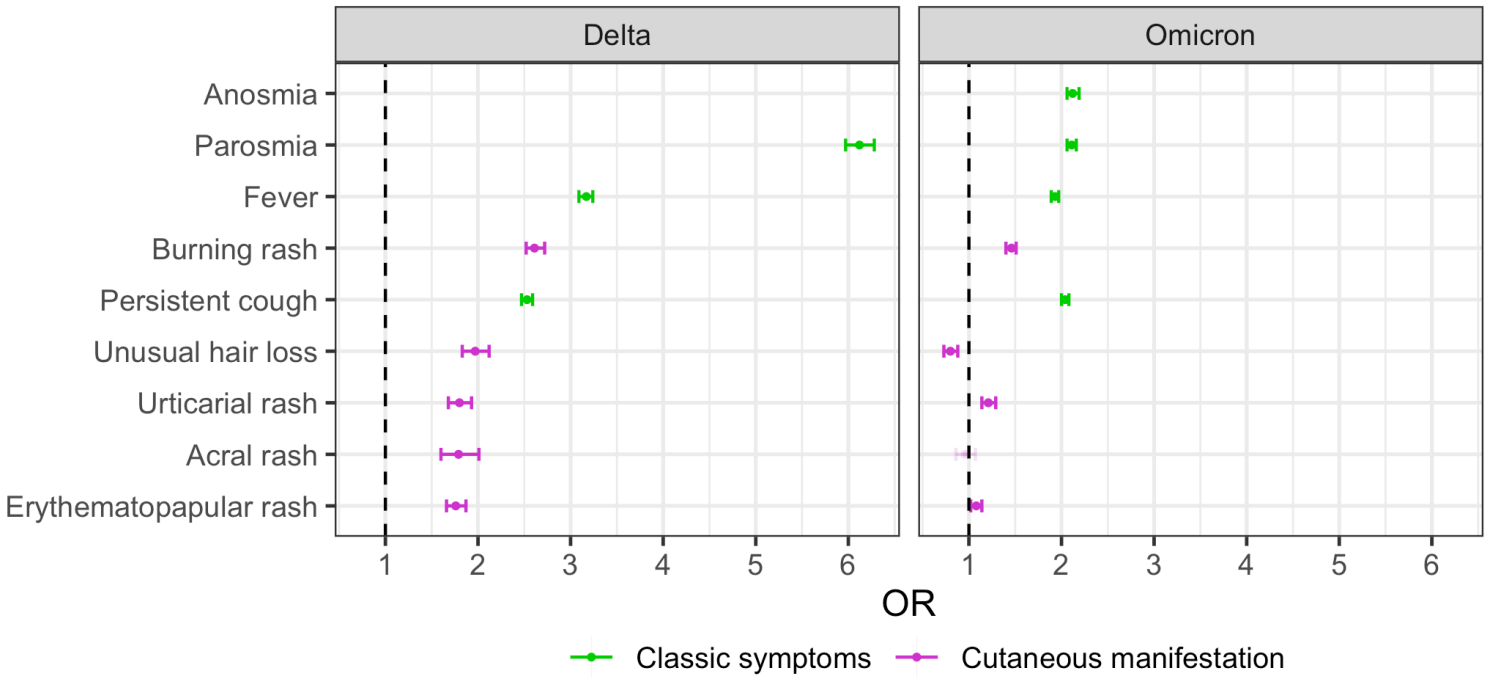
| | | | Delta wave | | | | Omicron wave | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **All users** | **All** | **Positive** | **Negative** | **P** | **All** | **Positive** | **Negative** | **P** |
| N | | 348,691 | 199,134 | 42,299 | 156,835 | - | 199,134 | 75,580 | 123,554 | - |
| Females | | 233,396 (66.9%) | 134,914 (67.8%) | 26,216 (62.0%) | 108,698 (69.3%) | $4.5\text{x}10^{-180}$ | 134,913 (67.7%) | 48,818 (64.6%) | 86,095 (69.7%) | $6.2\text{x}10^{-123}$ |
| Age (years) | | 46.5±17.7 | 46.3±17.6 | 44.6±18.2 | 46.7±17.4 | $6.9\text{x}10^{-77}$ | 46.3±17.6 | 44.1±18.7 | 47.6±16.8 | $<1.0\text{x}10^{-300}$ |
| Is vaccinated | | - | 155,849 (78.3%) | 31,556 (74.6%) | 124,293 (79.3%) | $5.7\text{x}10^{-94}$ | 155,849 (78.3%) | 56,857 (75.2%) | 98,992 (80.1%) | $1.8\text{x}10^{-145}$ |
| BMI ($kg/m^2$) | | 26.0±6.0 | 26.0±6.1 | 25.8±6.1 | 26.1±6.1 | 0.24 | 26.0±6.0 | 25.5±6.1 | 26.3±6.0 | $4.6\text{x}10^{-60}$ |
| Acral rash | | 2,847 (0.8%) | 1,428 (0.7%) | 456 (1.1%) | 972 (0.6%) | $2.6\text{x}10^{-24}$ | 1,471 (0.7%) | 539 (0.7%) | 932 (0.8%) | 0.49 |
| Burning rash | | 23,798 (6.8%) | 12,491 (6.3%) | 4,792 (11.3%) | 7,699 (4.9%) | $<1\text{x}10^{-300}$ | 12,023 (6.0%) | 5,408 (7.2%) | 6,615 (5.4%) | $7.7\text{x}10^{-86}$ |
| Erythematopapular rash | | 10,383 (3.0%) | 5,219 (2.6%) | 1,633 (3.9%) | 3,586 (2.3%) | $4.6\text{x}10^{-76}$ | 5,310 (2.7%) | 2,072 (2.7%) | 3,238 (2.6%) | $7.5\text{x}10^{-3}$ |
| Unusual hair loss | | 4,982 (1.4%) | 3,207 (1.6%) | 1,030 (2.4%) | 2,177 (1.4%) | $8.6\text{x}10^{-69}$ | 1,976 (1.0%) | 604 (0.8%) | 1,372 (1.1%) | $8.0\text{x}10^{-6}$ |
| Urticarial rash | | 7,990 (2.3%) | 3,890 (2.0%) | 1,226 (2.9%) | 2,664 (1.7%) | $2.9\text{x}10^{-62}$ | 4,218 (2.1%) | 1,752 (2.3%) | 2,466 (2.0%) | $1.7\text{x}10^{-9}$ |
| Ethnicity | Asian | 4,357 (1.2%) | 2,445 (1.2%) | 567 (1.3%) | 1.878 (1.2%) | | 2,425 (1.2%) | 964 (1.3%) | 1,461 (1.2%) | |
| | Black | 1,271 (0.4%) | 699 (0.4%) | 166 (0.4%) | 533 (0.3%) | | 742 (0.4%) | 257 (0.3%) | 485 (0.4%) | |
| | Chinese | 1,020 (0.3%) | 578 (0.3%) | 95 (0.2%) | 483 (0.3%) | | 573 (0.3%) | 253 (0.3%) | 320 (0.3%) | |
| | Middle East | 825 (0.2%) | 475 (0.2%) | 111 (0.3%) | 364 (0.2%) | $9.7\text{x}10^{-4}$ | 464 (0.2%) | 169 (0.2%) | 295 (0.2%) | $4.6\text{x}10^{-7}$ |
| | Mixed | 7,242 (2.1%) | 4146 (2.1%) | 834 (2.0%) | 3,312 (2.1%) | | 4,206 (2.1%) | 1,751 (2.3%) | 2,455 (2.0%) | |
| | Others | 1,689 (0.5%) | 984 (0.5%) | 184 (0.4%) | 800 (0.5%) | | 972 (0.5%) | 371 (0.5%) | 601 (0.5%) | |
| | White | 331,407 (95.0%) | 189,282 (95.1%) | 40,230 (95.1%) | 149,052 (95.0%) | | 189,274 (95.0%) | 71,642 (94.8%) | 117,632 (95.2%) | |
| | N/A | 880 (0.3%) | 525 (0.3%) | 112 (0.3%) | 413 (0.3%) | | 478 (0.2%) | 173 (0.2%) | 305 (0.2%) | |
| Has eczema | | 44,853 (12.9%) | 26,100 (13.1%) | 4,821 (11.4%) | 21,279 (13.6%) | $8.9\text{x}10^{-32}$ | 26,095 (13.1%) | 9,464 (12.5%) | 16,631 (13.5%) | $1.8\text{x}10^{-9}$ |
| Corticosteroids | | 24,073 (6.9%) | 14,020 (7.0%) | 2,564 (6.1%) | 11,456 (7.3%) | $8.2\text{x}10^{-19}$ | 13,893 (7.0%) | 4,393 (5.8%) | 9,500 (7.7%) | $3.2\text{x}10^{-57}$ |
| Immunosuppressants | | 13,965 (4.0%) | 8,184 (4.1%) | 1,557 (3.7%) | 6,627 (4.2%) | $6.0\text{x}10^{-7}$ | 7,985 (4.0%) | 2,584 (3.4%) | 5,401 (4.4%) | $8.5\text{x}10^{-26}$ |

**Table 2. Diagnostic value of cutaneous manifestations.** For each collected cutaneous manifestation of SARS-CoV-2, the table shows the odds ratio (OR) of a positive SARS-CoV-2 test result along with its 95% confidence interval (95% CI) and P value for the multivariate logistic regression after correction for age, sex, BMI, diagnosis of eczema, vaccination status, and corticosteroids and/or immunosuppressants administration. Users were considered vaccinated when they had at least two doses of vaccine and the start of the illness was at least 14 days but no more than 240 days (8 months) after the last dose. The analysis for the Delta and Omicron waves included 198,609 and 198,656 users, respectively.

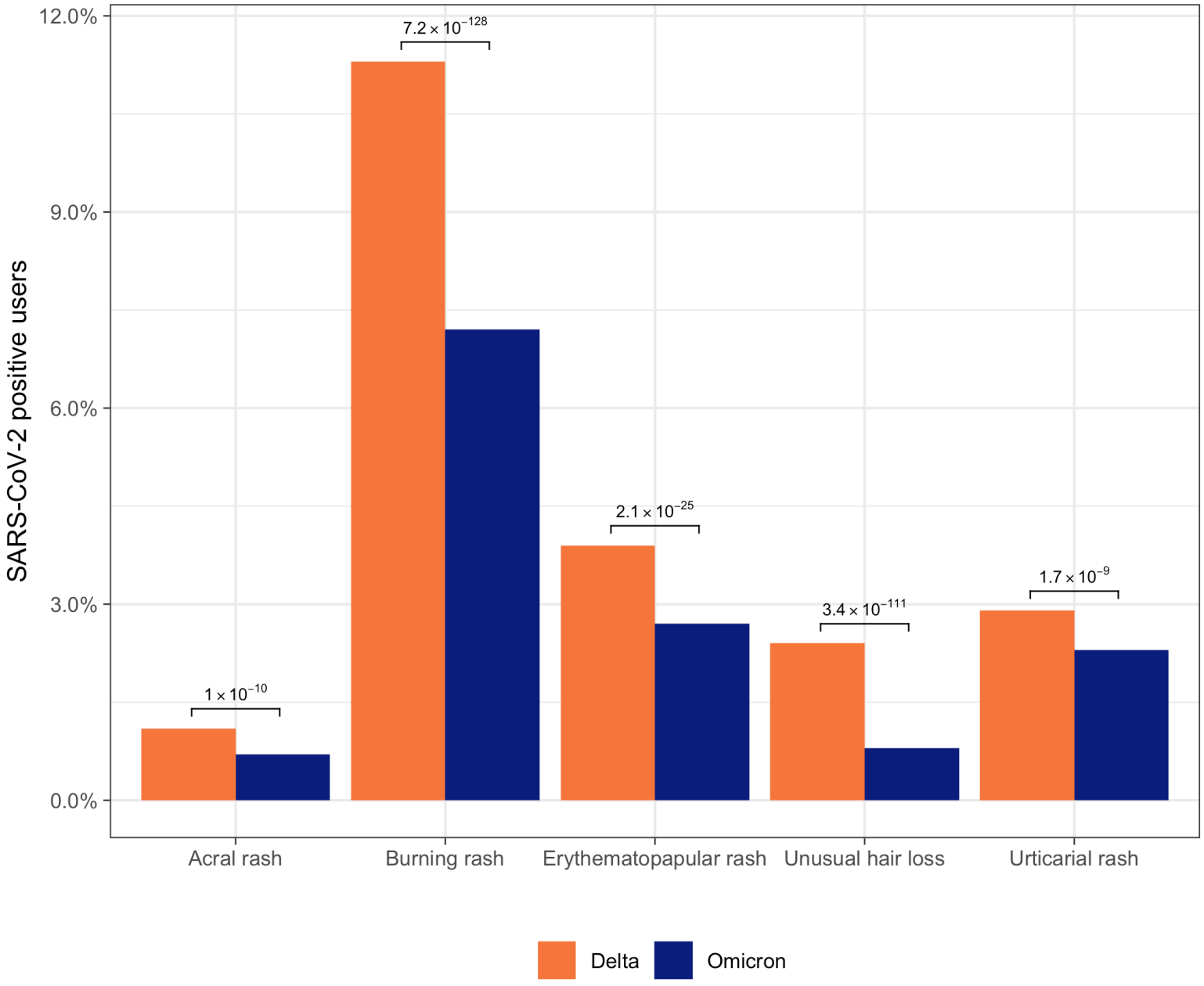
| | Delta wave | | | Omicron wave | | |
|---|---|---|---|---|---|---|
| | **OR** | **95% CI** | **P** | **OR** | **95% CI** | **P** |
| Acral rash | 1.79 | 1.60 - 2.01 | $2.6 \times 10^{-24}$ | 0.96 | 0.86 - 1.07 | 0.49 |
| Burning rash | 2.61 | 2.52 - 2.72 | $<1 \times 10^{-300}$ | 1.46 | 1.40 - 1.51 | $7.7 \times 10^{-86}$ |
| Erythematopapular rash | 1.76 | 1.66 - 1.87 | $4.6 \times 10^{-76}$ | 1.08 | 1.02 - 1.14 | $7.5 \times 10^{-3}$ |
| Unusual hair loss | 1.97 | 1.83 - 2.12 | $8.6 \times 10^{-69}$ | 0.80 | 0.73 - 0.88 | $8.0 \times 10^{-6}$ |
| Urticarial rash | 1.80 | 1.68 - 1.93 | $2.9 \times 10^{-62}$ | 1.21 | 1.14 - 1.29 | $1.7 \times 10^{-9}$ |

**Figure legends**

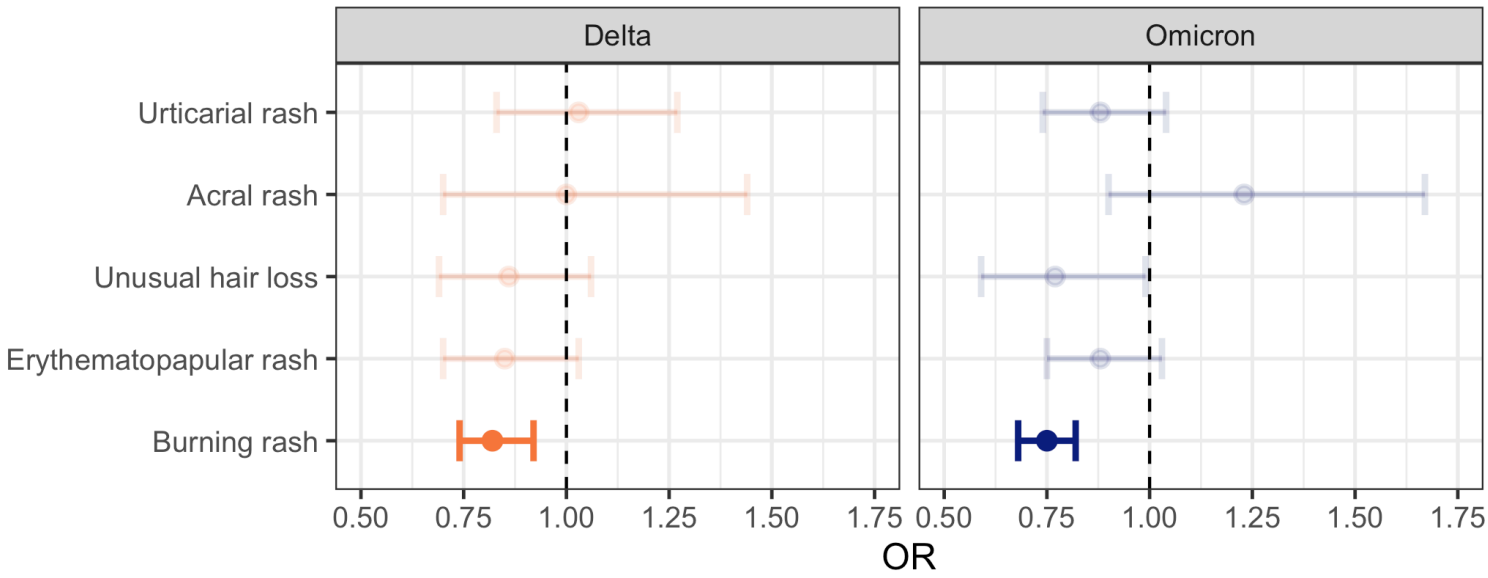
**Figure 1. a) Diagnostic value of cutaneous manifestations and classic symptoms of SARS-CoV-2 infection.** Forest plots showing the odds ratio (OR) of self-reporting a skin-related symptom or one of the classic COVID-19 symptoms, *i.e.,* those included in the UK National Health Service guidelines, during the Delta and Omicron waves. Odds ratios were calculated by multivariate linear regression using 198,609 illnesses reported by users matched 1:1 for age, sex, vaccination status, and self-reported eczema diagnosis. Error bars indicate the 95% confidence interval. Transparency indicates odds ratios which are not statistically significant ($P \geq 0.01$). The odds ratio for anosmia during the Delta wave is removed to improve the visualization and is reported here for the sake of completeness: OR=13.42, 95% CI=13.06-14.79. **b) Frequency of cutaneous manifestations in SARS-CoV-2 positive users.** The bar plot shows the percentage of infected users logging skin-related symptoms during the Delta and Omicron waves. P values were calculated using Fisher's exact test. SARS-CoV-2 infection was confirmed by a positive PCR or lateral flow test result. **c) Odds of reporting cutaneous symptoms in SARS-CoV-2 positive vaccinated compared to unvaccinated users**. Forest plots showing the odds ratio (OR) of self-reporting a skin-related symptom in 11,802 (Delta wave) and 20,290 (Omicron wave) users whose SARS-CoV-2 infection was confirmed by a positive PCR or lateral flow test result. Vaccinated and unvaccinated users were matched 1:1 for age, sex, and self-reported eczema diagnosis. An odds ratio lower than 1 indicates lower odds of reporting a symptom in vaccinated compared to unvaccinated users. Error bars indicate the 95% confidence interval. Transparency indicates odds ratios which are not statistically significant ($P \geq 0.01$).




BJD_21784_Figure_1a.tiff




BJD_21784_Figure_1b.tiff




BJD_21784_Figure_1c.tiff