Clinical Infectious Diseases

MAJOR ARTICLE

Post-acute sequelae after SARS-cov-2 infection by viral variant and vaccination status: a multicenter cross-sectional study

Christian R. Kahlert[1,2] MD, Carol Strahm[1] MD, Sabine Güsewell[1] PhD, Alexia Cusini[3] MD, Angela Brucher[4] MD, Stephan Goppel[5] MD, Elisabeth Möller[6] MD, J. Carsten Möller[7] MD, Manuela Ortner[8], Markus Ruetti[9] MD, Reto Stocker[10] MD, Danielle Vuichard-Gysin[11,12] MD, Ulrike Besold[13] MD, Allison McGeer[14] MD, Lorenz Risch[15,16,17] PhD, Andrée Friedl[18] MD, Matthias Schlegel[1] MD, Pietro Vernazza[1] MD, Stefan P. Kuster[1]* MD, Philipp Kohler[1]* MD, SURPRISE Study Group**

[1] Cantonal Hospital St Gallen, Division of Infectious Diseases and Hospital Epidemiology, St Gallen, Switzerland; [2] Children's Hospital of Eastern Switzerland, Department of Infectious Diseases and Hospital Epidemiology, St. Gallen, Switzerland; [3] Cantonal Hospital of Grisons, Division of Infectious Diseases, Chur, Switzerland; [4] Psychiatry Services of the Canton of St. Gallen (South), Switzerland; [5] Psychiatry Services of the Canton of St. Gallen (North), Switzerland; [6] Clienia Littenheid, Littenheid, Switzerland; [7] Center for Neurological Rehabilitation, Zihlschlacht, Switzerland; [8] Rheintal Werdenberg Sarganserland Hospital Group, Grabs, Switzerland; [9] Fuerstenland Toggenburg Hospital Group, Wil, Switzerland; [10] Hirslanden Clinic, Zurich, Switzerland; [11] Thurgau Hospital Group, Division of Infectious Diseases and Hospital Epidemiology, Muensterlingen, Switzerland; [12] Swiss National Centre for Infection Prevention (Swissnoso), Berne, Switzerland; [13] Geriatric Clinic St. Gallen, St. Gallen, Switzerland; [14] Sinai Health System, Toronto, Canada; [15] Labormedizinisches Zentrum Dr Risch Ostschweiz AG, Buchs, Switzerland; [16] Private Universität im Fürstentum Liechtenstein, Triesen,

*SPK and PK contributed equally to this article.
**Study Group team members are listed in the Acknowledgment Section
Corresponding author. Philipp Kohler, MD MSc, Cantonal Hospital St. Gallen, Division of Infectious Diseases and Hospital Epidemiology, Rorschacherstrasse 95, 9007 St. Gallen, Switzerland, Email philipp.kohler@kssg.ch

DOI: 10.1093/cid/ciad143

Liechtenstein; [17] Center of Laboratory Medicine, University Institute of Clinical Chemistry, University of Bern, Inselspital, Bern, Switzerland; [18] Cantonal Hospital Baden, Division of Infectious Diseases and Hospital Epidemiology, Baden, Switzerland

Background: Disentangling the effects of SARS-CoV-2 variants and vaccination on the occurrence of post-acute sequelae of SARS-CoV-2 (PASC) is crucial to estimate and reduce the burden of PASC.

Methods: We performed a cross-sectional analysis (May/June 2022) within a prospective multicenter healthcare worker (HCW) cohort in North-Eastern Switzerland. HCW were stratified by viral variant and vaccination status at time of their first positive SARS-CoV-2 nasopharyngeal swab. HCW without positive swab and with negative serology served as controls. The sum of eighteen self-reported PASC symptoms was modeled with univariable and multivariable negative-binomial regression to analyse the association of mean symptom number with viral variant and vaccination status.

Results: Among 2'912 participants (median age 44 years, 81.3% female), PASC symptoms were significantly more frequent after wild-type infection (estimated mean symptom number 1.12, p<0.001; median time since infection 18.3 months), after Alpha/Delta infection (0.67 symptoms, p<0.001; 6.5 months), and after Omicron BA.1 infections (0.52 symptoms, p=0.005; 3.1 months) compared to uninfected controls (0.39 symptoms). After Omicron BA.1 infection, the estimated mean symptom number was 0.36 for unvaccinated individuals, compared to 0.71 with 1-2 vaccinations (p=0.028) and 0.49 with ≥3 prior vaccinations (p=0.30). Adjusting for confounders, only wild-type (adjusted rate ratio [aRR] 2.81, 95% confidence interval [CI] 2.08-3.83) and Alpha/Delta infection (aRR 1.93, 95% CI 1.10-3.46) were significantly associated with the outcome.

Conclusions: Previous infection with pre-Omicron variants was the strongest risk factor for PASC symptoms among our HCW. Vaccination prior to Omicron BA.1 infection was not associated with a clear protective effect against PASC symptoms in this population.

Keywords. Long-COVID; Post-Acute Sequelae of SARS-CoV-2; healthcare workers; viral variant; vaccination

INTRODUCTION

Post-acute sequelae after SARS-CoV-2 (PASC) or Long COVID represents a significant challenge to healthcare systems [1]. The estimates on the frequency of Long COVID vary greatly, depending on definitions used, geographical region, and time elapsed since infection [2–5]. Omicron, the predominating SARS-CoV-2 variant in 2022, spreads even more efficiently but seems less pathogenic in acute disease [6]. As severity of acute infection has directly been associated with the risk of developing PASC [7,8], this condition might be less common after

Omicron infection compared to previous variants. Indeed, previous data show that compared to previous variants, the risk for PASC is reduced after Omicron [9,10]. Similarly, SARS-CoV-2 vaccination before infection has been associated with reduced risk for PASC after infection with pre-Omicron variants or mixed infections [10–13], whereas there is a scarcity of data looking at PASC after specifically Omicron infections [14]. Furthermore, an important limitation of many previous studies evaluating the burden of PASC is the lack of a control group, which is crucial to correctly attribute the often non-specific PASC symptoms to COVID-19 [15].

In this study, we aimed to compare symptoms compatible with PASC between HCW after infection with different SARS-CoV-2 variants and uninfected, seronegative controls. Also, we assessed the impact of mRNA COVID-19 vaccine on these symptoms.

METHODS

Setting and participants

The ethics committee of Eastern Switzerland approved the study. Written informed consent was obtained. The observational multicenter study included volunteer HCW from nine healthcare networks in Northern/Eastern Switzerland [16]. The study population consisted mostly of participants from a previous HCW cohort, which had been launched in July/August 2020, but also of newly recruited participants (**Supplementary Figure 1**).

Study procedures

Participants from the original cohort were prospectively followed between July/August 2020 and May/June 2022 with questionnaires capturing SARS-CoV-2 positive swabs and vaccinations; also, repetitive SARS-CoV-2 serologies were performed (**Supplementary Figure 2**) [17].

In May/June 2022, the cross-sectional study was performed including SARS-CoV-2 serology and an electronic questionnaire, asking about personal characteristics, risk factors (eg, comorbidities, medications, work type, COVID-19 patient exposure), dates of and acute symptoms associated with previous SARS-CoV-2-positive nasopharyngeal swabs, vaccinations, and PASC symptoms. Participants with multiple positive swabs and those with a first positive swab within 4 weeks or vaccination within 1 week prior to the questionnaire were excluded.

SARS-cov-2 diagnostics

Participants were asked to get tested for SARS-CoV-2 in case of compatible symptoms either by rapid antigen test or polymerase chain reaction, according to national recommendations. Self-reported nasopharyngeal swabs results were validated as previously described [17]. In May/June 2022, participants were screened for anti-spike (anti-S) and anti-nucleocapsid (anti-N) antibodies, to identify pauci-/asymptomatic infection [16]. The Roche Elecsys (Roche Diagnostics, Rotkreuz, Switzerland) electro-chemiluminescence immunoassay was used. For

anti-S, the sensitivity and specificity is 99.9% and 97.9%, respectively [18]; for anti-N, the sensitivity at 18 months after infection is 92% [19].

Definition of viral variant and vaccination status

We used sequencing data from Northeastern Switzerland to infer the most likely viral variant infecting a participant at time of the first positive swab [20]: wild-type infections (February 2020 to January 2021); Alpha variant (February-June 2021); Delta variant (July-December 2021); Omicron variant (B.1.1.529.1; BA.1) (January-June 2022) (**Supplementary Figure 2**). Infections during the Alpha period were merged with the Delta period due to the small number. Participants without previous positive SARS-CoV-2 swab and with negative anti-N in May/June 2022 were considered as uninfected controls. Those without positive SARS-CoV-2 swab but positive anti-N were excluded. Vaccination status was assessed based on self-reported data; >99% of vaccinated participants indicated receipt of either the mRNA-1273 or the BNT162b2 vaccine.

Outcomes

Participants were asked about presence of any of the following symptoms at time of the questionnaire for more than 7 days but not before the pandemic: loss of smell/taste, shortness of breath, chest pain, hair loss, brain fog, tiredness/weakness, skin rash, muscle/limb pain, joint point, headache, nausea/anorexia, dizziness, stomachache, diarrhea, burnout/exhaustion, fever >38° Celsius/fevery feeling, chills, and cough. The main outcome was the total symptom number; individual symptoms were also analyzed.

Additionally, participants answered the 9-item Fatigue Severity Scale (FSS) [21], the 7-item General Anxiety Disorder (GAD-7) score [22], the 9-item Patient Health Questionnaire (PHQ-9) for depression [23], reported their self-rated health (SRH) on a 5-point scale ("poor" to "excellent") [24], and indicated whether they think they would suffer from Long COVID (yes vs. no). If yes, the severity of Long COVID was assessed using the Post-COVID-19 Functional Status Scale (PCFS), a 5-point scale from "no restrictions in daily live" to "severe restrictions" (**Supplementary Table 1**) [25,26].

Statistical analysis (see also supplements)

We used descriptive statistics to compare baseline characteristics between those infected with the wild-type virus, Alpha/Delta variant, Omicron BA.1 variant, and uninfected controls. For the main analysis, mean PASC symptom scores were compared between each of the infected groups and controls, respectively, using univariable negative-binomial models. The same analyses were performed separately by vaccination status: unvaccinated, vaccinated after infection (controls with any vaccination), and vaccinated before infection with ≥1 vaccine dose (controls with any vaccination). Also, we compared the PASC symptom scores to the number of symptoms at time of acute infection.

Second, the frequency of individual symptoms was compared between each of the infected groups and controls, respectively, using logistic regression. This analysis was performed separately for those unvaccinated at time of infection (ie, never vaccinated individuals or vaccination after infection) and those with ≥1 vaccine dose before infection. Controls were uninfected individuals without and with any vaccination, respectively.

Third, we compared the mean symptom score between boosted (≥3 vaccinations at least 7 days before infection) and non-boosted (1-2 vaccinations) compared to unvaccinated (but also infected) participants using negative-binomial models. This analysis was restricted to participants infected in the Delta (without Alpha) and Omicron period, because booster vaccination was not available before.

Multivariable analysis

To assess the independent association of viral variant and vaccination status on symptom number, we used multivariable negative-binomial regression. Potential confounders included baseline health, social determinants, job details, and receipt of any COVID-19 vaccine, which were all included in the model (**Supplementary Table 1**) [7,27]. A complete case analysis was performed.

Sensitivity analyses

To minimize the risk of incorrect group assignment due to undetected earlier SARS-CoV-2 infection, we performed a sensitivity analysis including only individuals with all previous serology data available and excluding those with any positive anti-N before the first positive SARS-CoV-2 swab or before the survey (for controls). Because the variable burnout/exhaustion is similar to tiredness, we excluded burnout in another sensitivity analysis. To account for missing data, we ran a model using multiple imputation.

Additional analyses

Additional outcomes were analyzed between each of the infected group and controls. For this purpose, we used a negative-binomial model (FSS, GAD-7, PHQ-9), logistic regression (self-classification of having Long COVID), and proportional-odds logistic regression (distribution of SRH ratings and PCFS). These analyses were not stratified by vaccination status. This report follows the STROBE reporting guideline.

RESULTS

Study population and SARS-cov-2 infections

Of approximately 19’600 eligible HCW, 3’870 answered the questionnaire in May/June 2022; 2’912 (median age 44 years; 81% women) were included (**Supplementary Figure 1**). SARS-

CoV-2 infection was reported by 1'685 (57.9%) participants: 315 (18.7%) during wild-type, 288 (17.1%) during Alpha/Delta, and 1'082 (64.2%) during Omicron periods. Median time since infection was 18.3 months (interquartile range [IQR] 17.5-19.2) for wild-type, 6.5 (IQR 6.0-9-0) for Alpha/Delta, and 3.1 (IQR 2.6-4.0) for Omicron BA.1 infection. The group of uninfected controls consisted of 1'227 individuals. Of the 2'912 individuals, 2'570 reported baseline characteristics (**Table 1**). Comparing included and excluded HCW with available baseline data, excluded HCW were slightly younger, had less comorbidities, took less medications and had more patient contact (**Supplementary Table 2**).

PASC symptoms and viral variant

The 2'912 participants reported a mean of 0.55 symptoms (including those without symptoms). Mean symptom number in the three groups of previously infected participants significantly exceeded that of uninfected controls (0.39, 95% CI 0.34-0.45), but decreased with recency of the viral variant: 1.12 (95% CI 0.88-1.45, p<0.001) for wild-type, 0.67 (95% 0.51-0.89, p<0.001) for Alpha/Delta, and 0.52 (95% CI 0.45-0.61, p=0.005) for Omicron BA.1 infected participants (**Figure 1a, Supplementary Table 3/Supplementary Figure 3**). Similar decreasing trends across viral variants were observed for unvaccinated participants (**Figure 1b**), for those with vaccination before or after infection (**Figure 1c**), and in the sensitivity analysis considering only participants with previous serologies (**Supplementary Figure 4**). The frequency of PASC symptoms among excluded participants was similar to non-infected controls. This was also true for seropositive HCW without positive swab. However, HCW excluded due to re-infection had a similar symptom score as those with wild-type infection (**Supplementary Figure 5**). The number of symptoms at time of acute infection decreased from wild-type to Omicron BA.1 infection and was associated with the number of PASC symptoms. Even when adjusting for this association, more PASC symptoms were reported after wild-type than after Alpha/Delta and Omicron BA.1 infection (**Supplementary Figure 6**).

At least one symptom was reported by 695 (23.9%) participants: 38.7% for wild-type infected participants (p<0.001), 31.6% for Alpha/Delta (p=0.001), 23.8% for Omicron BA.1 (p=0.001), compared to 18.3% for uninfected individuals. The most commonly reported symptom was tiredness/weakness (14.7% in infected; 9.4% in uninfected participants). Symptoms consistently associated with SARS-CoV-2 infection across all variants were loss of smell/taste and hair loss for unvaccinated (**Supplementary Figure 7**), and loss of smell/taste and brain fog for vaccinated participants (**Supplementary Figure 8**).

PASC symptoms and vaccination status

Among participants infected during the Delta period, vaccinated individuals (+/- booster) reported on average fewer symptoms than unvaccinated participants; however, the differences were not statistically significant. After Omicron BA.1 infection, the mean reported symptom number was 0.49 (95% CI 0.41-0.58, p=0.30) for those with ≥3 prior vaccinations and 0.71 (95%

CI 0.53-0.95, p=0.028) for those with 1-2 previous vaccinations compared to 0.36 (95% CI 0.22-0.60) for unvaccinated individuals (**Figure 2, Supplementary Table 3**).

Multivariable analysis

Excluding those with missing data, we performed multivariable analysis including 2'452 individuals. Infection with the wild-type (adjusted rate ratio [aRR] 2.81, 95% CI 2.08–3.83) and with Alpha/Delta (aRR 1.93, 95% CI 1.10–3.46) were positively associated with the number of symptoms reported, whereas infection during the Omicron period (aRR 1.29, 95% CI 0.69–2.43) and vaccination before infection (aRR 1.27, 95% CI 0.82–1.94) were not. Other variables associated with the outcome were body mass index (BMI) >30m/kg^2 (aRR 1.43, 95% CI 1.08–1.92), having a pre-existing comorbidity (RR 1.35, 95% CI 1.11–1.65), being on any medication (aRR 1.49, 95% CI 1.20–1.86) and cumulative COVID-19 patient contact (aRR 1.11, 95% CI 1.01–1.21) (**Figure 3**, **Supplementary Table 4**). Sensitivity analyses and data imputation showed mostly similar results. However, when including only participants with all previous serology results being negative for anti-N, the effect sizes for viral variants increased slightly, whereas other co-variables, except being on any medication, were no longer associated with the outcome (**Supplementary Table 5**).

Additional analyses

The FSS, the PHQ-9 and the SRH were highest or lowest, respectively, for those after wild-type infection, while no difference was observed between those with Alpha/Delta or Omicron BA.1 infection and controls. For the GAD-7, no difference was observed between groups (**Table 2**). The percentage of participants who considered themselves suffering from Long COVID was substantially higher after wild-type (17.1%, p<0.001), Alpha/Delta (10.4%, p<0.001), and Omicron BA.1 infection (4.8%, p<0.001) compared to controls (0.9%). Those with self-reported Long COVID had a mean of 3.2 (95% CI 2.4–4.4) PASC symptoms compared to 0.41 (95% CI 0.37–0.44) in those without long COVID (p<0.001). Functional impairment in daily live (ie, PCFS score) was similar between groups suffering from Long COVID.

DISCUSSION

Within a well-defined HCW population, we show that the most decisive risk factor for reporting symptoms compatible with PASC is the viral variant causing the primary infection. Participants after wild-type SARS-CoV-2 and Alpha/Delta infections reported the highest numbers, even 18 and 6 months after infection, respectively. In contrast, those at 3 months after Omicron BA.1 infection are only minimally affected compared to uninfected controls. SARS-CoV-2 vaccination including receipt of booster vaccine before Omicron BA.1 infection was not associated with less PASC symptoms.

The viral variant was the most important risk factor associated with the presence of PASC symptoms, even after adjusting for important co-variables, such as age, sex, and BMI. Individuals after wild-type reported significantly more PASC symptoms, had higher fatigue and depression scores and a lower SRH than uninfected controls. This effect is partly related to the higher number of symptoms experienced during acute infection, as shown in our data and by others [7,8]. These findings are particularly worrying considering that wild-type infections occurred a median of 18 months before this survey. Few studies have reported such a long duration of PASC. Persistence of symptoms for 12 months or longer have been reported by several others, both in hospitalized and non-hospitalized populations [28–32]. In addition, some authors have suggested that loss of smell/taste, which was one of the symptoms showing a strong association with PASC in our study, might be a permanent sequela after COVID-19 [33]. Further research aiming at mitigating the PASC burden in those infected early on in the pandemic is urgently needed.

The frequency of Long COVID after infection with the Omicron variant has been reported to be 5% at ≥4 weeks after infection, which is about half compared to the Delta variant [9]. Comparing people infected with Omicron vs. previous variants, 5 vs. 55% reported ≥1 PASC symptom in another study [34]. However, both studies have not included an uninfected control group. In our study, participants after Omicron BA.1 infection still reported more symptoms than uninfected controls. However, we found that many symptoms typically associated with PASC, such as fatigue, exhaustion or muscle/limb pain were slightly or not at all more common after Omicron BA.1 infection compared to uninfected controls. Also, the high prevalence of some of these symptoms in uninfected individuals highlights the importance to consider other causes, besides COVID-19, underlying these symptoms. This includes conditions such as chronic fatigue syndrome/myalgic encephalomyelitis, which have been shown to be often related to other viral infections [35–37]. Importantly, in contrast to participants after wild-type infection, FSS, PHQ-9 and SRH were not any different between Omicron BA.1 infected and controls.

Although numbers were too small to reach statistical significance, vaccination prior to infection with the Delta variant was associated with decreased PASC symptom score. This finding is in line with several other studies, which included at least partly infections from the pre-Omicron period [10–12]. However, regarding the effect of previous vaccination on PASC after Omicron BA.1 infection, our results were ambiguous. Individuals with booster vaccination had a similar symptom score as unvaccinated individuals, but both groups had a lower score compared to those with only 1 or 2 vaccinations (**Figure 2**). These findings contrast results from a study specifically looking at Omicron infections [14], where a positive effect of previous vaccination on risk of PASC was found. In contrast to our study, Nehme *et al*. looked at adult outpatient populations of any age, including people with more severe disease receiving antiviral treatment. Also, partly vaccinated individuals were regarded as unvaccinated. We believe that further study is needed to better understand these contradicting results.

Important strengths of our study are the clearly defined infection and vaccine status of every individual study participant and the relatively large share of hitherto unvaccinated participants. This enabled us to adequately disentangle the effects of viral variant and of SARS-CoV-2 vaccination on the occurrence of PASC symptoms, a task which is increasingly becoming unrealizable due to high vaccination and infection rates [38]. The probably most important strength is the inclusion of uninfected controls using (repetitive) SARS-CoV-2 serologies. Many previous studies on Long COVID either completely lacked a control group [15], relied on electronic health record data for their case definition [39], and/or were unable to differentiate between truly non-infected and asymptomatically infected individuals [39,40].

Our study has limitations. First, definition of viral variants was based on population data and not on individual sequencing data. This might have led to misclassifications of viral variants in any direction and therefore to an underestimation of the observed differences. Second, the choice of our outcome definition can be debated. The large number of symptoms and the less strict time criterion (symptoms had to be present at least for 7 days) compared to other studies might overestimate, whereas the lack of some symptoms (eg, palpitations) could underestimate the PASC prevalence. Third, our data lack generalizability; ie, Omicron BA.1 infections occurring in the elderly or more comorbid populations, where acute infection might manifest itself more severely, might confer an increased risk of PASC. Also, our results are not necessarily applicable to newer Omicron variants. Fourth, we relied on anti-N negativity to exclude previous infection. We acknowledge that this definition may have missed a certain proportion of infected individuals due to lack of seroconversion or waning titers over time [19]. By considering both criteria, anti-N negativity and lack of positive swab, we think that our approach of defining controls is reasonable. Furthermore, results of the sensitivity analysis, which also considered previous serology results and excluded those with waning immunity over time, largely confirmed our main findings. Finally, PASC symptoms among only seropositive participants (which were excluded from the main analysis) were similar to controls, confirming our previous finding that asymptomatic SARS-CoV-2 infection is hardly associated with Long COVID [7].

To conclude, these data suggest that in a HCW population of predominantly young, healthy Caucasian females, individuals infected with the wild-type virus still report symptoms compatible with PASC after a median of 18 months, whereas the burden at 3 months after Omicron BA.1 infection is considerably lower and comparable to uninfected individuals. Vaccination prior to Omicron BA.1 infection was not associated with less PASC symptoms. Future research should primarily address the needs of individuals infected early on in the pandemic, whereas in individuals suffering from symptoms compatible with PASC after Omicron BA.1 infection, other aetiologies besides COVID-19 should be actively sought.

NOTES

Acknowledgments: We thank the participants of the SURPRISE study and the members of the study group (in alphabetical order): Ulrike Besold, MD (Geriatric Clinic St. Gallen), Angela Brucher, MD (Psychiatry Services South, St. Gallen), Alexia Cusini, MD (Cantonal Hospital Graubünden), Thomas Egger (Cantonal Hospital St. Gallen), Andrée Friedl, MD (Cantonal Hospital Baden), Stephan Goppel, MD (Psychiatry Services North, St. Gallen), Fabian Grässli, MSc (Cantonal Hospital St. Gallen), Christian R. Kahlert, MD (Children's Hospital of Eastern Switzerland, St. Gallen), Joelle Keller (Hirslanden Clinic Zurich), Simone Kessler (Cantonal Hospital St. Gallen), Philipp Kohler, MD MSc (Cantonal Hospital St. Gallen), Stefan P. Kuster, MD MSc (Cantonal Hospital St. Gallen), Onicio Leal, PhD (University of Zurich), Eva Lemmenmeier, MD (Clienia Littenheid), Allison McGeer, MD MSc (Mount Sinai Hospital, Toronto), Dorette Meier Kleeb, MD (Cantonal Hospital Baden), Elisabeth Möller (Clienia Littenheid), J. Carsten Möller, MD (Clinic Zihlschlacht), Maja F. Müller (Hirslanden Clinic Zurich), Vaxhid Musa (Cantonal Hospital St. Gallen), Manuela Ortner (Rheintal Werdenberg Sarganserland Hospital Group, Grabs), Philip Rieder, PhD (Hirslanden Clinic Zurich), Lorenz Risch, MD PhD (Laboratory Risch Buchs), Markus Ruetti, MD (Fuerstenland Toggenburg Hospital Group Wil), Matthias Schlegel, MD (Cantonal Hospital St. Gallen), Hans-Ruedi Schmid, PhD (Cantonal Hospital Baden), Reto Stocker, MD (Hirslanden Clinic Zurich), Pietro Vernazza, MD (Cantonal Hospital St. Gallen), Matthias von Kietzell MD (Clinic Stephanshorn St. Gallen), Danielle Vuichard-Gysin, MD MSc (Thurgau Hospital Group Muensterlingen), and Benedikt Wiggli, MD (Cantonal Hospital Baden).

Funding: This work was supported by the Swiss National Sciences Foundation (grant number 31CA30_196544; grant number PZ00P3_179919 to PK), the Federal Office of Public Health (grant number 20.008218/421-28/1), and the research fund of the Cantonal Hospital of St. Gallen. DV-G reports non-financial support from Roche Diagnostics (Switzerland) AG. The company provided the Elecsys anti-SARS CoV-2 assays and additional ancillary products to the Thurgau Hospital Group (one of the study sites). Funders played no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interests: AM has received Grant funding outside of the current work from Pfizer, SanofiPasteur, and Merck (paid to institution), consulting fees from Sienna Senior Living (paid to author), as well as Honoraria for advisory boards, webinars, and/or DSMB membership for AstraZeneca, Biogen, GlaxoSmithKline, Janssen, Medicago, Merck, Moderna, Novavax, Pfizer, and SanofiPasteur. AM also received travel support from Moderna. The authors have no other conflicts of interest to declare.

REFERENCES

1. Phillips S, Williams MA. Confronting Our Next National Health Disaster — Long-Haul Covid. N Engl J Med **2021**; 385:577–579.
2. Nasserie T, Hittle M, Goodman SN. Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review. JAMA Netw Open **2021**; 4:e2111417.
3. Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global Prevalence of Post-Coronavirus Disease 2019 (COVID-19) Condition or Long COVID: A Meta-Analysis and Systematic Review. J Infect Dis **2022**; 226:1593–1607.
4. Global Burden of Disease Long COVID Collaborators. Estimated Global Proportions of Individuals With Persistent Fatigue, Cognitive, and Respiratory Symptom Clusters Following Symptomatic COVID-19 in 2020 and 2021. JAMA **2022**; Available at: https://doi.org/10.1001/jama.2022.18931. Accessed 18 October 2022.
5. Peter RS, Nieters A, Kräusslich H-G, et al. Post-acute sequelae of covid-19 six to 12 months after infection: population based study. BMJ **2022**; 379:e071050.
6. Nyberg T, Ferguson NM, Nash SG, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. Lancet Lond Engl **2022**; 399:1303–1312.
7. Strahm C, Seneghini M, Güsewell S, et al. Symptoms compatible with long-COVID in healthcare workers with and without SARS-CoV-2 infection - results of a prospective multicenter cohort. Clin Infect Dis Off Publ Infect Dis Soc Am **2022**; :ciac054.
8. Bahmer T, Borzikowsky C, Lieb W, et al. Severity, predictors and clinical correlates of post-COVID syndrome (PCS) in Germany: A prospective, multi-centre, population-based cohort study. EClinicalMedicine **2022**; 51:101549.
9. Antonelli M, Pujol JC, Spector TD, Ourselin S, Steves CJ. Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2. The Lancet **2022**; 399:2263–2264.
10. Azzolini E, Levi R, Sarti R, et al. Association Between BNT162b2 Vaccination and Long COVID After Infections Not Requiring Hospitalization in Health Care Workers. JAMA **2022**; 328:676–678.
11. Al-Aly Z, Bowe B, Xie Y. Long COVID after breakthrough SARS-CoV-2 infection. Nat Med **2022**; 28:1461–1467.
12. Antonelli M, Penfold RS, Merino J, 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. Lancet Infect Dis **2022**; 22:43–55.
13. Perlis RH, Santillana M, Ognyanova K, et al. Prevalence and Correlates of Long COVID Symptoms Among US Adults. JAMA Netw Open **2022**; 5:e2238804.
14. Nehme M, Vetter P, Chappuis F, Kaiser L, Guessous I, the CoviCare Study team. Prevalence of post-COVID Condition 12 Weeks after Omicron Infection Compared to Negative Controls and Association with Vaccination Status. Clin Infect Dis **2022**; :ciac947.
15. Amin-Chowdhury Z, Ladhani SN. Causation or confounding: why controls are critical for characterizing long COVID. Nat Med **2021**; 27:1129–1130.

16. Kahlert CR, Persi R, Güsewell S, et al. Non-occupational and occupational factors associated with specific SARS-CoV-2 antibodies among hospital workers - A multicentre cross-sectional study. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis **2021**; 27:1336–1344.
17. Kohler P, Güsewell S, Seneghini M, et al. Impact of baseline SARS-CoV-2 antibody status on syndromic surveillance and the risk of subsequent COVID-19—a prospective multicenter cohort study. BMC Med **2021**; 19:270.
18. Riester E, Findeisen P, Hegel JK, et al. Performance evaluation of the Roche Elecsys Anti-SARS-CoV-2 S immunoassay. J Virol Methods **2021**; 297:114271.
19. Nakagama Y, Komase Y, Kaku N, et al. Detecting Waning Serological Response with Commercial Immunoassays: 18-Month Longitudinal Follow-up of Anti-SARS-CoV-2 Nucleocapsid Antibodies. Microbiol Spectr 10:e00986-22.
20. Federal Office of Public Health. Virus variants overview. Last accessed April 1st 2021. Available at: https://www.covid19.admin.ch/en/epidemiologic/virus-variants.
21. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The Fatigue Severity Scale: Application to Patients With Multiple Sclerosis and Systemic Lupus Erythematosus. Arch Neurol **1989**; 46:1121–1123.
22. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med **2006**; 166:1092–1097.
23. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9. J Gen Intern Med **2001**; 16:606–613.
24. Idler EL, Benyamini Y. Self-rated health and mortality: a review of twenty-seven community studies. J Health Soc Behav **1997**; 38:21–37.
25. Klok FA, Boon GJAM, Barco S, et al. The Post-COVID-19 Functional Status scale: a tool to measure functional status over time after COVID-19. Eur Respir J **2020**; 56:2001494.
26. Machado FVC, Meys R, Delbressine JM, et al. Construct validity of the Post-COVID-19 Functional Status Scale in adult subjects with COVID-19. Health Qual Life Outcomes **2021**; 19:40.
27. Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of long COVID. Nat Med **2021**; 27:626–631.
28. Pazukhina E, Andreeva M, Spiridonova E, et al. Prevalence and risk factors of post-COVID-19 condition in adults and children at 6 and 12 months after hospital discharge: a prospective, cohort study in Moscow (StopCOVID). BMC Med **2022**; 20:244.
29. Seeßle J, Waterboer T, Hippchen T, et al. Persistent Symptoms in Adult Patients 1 Year After Coronavirus Disease 2019 (COVID-19): A Prospective Cohort Study. Clin Infect Dis Off Publ Infect Dis Soc Am **2022**; 74:1191–1198.
30. Haddad A, Janda A, Renk H, et al. Long COVID symptoms in exposed and infected children, adolescents and their parents one year after SARS-CoV-2 infection: A prospective observational cohort study. EBioMedicine **2022**; 84:104245.
31. Fjelltveit EB, Blomberg B, Kuwelker K, et al. Symptom Burden and Immune Dynamics 6 to 18 Months Following Mild Severe Acute Respiratory Syndrome Coronavirus 2 Infection (SARS-CoV-2): A Case-control Study. Clin Infect Dis **2022**; :ciac655.
32. Helmsdal G, Hanusson KD, Kristiansen MF, et al. Long COVID in the Long Run—23-Month Follow-up Study of Persistent Symptoms. Open Forum Infect Dis **2022**; 9:ofac270.
33. Mendes Paranhos AC, Nazareth Dias ÁR, Machado da Silva LC, et al. Sociodemographic Characteristics and Comorbidities of Patients With Long COVID and Persistent Olfactory Dysfunction. JAMA Netw Open **2022**; 5:e2230637.

34. Morioka S, Tsuzuki S, Suzuki M, et al. Post COVID-19 condition of the Omicron variant of SARS-CoV-2. J Infect Chemother Off J Jpn Soc Chemother **2022**; 28:1546–1551.
35. Magnus P, Gunnes N, Tveito K, et al. Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is associated with pandemic influenza infection, but not with an adjuvanted pandemic influenza vaccine. Vaccine **2015**; 33:6173–6177.
36. Petersen I, Thomas JM, Hamilton WT, White PD. Risk and predictors of fatigue after infectious mononucleosis in a large primary-care cohort. QJM Mon J Assoc Physicians **2006**; 99:49–55.
37. Choutka J, Jansari V, Hornig M, Iwasaki A. Unexplained post-acute infection syndromes. Nat Med **2022**; 28:911–923.
38. Adriaenssens N, Scholtes B, Bruyndonckx R, et al. Prevalence, incidence and longevity of antibodies against SARS-CoV-2 among primary healthcare providers in Belgium: a prospective cohort study with 12 months of follow-up. BMJ Open **2022**; 12:e065897.
39. Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. PLoS Med **2021**; 18:e1003773.
40. Robertson MM, Qasmieh SA, Kulkarni SG, et al. The Epidemiology of Long COVID in US Adults. Clin Infect Dis **2022**; :ciac961.

TABLES

Table 1. Characteristics of 2'570 participants answering the study questionnaire by time of first positive SARS-CoV-2 swab.

Baseline characteristics	Wild-type infection *n* = 283	Alpha/Delta infection *n* = 268	Omicron infection *n* = 963	No infection *n* = 1056	*p*-value[b]
Age (years, median and IQR)	44 (33-54)	42 (32-49)	42 (34-52)	48 (37-56)	<0.001
Male gender	54 (19.1%)	47 (17.5%)	173 (18.0%)	206 (19.5%)	0.787
BMI >30 kg/m^2	40 (14.1%)	23 (8.6%)	97 (10.1%)	134 (12.7%)	0.055
Caucasian ethnicity	275 (97.2%)	259 (96.6%)	946 (98.2%)	1024 (97.0%)	0.442
Child ≤ 6 years in household	36 (12.7%)	36 (13.4%)	150 (15.6%)	91 (8.6%)	<0.001
Any comorbidity	143 (50.5%)	116 (43.3%)	467 (48.5%)	514 (48.7%)	0.343
Pollen allergy	86 (30.4%)	77 (28.7%)	322 (33.4%)	331 (31.3%)	0.438
Other comorbidities	86 (30.4%)	58 (21.6%)	254 (26.4%)	299 (28.3%)	0.085
Any medication	97 (34.3%)	66 (24.6%)	271 (28.1%)	335 (31.7%)	0.026
Active smoking	41 (14.5%)	44 (16.4%)	154 (16.0%)	200 (18.9%)	0.186
Alcohol (>1 drink per week)	113 (39.9%)	103 (38.4%)	424 (44.0%)	419 (39.7%)	0.089
Profession					<0.001
Nurse	175 (61.8%)	149 (55.6%)	459 (47.7%)	476 (45.1%)	
Physician	27 (9.5%)	23 (8.6%)	127 (13.2%)	163 (15.4%)	
Other	81 (28.6%)	96 (35.8%)	377 (39.1%)	417 (39.5%)	

Cumulative contact duration to COVID-19 patients (minutes, median and IQR)	400 (30-2250)	285 (1-1200)	150 (1-1000)	130 (1-750)	<0.001
Intensive care	52 (18.4%)	32 (11.9%)	133 (13.8%)	140 (13.3%)	0.113
Full-time work (>0.8 FTE)	147 (51.9%)	128 (47.8%)	475 (49.3%)	561 (53.1%)	0.239
Vaccination[a]					<0.001
before infection	0 (0.0%)	165 (61.6%)	876 (91.0%)	0 (0.0%)	
after or without infection	255 (90.1%)	35 (13.1%)	3 (0.3%)	1022 (96.8%)	
no vaccination	28 (9.9%)	68 (25.4%)	84 (8.7%)	34 (3.2%)	

IQR, Interquartile Range; BMI, Body Mass Index; FTE, Full Time Equivalent

[a] Note that numbers are slightly lower than in Figure 1 because 342 individuals only reported data on infections and vaccinations, but no further data.

[b] Global test for the significance of group differences. Kruskal-Wallis test for numeric variables (age, cumulative patient contact duration) and Chi-squared test for categorical variables (all others).

Table 2. Results of additional outcomes by time of first infection (or no infection) among 2'912 participants.

	Wild-type infection *n* = 315	Alpha/Delta infection *n* = 288	Omicron infection *n* = 1082	No infection *n* = 1227
Fatigue severity score, FSS (mean)[a]	22.5**	20.4^{ns}	20.4^{ns}	20.5^{ref}
GAD-7 anxiety score (mean)	2.8^{ns}	2.0^{ns}	2.3^{ns}	2.4^{ref}
PHQ-9 depression score (mean)	3.6**	2.5^{ns}	2.7^{ns}	3.0^{ref}
Self-reported health, SRH (mean)[a]	4.18*	4.36*	4.30^{ns}	4.30^{ref}
1 (Very bad)	0.6%	1.0%	0.5%	0.3%
2 (Bad)	0.3%	0.3%	0.7%	0.4%
3 (Average)	14.3%	7.6%	8.1%	8.0%
4 (Good)	49.5%	43.4%	49.5%	51.4%
5 (Very good)	35.2%	47.6%	41.1%	39.9%
Having long COVID (n [%])[a]	54 (17.1%)***	30 (10.4%)***	52 (4.8%)***	11 (0.9%)^{ref}
PCFS (mean)[a]	2.25^{ns}	2.14*	2.32^{ns}	2.73^{ref}
1 (No restrictions)[b]	14.8%	36.7%	17.3%	0%
2 (Negligible restrictions)[b]	53.7%	33.3%	44.2%	45.5%
3 (Restrictions, able to fulfill daily activities)[b]	24.1%	13.3%	26.9%	36.4%
4 (Restrictions, not able to fulfill daily activities)[b]	7.4%	16.7%	11.5 %	18.2%
5 (Severe restrictions)[b]	0%	0%	0%	0%

[a] Asterisks indicate statistically significant differences in outcome distribution between each infected group and uninfected controls, as given by p-values from Wald tests on the coefficients of a negative binomial model for FSS, proportional-odds logistic regression for SRH and PCFS, and ordinary logistic regression for having long COVID (***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$; ^{ns}, $p \geq 0.05$, ^{ref}, reference group).

[b] Percentages refer to the number of participants with self-reported long COVID

GAD-7, Generalized Anxiety Disorder 7; PHQ-9, Patient Health Questionnaire 9; PCFS, Post-COVID-19 Functional Status Scale (assessed only by those with self-reported long COVID)

FIGURE LEGENDS

Figure 1. Cross-sectional analysis of May/June 2022. Means and 95% confidence intervals of post-acute sequelae of SARS-CoV-2 symptom score by vaccination status and viral variant dominating at time of infection. Asterisks above bars indicate statistical significance in reference to uninfected participants with same vaccination status, respectively, as obtained through Wald tests on coefficients of negative binomial models with uninfected participants as reference group (***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$; ^{ns}, $p \geq 0.05$). N at the bottom of the bars designate number of participants. Note: there were no vaccinations before wild-type infection and only three individuals vaccinated after Omicron BA.1 infection (not shown in panel C).

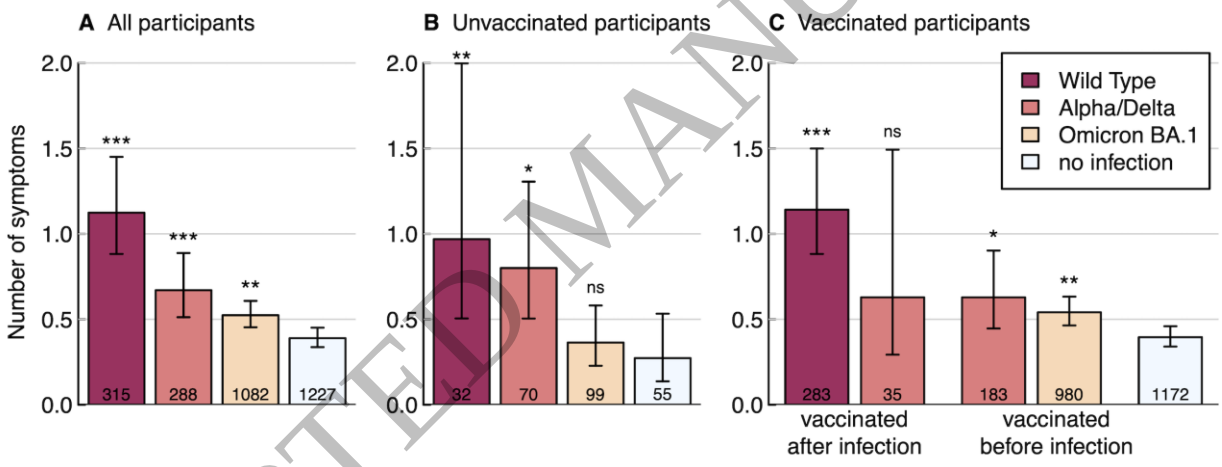


Figure 2. Means and 95% confidence intervals of post-acute sequelae of SARS-CoV-2 symptom score in relation to number of vaccine doses received before positive swab. Left: Participants after infection in Delta period (1 July 1st to December 31th 2021). Right: Participants after infection in Omicron BA.1 period (January 1st to June 30th 2022). Asterisks above bars indicate statistical significance in reference to unvaccinated participants infected in the same period, respectively, as obtained through Wald tests on coefficients of negative binomial models with group "none" as reference (*, $p < 0.05$; ^{ns}, $p \geq 0.05$).

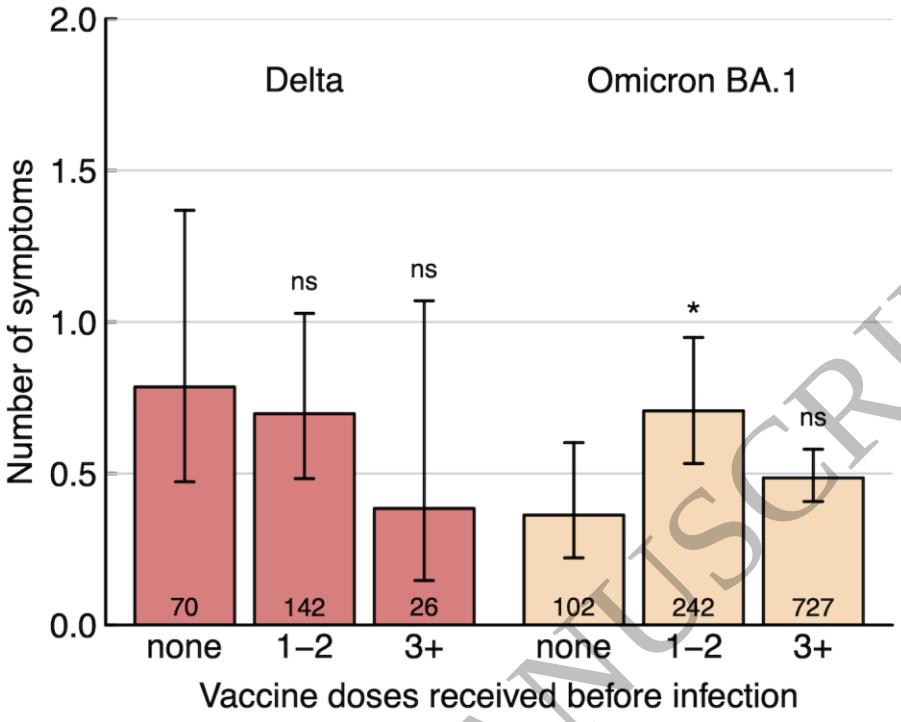
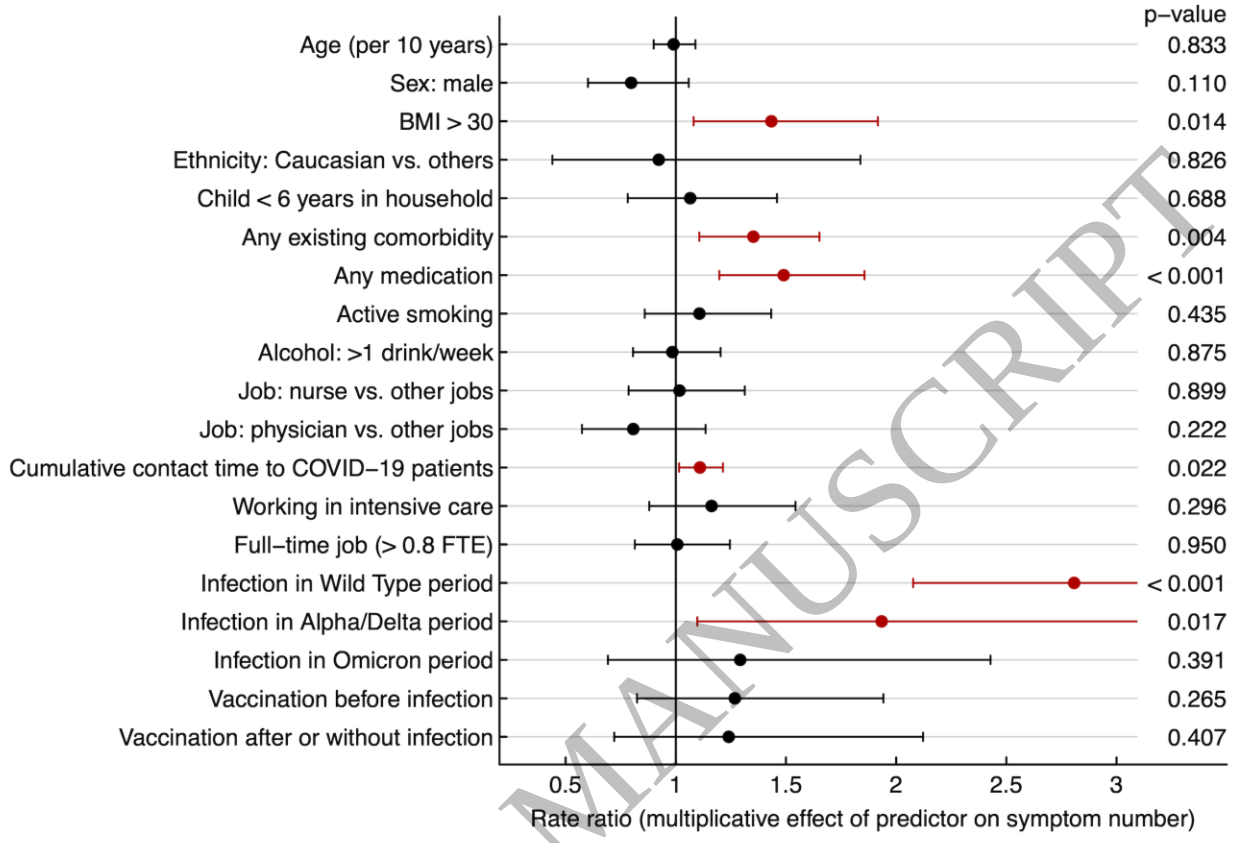
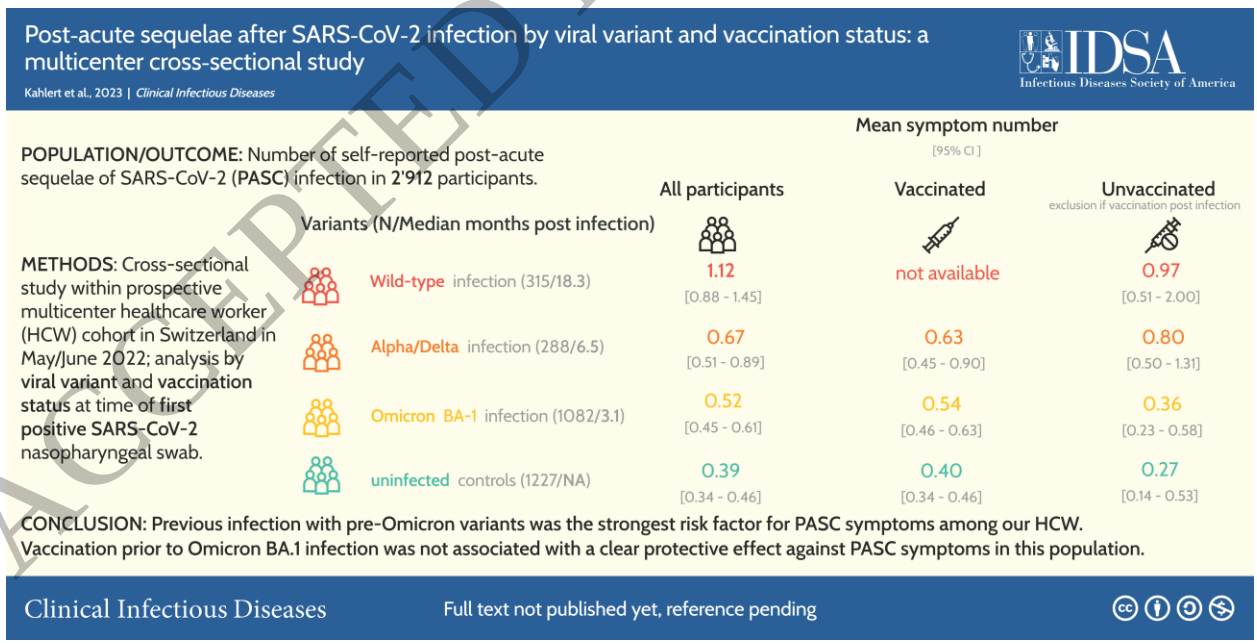


Figure 3. Results of multivariable negative binomial model regarding number of symptoms compatible with post-acute sequelae of SARS-CoV-2. Predictors positively associated with symptom number (i.e. 95% confidence interval for rate ratio entirely above 1) are highlighted in

red. For numeric values of point estimates and 95% confidence intervals see Table S4.





Graphical Abstract