

## MAJOR ARTICLE

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

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**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  $\geq 3$  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 pain, 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  $\geq 1$  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  $\geq 1$  vaccine dose before infection. Controls were uninfected individuals without and with any vaccination, respectively.

Third, we compared the mean symptom score between boosted ( $\geq 3$  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% CI 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  $\geq 3$  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)  $>30\text{m/kg}^2$  (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  $\geq 4$  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  $\geq 1$  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 asymptotically 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

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## 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 <i>n</i> = 283	Alpha/Delta infection <i>n</i> = 268	Omicron infection <i>n</i> = 963	No infection <i>n</i> = 1056	<i>p</i> -value <sup>b</sup>
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 <sup>2</sup>	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 <sup>a</sup>					<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

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

<sup>b</sup> 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.**

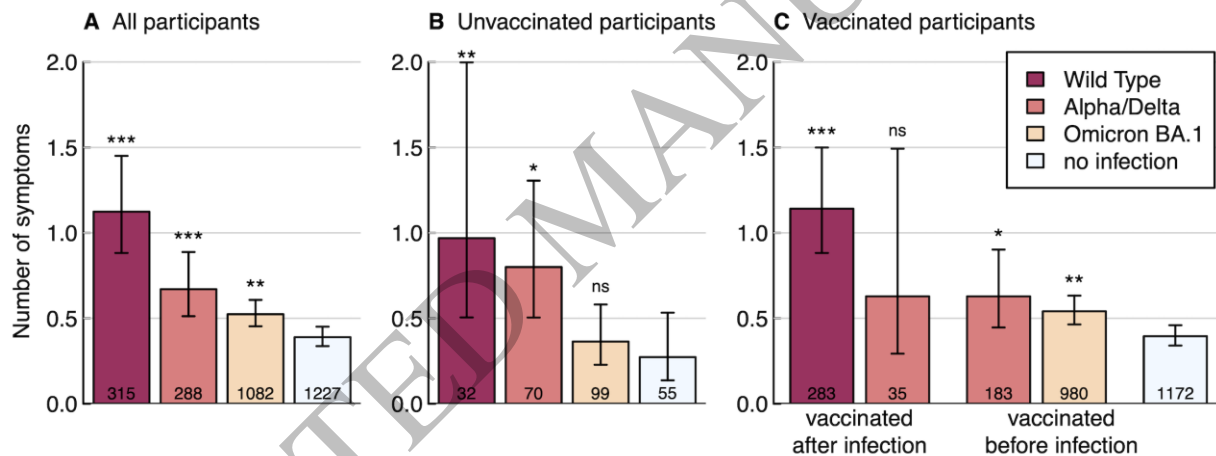
	Wild-type infection <i>n</i> = 315	Alpha/Delta infection <i>n</i> = 288	Omicron infection <i>n</i> = 1082	No infection <i>n</i> = 1227
Fatigue severity score, FSS (mean) <sup>a</sup>	22.5**	20.4 <sup>ns</sup>	20.4 <sup>ns</sup>	20.5 <sup>ref</sup>
GAD-7 anxiety score (mean)	2.8 <sup>ns</sup>	2.0 <sup>ns</sup>	2.3 <sup>ns</sup>	2.4 <sup>ref</sup>
PHQ-9 depression score (mean)	3.6**	2.5 <sup>ns</sup>	2.7 <sup>ns</sup>	3.0 <sup>ref</sup>
Self-reported health, SRH (mean) <sup>a</sup>	4.18*	4.36*	4.30 <sup>ns</sup>	4.30 <sup>ref</sup>
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 ( <i>n</i> [%]) <sup>a</sup>	54 (17.1%)***	30 (10.4%)***	52 (4.8%)***	11 (0.9%) <sup>ref</sup>
PCFS (mean) <sup>a</sup>	2.25 <sup>ns</sup>	2.14*	2.32 <sup>ns</sup>	2.73 <sup>ref</sup>
1 (No restrictions) <sup>b</sup>	14.8%	36.7%	17.3%	0%
2 (Negligible restrictions) <sup>b</sup>	53.7%	33.3%	44.2%	45.5%
3 (Restrictions, able to fulfill daily activities) <sup>b</sup>	24.1%	13.3%	26.9%	36.4%
4 (Restrictions, not able to fulfill daily activities) <sup>b</sup>	7.4%	16.7%	11.5%	18.2%
5 (Severe restrictions) <sup>b</sup>	0%	0%	0%	0%

<sup>a</sup> 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; <sup>ns</sup>, *p* ≥ 0.05, <sup>ref</sup>, reference group).

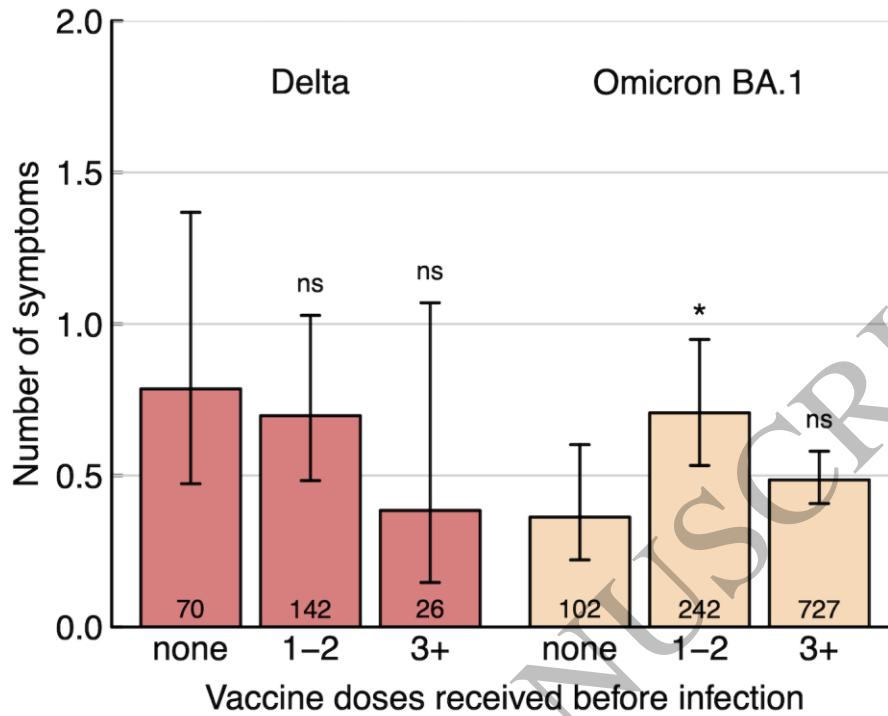
<sup>b</sup> Percentages refer to the number of participants with self-reported long COVID  
 GAD-7, Generalized Anxiety Disorder 7; PHQ-9, Patient Health Questionnaire 9; PCFS, Post-COVID-19  
 Functional Status Scale (assessed only by those with self-reported long COVID)

## 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).



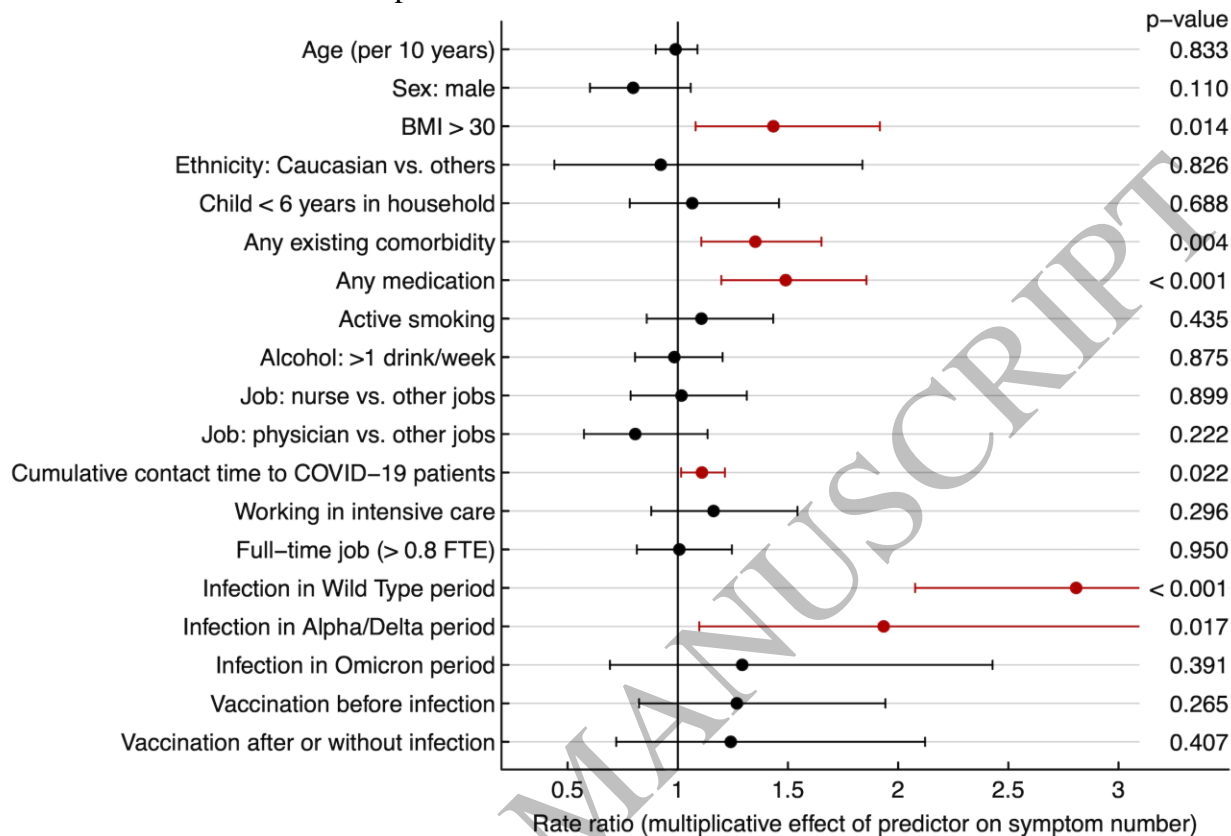
**Figure 2.** Means and 95% confidence intervals of post-acute sequelae of SARS-CoV-2 symptom score in relation to number of vaccine doses received before positive swab. Left: Participants after infection in Delta period (1 July 1<sup>st</sup> to December 31<sup>th</sup> 2021). Right: Participants after infection in Omicron BA.1 period (January 1<sup>st</sup> to June 30<sup>th</sup> 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.



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

Kahlert et al., 2023 | *Clinical Infectious Diseases*



Variants (N/Median months post infection)	Mean symptom number [95% CI]		
	All participants	Vaccinated	Unvaccinated <small>exclusion if vaccination post infection</small>
Wild-type infection (315/18.3)	1.12 [0.88 - 1.45]	not available	0.97 [0.51 - 2.00]
Alpha/Delta infection (288/6.5)	0.67 [0.51 - 0.89]	0.63 [0.45 - 0.90]	0.80 [0.50 - 1.31]
Omicron BA-1 infection (1082/3.1)	0.52 [0.45 - 0.61]	0.54 [0.46 - 0.63]	0.36 [0.23 - 0.58]
uninfected controls (1227/NA)	0.39 [0.34 - 0.46]	0.40 [0.34 - 0.46]	0.27 [0.14 - 0.53]

**CONCLUSION:** 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.

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Full text not published yet, reference pending



### Graphical Abstract