2-2-2023

Presence of Symptoms 6 Weeks After COVID-19 Among Vaccinated and Unvaccinated US Healthcare Personnel: A Prospective Cohort Study

Nicholas M. Mohr

Ian D. Plumb

Kari K. Harland

Tamara Pilishvili

Katherine E. Fleming-Dutra

See next page for additional authors

Authors

Nicholas M. Mohr, Ian D. Plumb, Kari K. Harland, Tamara Pilishvili, Katherine E. Fleming-Dutra, Anusha Krishnadasan, Karin F. Hoth, Sharon H. Saydah, Zachary Mankoff, John P. Haran, Melissa Briggs-Hagen, Eliezer Santos León, and David A. Talan

BMJ Open

Presence of symptoms 6 weeks after COVID-19 among vaccinated and unvaccinated US healthcare personnel: a prospective cohort study

Nicholas M Mohr ,[1,2] Ian D Plumb,[3] Kari K Harland,[1] Tamara Pilishvili,[3] Katherine E Fleming-Dutra,[3] Anusha Krishnadasan,[4] Karin F Hoth,[5] Sharon H Saydah,[3] Zachary Mankoff,[6] John P Haran,[7] Melissa Briggs-Hagen,[3] Eliezer Santos León,[1] David A Talan,[4,8] Project PREVENT Network

To cite: Mohr NM, Plumb ID, Harland KK, *et al*. Presence of symptoms 6 weeks after COVID-19 among vaccinated and unvaccinated US healthcare personnel: a prospective cohort study. *BMJ Open* 2023;**13**:e063141. doi:10.1136/bmjopen-2022-063141

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-063141).

NMM and IDP are joint first authors.

Received 25 March 2022
Accepted 12 January 2023

For numbered affiliations see end of article.

Correspondence to
Dr Nicholas M Mohr;
nicholas-mohr@uiowa.edu

ABSTRACT

Objectives Although COVID-19 vaccines offer protection against infection and severe disease, there is limited information on the effect of vaccination on prolonged symptoms following COVID-19. Our objective was to determine differences in prevalence of prolonged symptoms 6 weeks after onset of COVID-19 among healthcare personnel (HCP) by vaccination status, and to assess differences in timing of return to work.

Design Cohort analysis of HCP with COVID-19 enrolled in a multicentre vaccine effectiveness study. HCP with COVID-19 between December 2020 and August 2021 were followed up 6 weeks after illness onset.

Setting Health systems in 12 US states.

Participants HCP participating in a vaccine effectiveness study were eligible for inclusion if they had laboratory-confirmed symptomatic SARS-CoV-2 with mRNA vaccination (symptom onset ≥14 days after two doses) or no prior vaccination. Among 681 eligible participants, 419 (61%) completed a follow-up survey to assess symptoms reported 6 weeks after illness onset.

Exposures Two doses of a COVID-19 mRNA vaccine compared with no COVID-19 vaccine.

Main outcome measures Prevalence of symptoms 6 weeks after onset of COVID-19 illness and days to return to work.

Results Among 419 HCP with COVID-19, 298 (71%) reported one or more COVID-like symptoms 6 weeks after illness onset, with a lower prevalence among vaccinated participants compared with unvaccinated participants (60.6% vs 79.1%; adjusted risk ratio 0.70, 95% CI 0.58 to 0.84). Following their illness, vaccinated HCP returned to work a median 2.0 days (95% CI 1.0 to 3.0) sooner than unvaccinated HCP (adjusted HR 1.37, 95% CI 1.04 to 1.79).

Conclusions Receipt of two doses of a COVID-19 mRNA vaccine among HCP with COVID-19 illness was associated with decreased prevalence of COVID-like symptoms at 6 weeks and earlier return to work.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study reports a cohort of healthcare personnel with robust symptom inventories at 6 weeks and validated testing and vaccination data.
⇒ The cohort design is an observational study that could be open to residual confounding.
⇒ Our study period was conducted before booster doses.

INTRODUCTION

SARS-CoV-2 infection leads to a wide spectrum of illness from upper or lower respiratory tract infection to extrapulmonary manifestations including multiorgan complications.[1] Even with relatively mild initial illness, a proportion of individuals develop persistent or new symptoms that have been referred to as postacute sequelae of SARS-CoV-2 infection or 'long COVID'.[2 3] These sequelae reflect underlying pathology that is only partially elucidated.[3 4]

Prolonged symptoms occur in both hospitalised and non-hospitalised patients with COVID-19,[5] and commonly include fatigue, dyspnoea and neurocognitive deficits. Development of prolonged symptoms is more likely if acute illness is more severe.[6] Whether or not long-term sequelae occur, recovery of COVID-19 symptoms frequently takes several weeks and can limit return to usual activities.[6 7] For healthcare personnel (HCP), a return to health and work is important both personally and to maintain health system capacity.[8]

COVID-19 vaccination might limit the risk of a prolonged recovery from COVID-19 through several mechanisms: preventing COVID-19 infection, limiting the severity of acute illness through vaccine-mediated immunity and affecting the ongoing immune response even after acute infection. In a case series of 39 infections among healthcare workers vaccinated with two doses, symptoms

at 6 weeks were common.[9] Another study of self-reported vaccination status and symptoms among the general public found that COVID-19 symptoms 4 weeks after infection were less prevalent among the vaccinated.[10] An analysis of electronic medical record data suggested that vaccination might also prevent other postacute sequelae such as cardiovascular events, coagulation disorders, pulmonary disorders and other conditions associated with prolonged recovery.[11]

In this study, our primary objective was to compare the prevalence of symptoms 6 weeks after initial COVID-19 illness among HCP by vaccination status before their infection. We selected 6 weeks during study design in 2020 as the time period after which we anticipated most COVID-19 symptoms would have resolved, and we chose to analyse that time as an indicator of prolonged recovery from acute illness and a potential precursor of longer term symptoms.[6] We hypothesised that symptoms would be less common after 6 weeks among the vaccinated group because the initial illness among vaccine breakthrough cases is generally less severe, and severity of illness is one predictor of the likelihood of prolonged symptoms.[12 13] We conducted a secondary analysis to evaluate recovery from COVID-19 by assessing whether it took longer to return to work if unvaccinated.

METHODS

Study design, data collection and population

As part of the Preventing Emerging Infections through Vaccine Effectiveness Testing Project (Project PREVENT), we enrolled HCP who were working on-site at participating academic medical centres and who had been tested for SARS-CoV-2 infection for symptoms that started between 28 December 2020 and 26 August 2021 (prior to emergence of the Omicron SARS-CoV-2 variant). Characteristics of the 15 participating sites are summarised in online supplemental table S1, and details of study protocols and forms for the parent study are available online.[14] PREVENT sites and other platforms contributed to vaccine effectiveness analyses that have been reported previously.[15 16] This report satisfies the Strengthening the Reporting of Observational Studies in Epidemiology criteria (online supplemental table S2).[17]

For this cohort substudy, we included HCP enrolled in PREVENT sites with symptomatic SARS-CoV-2 infection (COVID-19), defined as a positive SARS-CoV-2 nucleic acid amplification test or antigen test and consistent symptoms (as listed in online supplemental table S3) within 14 days before or after the positive test. Participants provided data by electronic surveys or interviews (online, by phone or in person). Each participant completed an enrolment survey 14–60 days after his/her positive test and was offered a follow-up survey from 6 weeks (42 days) after symptom onset (or at the time of enrolment if later than 42 days) to determine symptoms 6 weeks after the positive test. We excluded participants from the analysis who had partial vaccination, had received a non-mRNA COVID-19 vaccine, did not have available vaccination records, did not complete the baseline survey within 60 days or did not complete the follow-up survey by 10 weeks after symptom onset. Only preillness vaccinations were included in our analysis. During the period of analysis, no participants had received more than two vaccine doses.

Definitions and data collection

The 6-week follow-up survey included questions on the presence of a variety of symptoms that we categorised into three overlapping groups. We defined *COVID-like symptoms* to be fever, cough, shortness of breath, chills, fatigue, joint pains or muscle aches, headache, loss of taste or smell, sore throat, sinus congestion, diarrhoea, nausea or vomiting.[18 19] We defined *neurological symptoms* as dizziness, headache, muscle weakness, movement problems, confusion, memory difficulties, concentration problems or loss of taste or smell.[2 20 21] We defined *any 6-week symptoms* as the symptoms listed above or others included in the 6-week survey: trouble sleeping, exercise problems, chest pain or abdominal pain. For each symptom included in the 6-week survey, participants were asked to rate perceived severity as mild, moderate or severe. For participants who responded to the survey later than 6 weeks, we asked them to base responses on symptoms present at 6 weeks.

The study team verified vaccine status and testing results via confirmed records from occupational health clinics, vaccine cards, state registries or medical records as part of the overall study protocol. We considered participants to be unvaccinated if they had not received any COVID-19 vaccine doses and vaccinated if they had received a second dose of a COVID-19 mRNA vaccine ≥14 days prior to the positive test. We considered comorbidities to be present at the time of infection if reported on the survey or identified in medical records from the period of acute illness. We classified participants as having two or more comorbidities (since 2 was the median number of comorbidities in the sample) if they had at least two diagnoses from our predefined list including cardiopulmonary, immunological and mental health-related comorbidities (full list available in online supplemental table S4). Several of these conditions have been identified both as risk factors for severe COVID-19 outcomes and long-term symptoms following COVID-19 illness.[22 23]

As part of the follow-up survey, we asked participants to report the dates when they resumed work. We calculated time to return to work as the number of days from onset of symptoms until the first day at work after illness. None of the participating sites had return-to-work guidance that differed based on vaccination status.

Patient and public involvement

No patients or members of the public were involved in the conception, design or conduct of the study.

Statistical analysis

We defined our primary outcome as the prevalence of COVID-like symptoms at the time of the 6-week follow-up survey. We conducted additional analyses for neurological symptoms and for any 6-week symptoms, and we assessed whether symptoms at 6 weeks were also present within 14 days of the date of the positive test. For assessment of all symptom groups, we performed a sensitivity analysis restricted to symptoms rated by participants as 'moderate' or 'severe', and we also conducted a sensitivity analysis of only symptoms present at both the time of initial illness and also at the 6-week survey (excluding new symptoms developing during the follow-up period). To assess the role of time since vaccination, we conducted a subgroup analysis of those infected within 16 weeks versus those infected after 16 weeks, based on data that vaccine protection wanes after 16 weeks.[16 24] Because of our data validation steps, no data on symptom onset, exposures, outcomes or covariates included in models were missing.

We used multivariable Poisson regression with a sandwich variance estimator to model the relative risk of having symptoms at the 6-week follow-up for complete vaccination compared with no vaccination.[25] In the multivariable model, we included categorical variables of age, race and ethnicity, and comorbidities selected a priori. Comorbidities were represented in a dichotomous variable of two or more comorbidities at baseline to indicate whether chronic illness was present.[26] We included categorical variables for calendar month of illness and number of weeks from symptom onset and follow-up survey completion to account for temporal changes in the prevalence of symptoms. Using Poisson regression, we also calculated the adjusted risk difference as the difference in proportions of participants reporting symptoms in the follow-up survey by vaccination status.[27]

We compared median differences in time to return to work by vaccination status using the Wilcoxon rank-sum test. To compare the rate of return to work by vaccination status, we constructed Kaplan-Meier survival curves and used the log-rank test. We used a Cox proportional hazards model to calculate an adjusted HR (aHR) to compare time to return to work between vaccinated and unvaccinated participants, counting zero day if there were no days off work after symptom onset. We included the same covariates as we did in our multivariable Poisson regression, except for time to follow-up survey response. We assessed Schoenfeld residuals to ensure that the proportional hazards assumption was met.

We compared individual symptoms on the follow-up survey between vaccinated and unvaccinated cohorts using unadjusted prevalence, relative risk and risk difference (defined as the prevalence in vaccinated minus the prevalence in unvaccinated participants).[28]

RESULTS

Among 1012 HCP with laboratory-confirmed COVID-19, 331 were excluded because they were partially vaccinated,

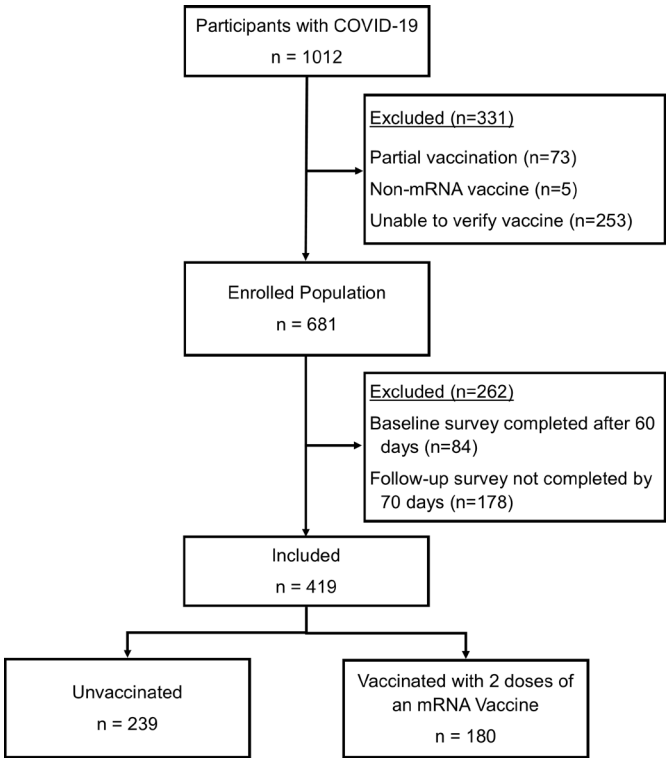


Figure 1 Enrolment of COVID-19 vaccinated and unvaccinated US healthcare personnel.

they received a non-mRNA vaccine or vaccination records were unavailable. Among the remaining 681 HCP, 597 (88%) completed the baseline survey by 60 days, and 419 (72%) also completed the follow-up survey between 42 and 70 days after symptom onset. Those who did not complete the follow-up survey had fewer comorbidities and were less likely to be white non-Hispanic (online supplemental table S5). We included 419 HCP: 180 (43.0%) who were vaccinated with two doses of an mRNA vaccine and 239 (57.0%) who were not vaccinated (figure 1). Among vaccinated participants there was a median of 24.1 weeks (IQR 15.3–28.1 weeks) between the second vaccine dose and the date of illness onset. Most vaccinated participants received the Pfizer-BioNTech vaccine (n=158, 87.8%); 22 (12.2%) received the Moderna vaccine. Vaccination status varied by race/ethnicity and education (table 1, online supplemental table S6). Ninety-five per cent (n=399) had symptoms prior to being tested. Among the 419 participants included in the analysis, 260 (62.1%) provided direct clinical care, and 296 (70.6%) worked in acute care hospitals. Only one participant (0.2%) required hospital admission for acute COVID-19, and no participants died.

Among the participants included in the analysis, baseline surveys were completed at a median of 3.1 weeks after first symptoms (IQR 2.3–4.4) and follow-up surveys were completed at a median of 6.0 weeks after first symptoms (IQR 6.0–6.3). Overall, 298 (71.1%) participants reported at least one COVID-like symptom present at 6 weeks, 236 (56.3%) reported at least one neurological symptom and 318 (75.9%) reported any symptom (figure 2). Among those who reported COVID-like symptoms at 6 weeks,

Table 1 Demographic characteristics and comorbidities of vaccinated and unvaccinated US healthcare personnel with COVID-19

	All participants (n=419) n (%)	Vaccinated (n=180) n (%)	Not vaccinated (n=239) n (%)	P value†
Age group (years)				0.019*
18–29	90 (21.5)	27 (15.0)	63 (26.4)	
30–39	167 (39.9)	73 (40.6)	94 (39.3)	
40–49	85 (20.3)	45 (25.0)	40 (16.7)	
50–64	77 (18.4)	35 (19.4)	42 (17.6)	
Sex				0.342
Male	64 (15.3)	32 (17.8)	32 (13.4)	
Female	352 (84.0)	146 (81.1)	206 (86.2)	
Non-binary	1 (0.2)	1 (0.6)	0	
Missing data	2 (0.5)	1 (0.6)	1 (0.4)	
Race and ethnic group				<0.001*
White, non-Hispanic	303 (72.3)	145 (80.6)	158 (66.1)	
Black, non-Hispanic	47 (11.2)	9 (5.0)	38 (15.9)	
Hispanic or Latino	41 (9.8)	13 (7.2)	28 (11.7)	
Other, non-Hispanic	28 (6.7)	13 (7.2)	15 (6.3)	
Education level				<0.001*
High school or less	25 (6.0)	6 (3.3)	19 (8.0)	
Undergraduate or technical degree	293 (69.9)	109 (60.6)	184 (77.0)	
Graduate or professional degree	101 (24.1)	65 (36.1)	36 (15.1)	
Job classification				<0.001*
Non-clinical	128 (30.5)	46 (25.6)	82 (34.3)	
Physician	20 (4.8)	18 (10.0)	2 (0.8)	
Advanced practice provider	12 (2.9)	10 (5.6)	2 (0.8)	
Nurse/nurse assistant	164 (39.1)	57 (31.7)	107 (44.8)	
Housekeeping	2 (0.5)	0	2 (0.8)	
Other clinical	48 (11.5)	27 (15.0)	21 (8.8)	
Other	45 (10.7)	22 (12.2)	23 (9.6)	
Health insurance				0.004*
Private	385 (91.9)	175 (97.2)	210 (87.9)	
Government	17 (4.1)	3 (1.7)	14 (5.9)	
None	3 (0.7)	0	3 (1.3)	
Unknown	14 (3.3)	2 (1.1)	12 (5.0)	
Presence of two or more comorbidities (see online supplemental table S6 for details)	216 (51.6)	98 (54.4)	118 (49.4)	0.325
Time from symptom onset to baseline (weeks), median (IQR)	3.1 (2.3–4.4)	3.0 (2.1–3.7)	3.4 (2.4–5.1)	<0.001*
Time from symptom onset to follow-up survey (weeks), median (IQR)	6.0 (6.0–6.3)	6.0 (6.0–6.3)	6.0 (6.0–6.6)	<0.001*

*P<0.05.
†Calculated using Fisher's exact test for categorical variables and Wilcoxon rank-sum test for numerical variables.

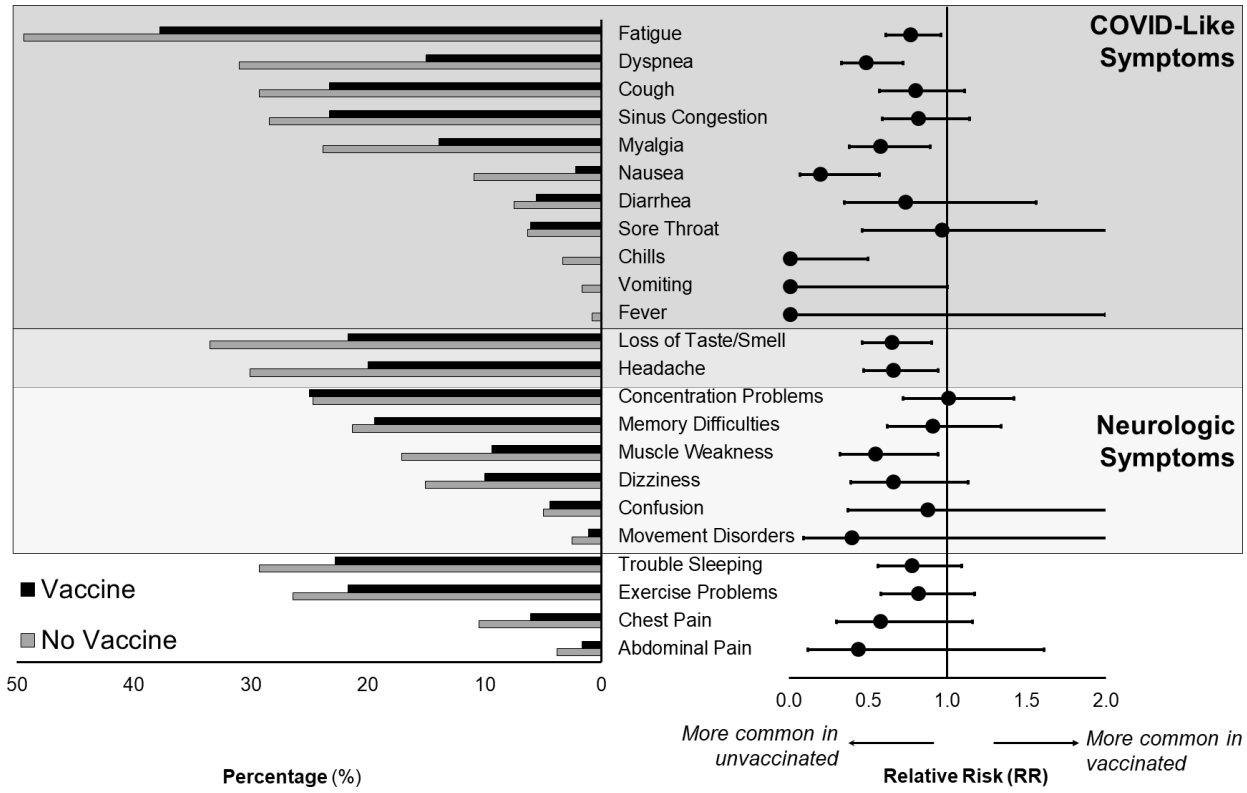


Figure 2 Prevalence of new or persistent symptoms 6 weeks after COVID-19 symptom onset among US healthcare personnel. Each bar in the left pane shows the percentage of participants reporting symptoms at the 6-week follow-up, stratified by vaccination status. For each symptom, the relative risk (RR, unadjusted) and 95% CI are shown on the forest plot to the right. For RR <1.0, the symptom is less prevalent among the vaccinated. Note that several symptoms are part of both COVID-19 symptoms and neurological symptoms. *COVID-like symptoms* included fever, cough, dyspnoea, chills, fatigue, myalgia, headache, new loss of taste or smell, sore throat, nasal congestion, diarrhoea and nausea or vomiting. *Neurological symptoms* included dizziness, headache, muscle weakness, movement disorders, confusion, memory difficulties, concentration problems or loss of taste or smell. *Any symptoms* included trouble sleeping, exercise problems, chest pain or abdominal pain, in addition to COVID-19 symptoms and neurological symptoms, defined above.

245 (95.7%) reported symptoms that were also reported during the initial illness. Within 2 weeks of symptom onset, 323 (77.1%) participants had returned to work; by 6 weeks, only seven (1.7%) still had not returned.

Vaccinated participants had a lower prevalence of COVID-like symptoms at 6 weeks compared with those who were not vaccinated (60.6% vs 79.1%), with an unadjusted relative risk of 0.77 (95% CI 0.67 to 0.88) and an adjusted relative risk of 0.70 (95% CI 0.58 to 0.84). This risk ratio (RR) corresponded to an adjusted risk difference after 6 weeks of 24.1 percentage points (95% CI 11.6 to 36.6). Other classifications of symptoms were also less likely after vaccination—for neurological symptoms the adjusted risk ratio (aRR) was 0.71 (95% CI 0.55 to 0.93) with a 17.9 percentage point reduction (95% CI 5.1 to 30.7); for any 6-week symptoms the aRR was 0.76 (95% CI 0.65 to 0.90) with a 20.1 percentage point reduction (95% CI 8.0 to 32.1) if vaccinated (figure 3, online supplemental table S7).

Prolonged symptoms 6 weeks after symptom onset that were associated with being unvaccinated included dyspnoea, myalgia, muscle weakness, fatigue, chills, loss of taste or smell, headache and nausea; prevalence of other individual symptoms reported at 6 weeks was similar between vaccinated and unvaccinated participants (figure 2). Sensitivity analysis restricted to persistent symptoms (excluding symptoms developing between illness and follow-up) revealed similar findings (online supplemental figure S1). Subgroup analysis, stratified on time since vaccination, showed that the affect was somewhat attenuated for COVID-like symptoms and any symptoms for those vaccinated more than 16 weeks prior to infection (online supplemental table S8).

Median time from symptom onset to return to work (among those who had returned to work before follow-up) was 13 days (IQR 11–16 days). Vaccinated participants returned to work a median of 2.0 days (95% CI 1.0 to 3.0) sooner than the unvaccinated and were less likely to return to work more than 10 days after illness onset (78.9% vs 87.5%; RR 0.90, 95% CI 0.82 to 0.99). Adjusting for covariates, vaccinated participants returned to work sooner than unvaccinated participants (aHR 1.37, 95% CI 1.04 to 1.79; online supplemental table S9). Vaccinated participants were also less likely to have COVID-like symptoms on return to work, although without statistical significance (49.4% vs 66.2%; RR 0.83, 95% CI 0.67 to

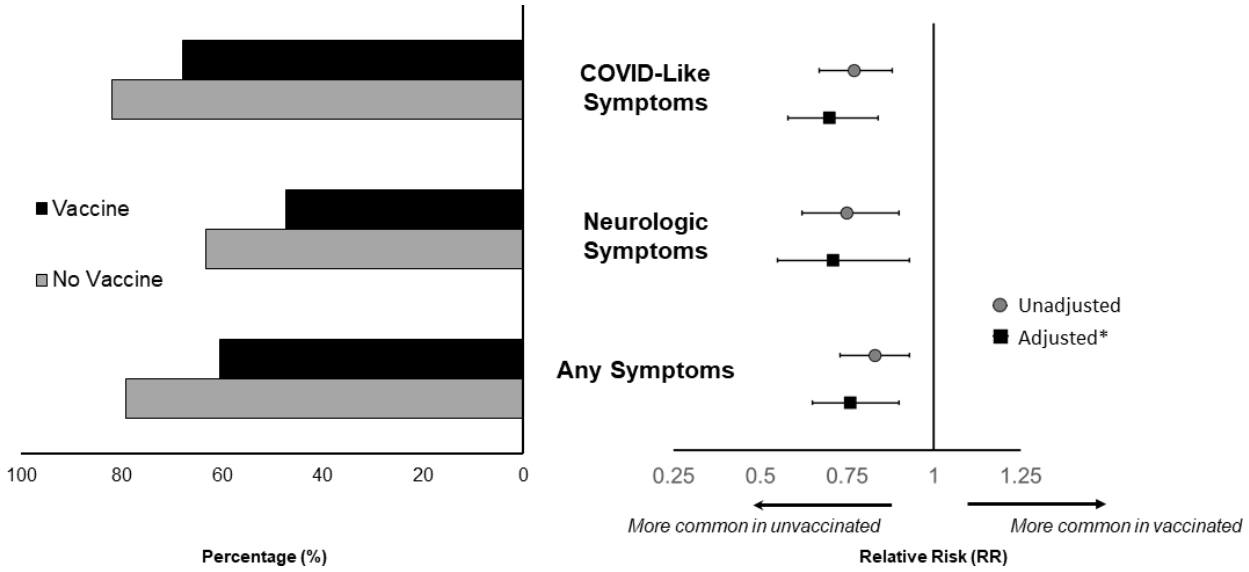


Figure 3 New or persistent symptoms at 6 weeks after COVID-19 symptom onset in vaccinated versus unvaccinated US healthcare personnel. Each bar in the left pane shows the percentage of participants reporting symptoms at the 6-week follow-up, stratified by vaccination status. This forest plot in the right pane shows the estimated risk of new or persistent symptoms present at the 6-week survey. The relative risk (RR) shows the ratio between the probability of having symptoms in the vaccinated versus the unvaccinated (values <1.0 indicate that the prevalence of symptoms is lower in the vaccinated than the unvaccinated group). Grey circles show the unadjusted estimates and black squares show the estimates adjusted for age, race, ethnicity, comorbidities, calendar month of diagnosis and weeks since symptoms started. Error bars indicate 95% CIs around the point estimate. *COVID-like symptoms* included fever, cough, dyspnoea, chills, fatigue, myalgia, headache, new loss of taste or smell, sore throat, nasal congestion, diarrhoea and nausea or vomiting. *Neurological symptoms* included dizziness, headache, muscle weakness, movement disorders, confusion, memory difficulties, concentration problems or loss of taste or smell. *Any symptoms* included trouble sleeping, exercise problems, chest pain or abdominal pain, in addition to COVID-19 symptoms and neurological symptoms, defined above. *Adjusted for age, race, ethnicity, comorbidities, calendar month of diagnosis and weeks since symptoms started.

1.03). Participants who reported COVID-like symptoms on return to work were more likely than those without to report COVID-like symptoms at 6 weeks (84.7% vs 50.9%; RR 1.36, 95% CI 1.11 to 1.67). The time to return to work by vaccination status is shown in figure 4.

DISCUSSION

In this study of HCP with COVID-19 between December 2020 and August 2021, we observed that 71% of participants with a confirmed diagnosis of COVID-19 reported at least one COVID-like symptom was present 6 weeks after symptom onset, and 76% reported any symptoms were present. This high proportion of symptoms at 6 weeks suggests that HCP might experience a substantial disease burden; during this period the most frequently reported symptoms were fatigue, dyspnoea, loss of taste/smell and headache. We observed that COVID-19 infection after full vaccination (breakthrough infection) was associated with a 24 percentage point absolute risk reduction of symptoms at 6 weeks compared with COVID-19 in unvaccinated HCP.

We found that several specific symptoms 6 weeks after illness onset were most strongly associated with having no prior vaccination, including nausea, dyspnoea, muscle weakness, myalgia, loss of taste or smell and headache. Other symptoms had point estimates in the direction of vaccine effectiveness, even if the magnitude of effect did not reach statistical significance. These findings are important because neurological and other symptoms are frequently reported several months after COVID-19.[29] The differential association with vaccination of these symptoms might provide insight into their pathophysiology. Lower frequency of these symptoms following vaccination could be associated with decreased severity of initial illness, as vaccination is known to decrease severity of disease, and prior studies have found that prolonged symptoms might be more common among those with severe COVID-19 illness.[13 23] Because an effect of vaccines in preventing prolonged symptoms is likely to be mediated by the immune response, further research is needed to understand the mechanisms of prolonged symptoms that might be amenable to other prevention strategies.

COVID-19 mRNA vaccines have been shown to be both safe and effective,[13 16 30] but the effect on duration of symptoms following infection is less clear. The UK-based COVID Symptom Study using self-reported data from a mobile app-based data collection instrument with unvalidated vaccination status and COVID-19 diagnosis found that any of 32 symptoms lasting ≥28 days were less prevalent among those who were vaccinated with two doses (adjusted OR 0.51, 95% CI 0.32 to 0.82).[10] This effect size is similar to findings in our study. Recent preliminary

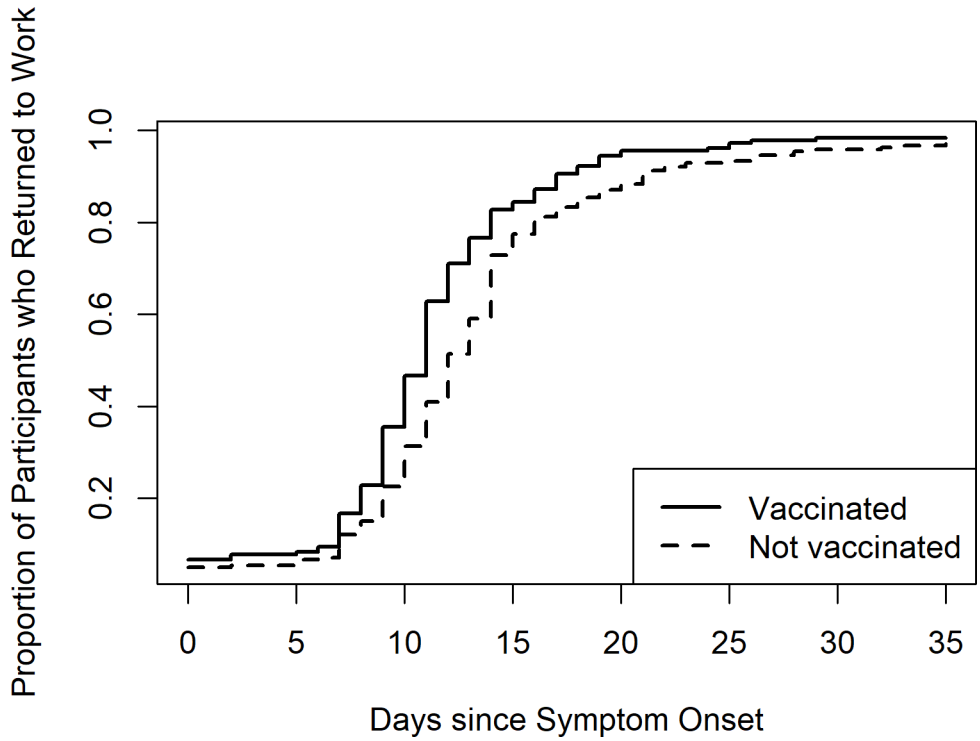


Figure 4 Kaplan-Meier plot of proportion of US healthcare personnel returning to work after onset of COVID-19 symptoms, stratified on COVID-19 vaccination. The Kaplan-Meier plot shows the actual time to return to work, stratified by vaccination status (log-rank test, p<0.001). A Cox proportional hazards model was constructed, adjusting for age, race, ethnicity, comorbidities and calendar month of diagnosis. The adjusted HR (aHR) for the adjusted model is 1.37 (95% CI 1.04 to 1.79). Note that aHR >1.0 indicates that participants *resume work* more quickly.

reports have also noted a lower prevalence of reported symptoms if infection occurred after vaccination, as well as a lower risk of medical encounters after illness.[11 31–33] Strengths of the current analysis include the validation of testing and vaccination status, a separate baseline and follow-up survey, assessment of symptoms at defined time points and follow-up of a broad cohort of HCP.

Reduced likelihood of prolonged symptoms after COVID-19 indicates a benefit of vaccination that is in addition to prevention of initial illness, and it is consistent with other recent analyses on this topic. Vaccination is therefore likely to prevent prolonged symptoms both by preventing infection in the first place[15 16] and by hastening recovery from infections that occur after vaccination. As a result of both effects, vaccine effectiveness against developing COVID-19 with prolonged symptoms is likely to be higher than effectiveness against COVID-19 alone.[34] Vaccine effectiveness against symptomatic infection has been previously assessed using the same study platform as this analysis.[16]

Vaccinated participants also returned to work 2 days sooner than non-vaccinated participants. It appears that vaccinated HCP were able to return to work sooner after infection due to fewer ongoing symptoms. Any effect, magnified over 22 million HCP in the USA, is in addition to the benefit of vaccines in preventing infections, which can affect health system capacity and the ability to respond to public health emergencies.[35] Similar effects might be expected among vaccinated employees in other critical industries.

Our study has several limitations. First, our follow-up was limited to 6 weeks after symptom onset. Although many persistent symptoms are likely to develop by this time, the prevalence of symptoms is likely to decay over time, and we did not assess longer term effects.[6] We also designed our data collection prior to widespread recognition of the prevalence of persistent COVID-19 symptoms. We were also not able to determine whether symptoms were directly caused by SARS-CoV-2 infection because our analysis only compared symptoms by vaccination status among patients with COVID-19. However, a study of 4182 patients with COVID-19 with longitudinal self-reported symptom inventories indicated that symptoms reported 6 weeks after illness onset are usually specific to COVID-19.[6] Second, we relied on self-reported symptoms (rather than diagnoses) in participants who knew their vaccination status. Many reported symptoms are subjective, leaving open the possibility that vaccinated participants had more confidence that their symptoms would resolve quickly. To consider whether symptom severity might have affected response rates, we conducted a sensitivity analysis that yielded similar findings after excluding symptoms that were rated as mild by participants. Third, our study period preceded recommendations for booster doses and the introduction of the Omicron variant and precluded analysis of booster doses—bivalent mRNA booster doses have

since been recommended in the USA.[36 37] It is possible that booster doses might provide additional protection against symptoms after initial COVID-19. Our analysis was also limited to infections before introduction of the Omicron variant, which might lead to a different spectrum of illness because of relative tropism to the upper respiratory tract.[38–40] Finally, there could be differences between those vaccinated and unvaccinated that predispose some participants to having persistent symptoms or returning to work more quickly. We attempted to account for the most influential of these factors in our regression models, and sensitivity analyses yielded similar findings to our primary analysis, but residual confounding could still have influenced our results.

In conclusion, a primary series of COVID-19 vaccination was associated with a decreased adjusted prevalence of new or persistent symptoms at 6 weeks and sooner return to work in a cohort of HCP. Future work is warranted to assess underlying biological mechanisms and the association between vaccination on longer term symptoms, daily function, quality of life and the effect in other populations.

Author affiliations
[1]Emergency Medicine, The University of Iowa Roy J and Lucille A Carver College of Medicine, Iowa, Iowa, USA
[2]Anesthesia, University of Iowa Carver College of Medicine, Iowa City, Iowa, USA
[3]COVID-19 Response Team, Centers for Disease Control and Prevention, Atlanta, Georgia, USA
[4]Olive View and Ronald Reagan-UCLA Medical Center Emergency Medicine, University of California - Los Angeles, Los Angeles, California, USA
[5]Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, Iowa, USA
[6]Emergency Medicine, Thomas Jefferson University, Philadelphia, Pennsylvania, USA
[7]Emergency Medicine, University of Massachusetts Chan Medical School, Worcester, Massachusetts, USA
[8]Internal Medicine Division of Infectious Diseases, University of California - Los Angeles, Los Angeles, California, USA

Acknowledgements The authors acknowledge the following participating Project PREVENT medical centres: Baystate Medical Center, Springfield, Massachusetts; Brigham and Women's Hospital, Boston, Massachusetts; Jackson Memorial Hospital, Miami, Florida; University Medical Center New Orleans, Louisiana State University Health Sciences Center New Orleans, New Orleans, Louisiana; Olive View–University of California Los Angeles Medical Center, Los Angeles, California; Jefferson Health, Philadelphia, Pennsylvania; University Health–Truman Medical Center/University of Missouri–Kansas City, Kansas City, Missouri; University of Chicago, Chicago, Illinois; University of Iowa Carver College of Medicine, Iowa City, Iowa; University of Massachusetts Chan Medical School, Worcester, Massachusetts; University of Mississippi Medical Center, Jackson, Mississippi; University of Alabama at Birmingham, Birmingham, Alabama; Community Medical Centers, Fresno, California; University of Washington, Seattle, Washington; and Valleywise Health Medical Center, Phoenix, Arizona. The authors would also like to acknowledge the following individuals: Allison Schuette; Brianna M DiFronzo; Karen Hopcia; Theresa M Orechia; Alexander B Hill; Gabrielle Donohoe; Lily R Johnsky; Jordyn M Fofi; Steven E Miyawaki; Jenson J Kaithamattam; Michelle Chung; Nikita A Umale; Mohammad Adrian Hasdianda; Guruprasad Jambaulikar; Tala Teymour; Maria Davila; Suzette Fernandez; Joshua Tiao; Alexandria Henderson; Reynaldo Padilla; Cynthia Delgado; Madeleine Manahan; Melanie Potts; Jessica Kuo; Alyssa Fowlds; Zoe Speight; Laurie Kemble; Danielle Beckham; Lori Wilkerson; Geneatra Green; Rachel Marrs; Katherine Schneider; Cathy Fairfield; Fred Ullrich; Virginia Mangolds; Morgan Nelson; Abigail Lopes; Scott Pelletier; Gloria Essien; Rebekah Peacock; Alan Jones; Bhagyashri Navalkele; Savannah Vann; Andrea William; Brooke Park; Eugene Melvin; Joel Rodgers; Nivedita Patkar; Delissa Tidwell-Hand; Whitney Covington; Michael C Kurz; Peter Poerzgen; Layla A Anderson; Kyle A Steinbock; Jennifer Smith; Amy Dakos; Denise Tritt; Stacey Wisniewski; Gaynell Bernadas Hunt; Christine D Crider; Susana Hacopian; Vincent E Yu; Lidia Choxom; and Nathan R Kramer.

Collaborators The Project PREVENT Network includes the following: Howard A Smithline, MD, MS; Peter C Hou, MD; Lilly C Lee, MD, SM; Stephen C Lim, MD; Gregory J Moran, MD; Mark T Steele, MD; David G Beiser, MD, MS; Brett Faine, PharmD, MS; Utsav Nandi, MD, MSCI; Walter A Schrading, MD; Brian Chinnock, MD; Anne Chipman, MD, MS; Megan Fuentes, BS; Frank LoVecchio, DO, MPH; Bradley Clinansmith, BS; Shannon Landers, BA; Alysia Horcher, MPAS, PA-C; Kelli Wallace, MS; Lisandra Uribe, BS; Kavitha Pathmarajah, MPH; Kye E Poronsky, MS; Dean M Hashimoto, MD; Monica Bahamon, MPH; Michelle St Romain, MD; Efrat Kean, MD; Elizabeth Krebs, MD, MSc; Amy Stubbs, MD; Sara Roy, MSCR; Gregory Volturo, MD; Amanda Higgins, MS; James Galbraith, MD; James C Crosby, MD; Mary Mulrow, MA, MN; Eva Gonzalez, BA; Ryan Gierke, MPH; Jennifer L Farrar, MPH; Wei Xing; Yunmi Chung, MPH; Anna Yousaf, MD; Jennifer Onukwube Okaro, MPH; Melissa Briggs-Hagen, MD, MPH; Glen R Abedi, MPH; Sankan Nyanseor, MPH; Christopher K Watts, MPH.

Contributors NMM was responsible for overall study design, interpretation of findings, drafting the manuscript, securing funding, approval of the final manuscript, and takes overall responsibility for the conduct of the study and guarantor of the data. IDP was responsible for interpretation of findings, drafting the manuscript, approval of the final manuscript, and takes overall responsibility for the conduct of the study. KKH and ESL were responsible for study design, data analysis, critical revision of the manuscript and approval of the final manuscript. TP and KEF-D were responsible for overall study design, interpretation of findings, critical revision of the manuscript and approval of the final manuscript. AK was responsible for overall oversight and coordination of the study, interpretation of findings, critical revision of the manuscript and approval of the final manuscript. KFH, SHS, ZM, JPH and MB-H were responsible for interpretation of findings, critical revision of the manuscript and approval of the final manuscript. DAT was responsible for overall study oversight, study design, critical revision of the manuscript and approval of the final manuscript. All members of the Project PREVENT Network were responsible for data collection, interpretation of findings, critical revision of the manuscript and approval of the final manuscript.

Funding This project was funded by the Centers for Disease Control and Prevention (CDC) (U01CK000480). The project was additionally supported by the Institute for Clinical and Translational Science at the University of Iowa through a grant from the National Center for Advancing Translational Sciences at the National Institutes of Health (UL1TR002537).

Disclaimer The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and this activity was reviewed by the US Centers for Disease Control and Prevention (CDC) Institutional Review Board (project number: 0900f3eb81b25a55) and was conducted consistent with applicable federal law and CDC policy as public health surveillance. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Deidentified data will be available on reasonable request to the corresponding author.

ORCID iD
Nicholas M Mohr http://orcid.org/0000-0003-0497-5828

REFERENCES

1 Gupta A, Madhavan MV, Sehgal K, *et al*. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020;26:1017–32.
2 Nalbandian A, Sehgal K, Gupta A, *et al*. Post-Acute COVID-19 syndrome. *Nat Med* 2021;27:601–15.
3 *Long COVID or post-COVID conditions ATLANTA*. GEORGIA: Centers for Disease Control and Prevention, 2022.
4 Mehandru S, Merad M. Pathological sequelae of long-haul COVID. *Nat Immunol* 2022;23:194–202.
5 Bell ML, Catalfamo CJ, Farland LV, *et al*. Post-Acute sequelae of COVID-19 in a non-hospitalized cohort: results from the Arizona covhort. *PLOS ONE* 2021;16:e0254347.
6 Sudre CH, Murray B, Varsavsky T, *et al*. Attributes and predictors of long COVID. *Nat Med* 2021;27:626–31.
7 Chopra V, Flanders SA, O'Malley M, *et al*. Sixty-day outcomes among patients hospitalized with COVID-19. *Ann Intern Med* 2021;174:576–8.
8 Gaber T-Z, Ashish A, Unsworth A. Persistent post-covid symptoms in healthcare workers. *Occup Med (Lond)* 2021;71:144–6.
9 Bergwerk M, Gonen T, Lustig Y, *et al*. Covid-19 breakthrough infections in vaccinated health care workers. *N Engl J Med* 2021;385:1474–84.
10 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.
11 Al-Aly Z, Bowe B, Xie Y. Long COVID after breakthrough COVID-19: the post-acute sequelae of breakthrough COVID-19. *In Review* [Preprint] 2021.
12 Blomberg B, Mohn KG-I, Brokstad KA, *et al*. Long COVID in a prospective cohort of home-isolated patients. *Nat Med* 2021;27:1607–13.
13 Tenforde MW, Self WH, Adams K, *et al*. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. *JAMA* 2021;326:2043–54.
14 *PReventing emerging infections through vaccine effectiveness testing (PREVENT) project: project tools iowa city*. Iowa: Project PREVENT Study Team, 2021. Available: https://medicine.uiowa.edu/content/project-tools
15 Pilishvili T, Fleming-Dutra KE, Farrar JL, *et al*. Interim estimates of vaccine effectiveness of pfizer-biontech and moderna COVID-19 vaccines among health care personnel-33 U.S. sites, january-march 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:753–8.
16 Pilishvili T, Gierke R, Fleming-Dutra KE, *et al*. Effectiveness of mrna covid-19 vaccine among U.S. health care personnel. *N Engl J Med* 2021;385:e90.
17 von Elm E, Altman DG, Egger M, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;370:1453–7.
18 US Centers for Disease Control and Prevention. Symptoms of COVID-19. atlanta, georgia: centers for disease control and prevention. 2022. Available: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html [Accessed 1 Dec 2021].
19 Parisi S, Borrelli R, Bianchi S, *et al*. Viral arthritis and COVID-19. *Lancet Rheumatol* 2020;2:e655–7.
20 Zubair AS, McAlpine LS, Gardin T, *et al*. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA Neurol* 2020;77:1018–27.
21 Rogers JP, Watson CJ, Badenoch J, *et al*. Neurology and neuropsychiatry of COVID-19: a systematic review and meta-analysis of the early literature reveals frequent CNS manifestations and key emerging narratives. *J Neurol Neurosurg Psychiatry* 2021;92:932–41.
22 *Underlying medical conditions associated with higher risk for severe COVID-19: information for healthcare providers*. Atlanta, GA: CDC, 2021. Available: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html
23 Crook H, Raza S, Nowell J, *et al*. Long covid—mechanisms, risk factors, and management. *BMJ* 2021;374:1648.
24 Feikin DR, Higdon MM, Abu-Raddad LJ, *et al*. Duration of effectiveness of vaccines against SARS-cov-2 infection and COVID-19 disease: results of a systematic review and meta-regression. *Lancet* 2022;399:924–44.
25 Zou GY, Donner A. Extension of the modified poisson regression model to prospective studies with correlated binary data. *Stat Methods Med Res* 2013;22:661–70.
26 US Centers for Disease Control and Prevention. Chronic diseases in america ATLANTA, GEORGIA: centers for disease control and prevention. 2021. Available: https://www.cdc.gov/chronicdisease/resources/infographic/chronic-diseases.htm [Accessed 31 Oct 2022].
27 Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. *Am J Epidemiol* 2005;162:199–200.
28 Rothman KJ. *Epidemiology: an introduction*. 2nd edn. Oxford, England: Oxford University Press, 2012.
29 Groff D, Sun A, Ssentongo AE, *et al*. Short-term and long-term rates of postacute sequelae of SARS-cov-2 infection: a systematic review. *JAMA Netw Open* 2021;4:e2128568.
30 Dooling K, Gargano JW, Moulia D, *et al*. Use of pfizer-biontech COVID-19 vaccine in persons aged ≥16 years: recommendations of the Advisory Committee on immunization practices-United States, September 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1344–8.
31 Senjam SS, Balhara YPS, Kumar P, *et al*. Assessment of post COVID-19 health problems and its determinants in north india: A descriptive cross section study. *Public and Global Health* [Preprint].
32 Arjun MC, Singh AK, Pal D, *et al*. Prevalence, characteristics, and predictors of long COVID among diagnosed cases of COVID-19. *Epidemiology* [Preprint].
33 Simon MA, Luginbuhl RD, Parker R. Reduced incidence of long-COVID symptoms related to administration of COVID-19 vaccines both before COVID-19 diagnosis and up to 12 weeks after. *Infectious Diseases (except HIV/AIDS)* [Preprint].
34 Harrison S, Walters B, Simmons Z, *et al*. *The effectiveness of vaccination against long COVID: A rapid evidence briefing*. UK Health Security Agency, 2022.
35 Laughlin L, Anderson A, Martinez A, *et al*. *22 million employed in health care fight against COVID-19*. Washington D.C: United States Census Bureau, 2021. Available: https://www.census.gov/library/stories/2021/04/who-are-our-health-care-workers.html
36 US Centers for Disease Control and Prevention. COVID-19 vaccine booster shots [Available from]. Available: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/booster-shot.html [Accessed 16 Dec 2021].
37 Lambrou AS, Shirk P, Steele MK, *et al*. Genomic surveillance for SARS-cov-2 variants: predominance of the delta (B.1.617.2) and omicron (B.1.1.529) variants - united states, june 2021-january 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:206–11. 10.15585/mmwr.mm7106a4 Available: https://www.cdc.gov/mmwr/volumes/71/wr/mm7106a4.htm
38 Meng B, Abdullahi A, Ferreira IATM, *et al*. Altered TMPRSS2 usage by SARS-cov-2 omicron impacts infectivity and fusogenicity. *Nature* 2022;603:706–14.
39 Chan MCW, Hui KP, Ho J, *et al*. SARS-cov-2 omicron variant replication in human respiratory tract ex vivo. *In Review* [Preprint] 2022.
40 Nealon J, Cowling BJ. Omicron severity: milder but not mild. *Lancet* 2022;399:412–3.

SUPPLEMENTAL TABLES AND FIGURES

TABLES **PAGE**

FIGURES

Mohr NM, *et al. BMJ Open* 2023; 13:e063141. doi: 10.1136/bmjopen-2022-063141

Supplemental Table S1. Characteristics of Participating Medical Centers.

	Medical Centers (n=15)
Total employees, median (IQR)	12,761 (10,544-16,750)
Region, n (%)	
Northeast	4 (27)
Southeast	4 (27)
Midwest	3 (20)
West	4 (27)
Academic medical center, n (%)	15 (100)
Services, n (%)	
Acute care hospital	15 (100)
Long-term care facility	2 (13)
Urgent Care	11 (73)
Vaccination coverage in Sept 2021 (%), median (IQR)*	84 73-91)

* Note that data collection occurred from Jan-Sept, so coverage at the time of enrollment varied through the study period.

Supplemental Table S2: STROBE Statement—Checklist.

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	Presence of Symptoms 6 Weeks After COVID-19 Among Vaccinated and Unvaccinated U.S. Healthcare Personnel
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3	A history of COVID-19 mRNA vaccination among U.S. HCP with COVID-19 illness was associated with decreased risk of COVID-like symptoms at 6 weeks and earlier to return to work.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6	Vaccination may prevent prolonged COVID-19 symptoms through several mechanisms: preventing COVID-19 infection , limiting the severity of acute illness in vaccine breakthrough cases through vaccine-mediated immunity, and affecting the ongoing immune response even after acute infection.
Objectives	3	State specific objectives, including any prespecified hypotheses	7	In this study our primary objective was to measure the association between prior mRNA COVID-19 vaccination and symptoms 6 weeks after acute COVID-19 infection

	Item No.	Recommendation	Page No.	Relevant text from manuscript
				among healthcare personnel (HCP).
Methods				
Study design	4	Present key elements of study design early in the paper	7	For this nested cohort study…
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7	Characteristics of the 15 participating sites are summarized in Supplemental Table S1, and details of study protocols and forms for the parent study are available online.19
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7	we included HCP if they had a positive SARS-CoV-2 nucleic acid amplification test or antigen test and had symptoms consistent with COVID-19 (as listed in Supplemental Table S2) within 14 days of the positive test… Each participant completed an enrollment survey 14 to 60 days after his/her positive test, and was offered a follow-up survey 6 weeks after symptom onset.
		(*b*) *Cohort study*—For matched studies, give matching criteria		

	Item No.	Recommendation	Page No.	Relevant text from manuscript
		and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8	The 6-week survey included questions on a variety of symptoms which we categorized into three overlapping groups…
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9	As part of the follow-up survey we asked participants to report the dates when they left and resumed work. We calculated time to return to work as the number of days from onset of symptoms until the first day at work after illness.
Bias	9	Describe any efforts to address potential sources of bias	10	We included in our multivariable model categorical variables of age, race, ethnicity, and a dichotomous variable for two or more comorbidities at baseline.
Study size	10	Explain how the study size was arrived at	7	As part of the PReventing Emerging Infections through Vaccine EffectiveNess Testing Project (Project PREVENT), we enrolled HCP who were working on-site at participating academic medical centers who

	Item No.	Recommendation	Page No.	Relevant text from manuscript
				had been tested for SARS-CoV-2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10	We used a Cox proportional hazards model to calculate an adjusted hazard ratio (aHR) to compare time to return to work between fully vaccinated and unvaccinated participants, counting zero days if there were no days off work after symptom onset.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11	We used multivariable Poisson regression with a sandwich variance estimator to predict the relative risk of having symptoms at the 6-week follow-up for complete vaccination compared with no vaccination
		(*b*) Describe any methods used to examine subgroups and interactions	9	We defined our primary outcome as the presence of COVID-like symptoms at the time of the 6-week survey. We conducted additional analyses for neurologic symptoms and for any 6-week symptoms, and we assessed whether symptoms at 6 weeks were also present within 14 days of the date of the positive test
		(*c*) Explain how missing data were addressed	11	We included 419 HCP who were diagnosed with COVID-19 between December 28, 2020 and August 26, 2021, including 180 (43.0%) who were fully vaccinated with an mRNA vaccine and 239 (57.0%) who were not vaccinated; 41 were excluded because of unverified vaccination status and 143 were

	Item No.	Recommendation	Page No.	Relevant text from manuscript
				partially vaccinated (Figure 1).
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	11	Those who did not complete the follow-up survey had fewer comorbidities and were less likely to be White non-Hispanic (Supplemental Table S4).
		(*e*) Describe any sensitivity analyses	9	For assessment of all symptom groups we performed a sensitivity analysis restricted to symptoms rated by participants as "moderate" or "severe".
		Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	F1	See Figure 1
		(b) Give reasons for non-participation at each stage	F1	See Figure 1
		(c) Consider use of a flow diagram	F1	See Figure 1

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11	See Table 1, Table S5
		(b) Indicate number of participants with missing data for each variable of interest	T1	See Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11	Follow-up surveys were completed at a median of 6.0 weeks after first symptoms (IQR 6.0-6.3).
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11	Symptoms were common at 6 weeks, with 298 (71.1%) reporting at least one COVID-like symptom, 236 (56.3%) reporting at least one neurologic symptom, and 318 (75.9%) reporting any symptom (Figure 2).
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	11	The relative risk for COVID-like symptoms was 0.77

	Item No.	Recommendation	Page No.	Relevant text from manuscript
		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		(95% confidence interval [CI], 0.67 to 0.88) before adjustment and 0.70 (CI, 0.58 to 0.84) after adjustment for covariates.
		(*b*) Report category boundaries when continuous variables were categorized	T1	See Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-12	This risk ratio corresponds with an adjusted risk difference after 6 weeks of 24.1-percentage points (95% CI, 11.6 to 36.6 percentage points).
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12	Neurologic or any 6-week symptoms after COVID-19 were also less prevalent among vaccinated compared with unvaccinated participants, and these findings were preserved restricting analysis to moderate or severe symptoms (Figure 3, Supplemental Table S6).
Discussion				
Key results	18	Summarise key results with reference to study objectives	13	We observed that COVID-19 infection after full vaccination (breakthrough infection) was associated with a 24-percentage

	Item No.	Recommendation	Page No.	Relevant text from manuscript
				point absolute risk reduction of symptoms at 6 weeks compared with COVID-19 in unvaccinated HCP.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15	Our study has several limitations. First, our follow-up was limited to 6 weeks after symptom onset..
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16	In conclusion, COVID-19 vaccination was associated with decreased risk of having new or persistent symptoms at 6 weeks and returning to work sooner in a cohort of HCP.
Generalisability	21	Discuss the generalisability (external validity) of the study results	16	Future work is warranted to assess the effect of vaccination on longer term symptoms, daily function, quality of life, and the effect in those who do not work in healthcare.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1-2	This project was funded by the Centers for Disease Control and Prevention (CDC) (U01CK000480). The project is additionally supported by the Institute for Clinical and

Item No.	Recommendation	Page No.	Relevant text from manuscript
			Translational Science at the University of Iowa through a grant from the National Center for Advancing Translational Sciences at the National Institutes of Health (UL1TR002537).

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Supplemental Table S3. Qualifying Symptoms and Definitions. This table details the definitions for qualifying possible symptoms of COVID-19 that qualified for inclusion in the study cohort and for analysis of which symptoms were present at 6 weeks.

Symptoms	Enrollment symptoms[1] (within 14 days of positive SARS-CoV-2 test)	COVID-like symptoms (at 6 weeks)	Neurologic symptoms (at 6 weeks)	Any 6-week symptoms (at 6 weeks)
Abdominal pain	X			X
Bruised toes or feet	X			
Chest pain	X			X
Chills	X	X		X
Concentration problems			X	X
Confusion			X	X
Cough	X	X		X
Diarrhea	X	X		X
Difficulty with exercise				X
Dizziness			X	X
Fatigue	X	X		X
Fever	X	X		X
Headache	X	X	X	X
Loss of appetite	X			
Loss of taste or smell	X	X	X	X
Memory difficulties			X	X
Movement problems			X	X
Muscle weakness		X	X	X
Nausea, or vomiting	X	X		X
Persistent joint pains or muscle aches	X	X		X
Rigors	X			
Runny nose	X			
Severe respiratory illness	X			
Shortness of breath	X	X		X
Sinus congestion	X	X		X
Sore throat	X	X		X
Trouble sleeping				X

[1]Included in the enrollment survey. Some terms differed in the enrollment survey: 'chest pain or tightness' was asked instead of 'chest pain'; fever was specified as temperature ≥37.8°C or subjective fever; 'altered taste or smell' was asked instead of 'loss of taste or smell'; 'muscle aches' was asked instead of 'persistent joint pains or muscle aches', and 'sinus or nasal congestion' was asked instead of 'sinus congestion'. These terms were considered equivalent for purposes of analysis of which 6-week symptoms were 'persistent'

Supplemental Table S4: Definition of Underlying Conditions for Analysis of Persistent Symptoms by Vaccination Status.

This table details the recorded comorbidities (from which participants were dichotomized as having none versus 2 or greater).

Participants were considered to have two or more comorbidities if at least two conditions were present from the following list of conditions verified by self-report or the medical record:

- Active cancer;
- Alcohol use disorder;
- Allergic rhinitis;
- Anxiety/obsessive-compulsive/trauma or stressor related disorder;
- Asthma;
- Autoimmune rheumatologic disease;
- Chronic kidney disease;
- Chronic liver disease;
- Cognitive/neurodevelopmental disorder;
- COPD/emphysema;
- Coronary artery disease;
- Deep vein thrombosis or pulmonary embolism;
- Depression or other mood disorder;
- Diabetes mellitus;
- Dialysis;
- Hematopoietic stem cell transplant;
- Hypertension;
- Movement or motor disorders;
- Other chronic lung disease;
- Other heart condition;
- Other immunosuppressing condition;
- Other mental health condition;
- Sleep disorder;
- Solid organ transplant; or
- Stroke.

Supplemental Table S5. Demographic and Employment Factors of U.S. Healthcare Personnel Who Completed the 6-Week Survey Versus Those Who Did Not. Participants who did not complete the follow-up survey met all other criteria for inclusion, but did not complete the 6-week survey for inclusion in the study.

	Completed 6-Week Survey[1] (n=419) n (%)	Did Not Complete 6-Week Survey[2] (n=141) n (%)	*p*[3]
Age			0.2684
18-29 y	90 (21.5)	69 (26.4)	
30-39 y	167 (39.9)	86 (33.0)	
40-49 y	85 (20.3)	56 (21.5)	
50-64 y	77 (18.4)	50 (19.2)	
Sex			0.5491
Male	64 (15.4)	43 (16.7)	
Female	352 (84.4)	214 (83.0)	
Non-binary	1 (0.2)	1 (0.3)	
Race and Ethnic Group			0.0072*
White, non-Hispanic	303 (72.3)	157 (60.2)	
Black, non-Hispanic	47 (11.2)	35 (13.4)	
Hispanic or Latino	41 (9.8)	40 (15.3)	
Other, non-Hispanic	28 (6.7)	29 (11.1)	
Education Level			0.6669
High school or less	25 (6.0)	15 (5.9)	
Undergraduate or technical degree	293 (69.9)	187 (73.1)	
Graduate or professional degree	101 (24.1)	54 (21.1)	
Job Classification			0.3525
Non-clinical	128 (30.6)	71 (27.2)	
Physician	20 (4.8)	13 (5.0)	
Advanced Practice Provider	12 (2.9)	7 (2.7)	
Nurse/Nurse Assistant	128 (30.6)	71 (27.2)	
Housekeeping	2 (0.5)	0	
Other Clinical	48 (11.5)	20 (7.7)	
Other	45 (10.7)	26 (10.0)	
Health Insurance			0.0123*
Private	385 (91.9)	220 (84.3)	
Government	17 (4.1)	18 (6.9)	
None	3 (0.7)	2 (0.8)	
Unknown	14 (3.3)	21 (8.1)	
Presence of 2 or more Comorbidities (see Supplemental Table 3 for Details)	207 (49.4)	107 (41.0)	0.0331*
Received Any COVID-19 Vaccine[2]	192 (45.9)	122 (46.7)	0.0604

[1] Completed follow-up survey with 10 weeks of index test. Those completing after 10 weeks are excluded from this analysis.

[2] For those who did not complete follow-up survey, vaccine status is determined by self-report.

[3] Calculated using Fisher's exact test

* $p < 0.05$

Supplemental Table S6. Comorbidities of U.S. Healthcare Personnel. This table compares the comorbidities between vaccinated and unvaccinated participants.

	All Participants (n=419) n (%)	Vaccinated (n=180) n (%)	Not Vaccinated (n=239) n (%)	*p*[1]
Comorbidities				
Asthma	49 (11.7)	19 (10.6)	30 (12.6)	0.544
Allergic Rhinitis	32 (7.6)	19 (10.6)	13 (5.4)	0.063
COPD/emphysema	0	0	0	0.999
Other Chronic Lung Disease	3 (0.7)	3 (1.7)	0	0.079
Hypertension	63 (15.0)	29 (16.1)	34 (14.2)	0.679
Coronary Artery Disease	1 (0.2)	1 (0.6)	0	0.430
Other Heart Condition	9 (2.1)	7 (3.9)	2 (0.8)	0.042
Stroke	0	0	0	0.999
Diabetes	25 (6.0)	12 (6.7)	13 (5.4)	0.679
Chronic Kidney Disease	0	0	0	0.999
Dialysis	1 (0.2)	0	1 (0.4)	0.999
Solid Organ Transplant	1 (0.2)	0	1 (0.4)	0.999
Hematopoietic Stem Cell Transplant	0	0	0	0.999
Autoimmune Rheumatologic Disease	16 (3.8)	9 (5.0)	7 (2.9)	0.310
Other Immunosuppressing Condition	3 (0.7)	1 (0.6)	2 (0.8)	0.999
Active Cancer	2 (0.5)	0	2 (0.8)	0.509
Deep Vein Thrombosis or Pulmonary Embolism	3 (0.7)	2 (1.1)	1 (0.4)	0.579
Chronic Liver Disease	1 (0.2)	1 (0.6)	0	0.430
Depression or Other Mood Disorder	53 (12.6)	31 (17.2)	22 (9.2)	0.017*
Anxiety/Obsessive-Compulsive/Trauma or Stressor Related Disorder	63 (15.0)	32 (17.8)	31 (13.0)	0.214
Other Mental Health Condition	3 (0.7)	2 (1.1)	1 (0.4)	0.579
Movement or Motor Disorders	1 (0.2)	1 (0.6)	0	0.430
Alcohol use disorder	0	0	0	0.999
Sleep Disorder	21 (5.0)	12 (6.7)	9 (3.8)	0.184
Cognitive/Neurodevelopmental Disorder	2 (0.5)	2 (1.1)	0	0.184

[1]Calculated using Fisher's exact test

* $p < 0.05$

Supplemental Table S7. Relative Risk of Symptoms at 6 Weeks after COVID-19 Symptom Onset among U.S. Healthcare Personnel ≥14 days After Two Doses of an mRNA Vaccination Compared with No Vaccination.

	Presence of Symptoms			Moderate Symptoms or Worse†	
Symptoms	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)**	**Adjusted Absolute Risk Difference% (95% CI)**	**Unadjusted RR (95% CI)**	**Adjusted RR (95% CI)**
COVID-like Symptoms	0.77 (0.67–0.88)	0.70 (0.58–0.84)	-24.1 ([-36.6]–[-11.6])	0.69 (0.52–0.93)	0.67 (0.44–1.02)
Neurologic Symptoms	0.75 (0.62–.90)	0.71 (0.55–0.93)	-17.9 ([-30.7]–[-5.1])	0.58 (0.39–0.86)	0.43 (0.26–0.73)
Any 6-week Symptoms	0.83 (0.73–0.93)	0.76 (0.65–0.90)	-20.1 ([-32.1]–[-8.0])	0.72 (0.55–0.95)	0.70 (0.48–1.03)

COVID-19 symptoms included fever, cough, dyspnea, chills, fatigue, myalgia, headache, loss of taste or smell, sore throat, nasal congestion or rhinorrhea, diarrhea, and nausea or vomiting. *Neurologic symptoms* included dizziness, headache, muscle weakness, movement disorders, confusion, memory difficulties, concentration problems, or loss of taste or smell. *Any symptoms* included fatigue, sinus congestion, trouble sleeping, exercise problems, chest pain, nausea, or abdominal pain, in addition to COVID-19 symptoms and neurologic symptoms, defined above.

† Severity of illness was classified for each symptom by self-report into mild, moderate, or severe. "Moderate symptoms or worse" includes all symptoms rated as moderate or severe.

RR, relative risk; 95% CI, 95% confidence interval

Table S8. Relative Risk of Symptoms at 6 Weeks after COVID-19 Symptoms Onset among U.S. Healthcare Personnel, Stratified by the Duration of Time since Vaccination. Each

	Duration of Time Since COVID-19 Vaccination			
	≤16 weeks		>16 weeks	
Symptoms	**Unadjusted RR (95% CI)**	**Adjusted† RR (95% CI)**	**Unadjusted RR (95% CI)**	**Adjusted† RR (95% CI)**
COVID-like Symptoms	0.66 (0.52-0.85)	0.67 (0.51-0.87)	0.82 (0.70-0.95)	0.72 (0.59-0.88)
Neurologic Symptoms	0.67 (0.49-0.92)	0.72 (0.51-1.01)	0.78 (0.64-0.97)	0.69 (0.51-0.95)
Any 6-week Symptoms	0.72 (0.58-0.90)	0.73 (0.57-0.92)	0.88 (0.78-1.00)	0.80 (0.66-0.95)

COVID-19 symptoms included fever, cough, dyspnea, chills, fatigue, myalgia, headache, loss of taste or smell, sore throat, nasal congestion or rhinorrhea, diarrhea, and nausea or vomiting. *Neurologic symptoms* included dizziness, headache, muscle weakness, movement disorders, confusion, memory difficulties, concentration problems, or loss of taste or smell. *Any symptoms* included fatigue, sinus congestion, trouble sleeping, exercise problems, chest pain, nausea, or abdominal pain, in addition to COVID-19 symptoms and neurologic symptoms, defined above. All symptoms in this table are at least mild or worse in severity, as assessed by the participant.

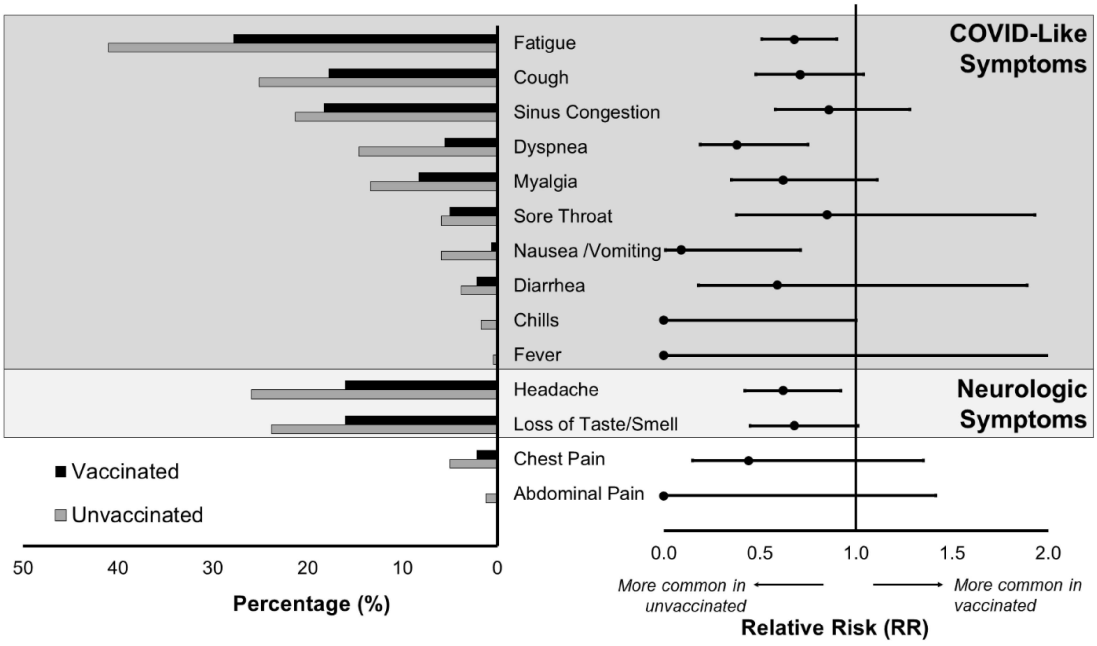
†Adjusted for age, race, ethnicity, comorbidities, calendar month of diagnosis, and weeks since symptoms started.

RR, relative risk; 95% CI, 95% confidence interval

Supplemental Table S9. Cox Proportional Hazards Model for Time to Return to Work among U.S. Healthcare Personnel. The outcome of this model is return to work, so hazard ratios (HR)>1.0 indicate a factor is associated with returning to work sooner.

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Vaccination Status		
No Vaccination	Ref	Ref
Full Vaccination	1.401 (1.151–1.704)	1.367 (1.043–1.793)
Calendar Month		
December	–	Ref
January	–	1.477 (1.002–2.176)
February	–	1.165 (0.712–1.908)
March	–	0.973 (0.582–1.625)
April	–	1.287 (0.765–2.167)
May	–	1.231 (0.706–2.145)
June	–	1.324 (0.746–2.351)
July	–	1.331 (0.856–2.068)
August	–	1.363 (0.582–2.181)
Age group (years)		
18–29	–	Ref
30–39	–	1.113 (0.854–1.450)
40–49	–	1.024 (0.749–1.401)
50–64	–	0.912 (0.662–1.256)
Race/Ethnicity		
White, non-Hispanic	–	Ref
Black, non-Hispanic	–	0.877 (0.637–1.206)
Hispanic or Latino	–	0.742 (0.597–1.187)
Other, non-Hispanic	–	0.867 (0.578–1.303)
Comorbid Risk Factors		
None or 1	–	Ref
2 or more	–	0.802 (0.654–0.982)

Supplemental Figure S1. Prevalence of Persistent Symptoms 6 Weeks after COVID-19 Symptom Onset among U.S. Healthcare Personnel. Compared with Figure 2, this figure removes symptoms that developed between 2 and 6 weeks. Each bar in the left pane reports the percentage of participants reporting symptoms at the 6-week follow-up, stratified by vaccination status. For each symptom, the relative risk (RR) and 95% confidence interval are listed to the right of the bar. For RR <1.0, the symptom is more prevalent among the unvaccinated. Note that several symptoms are part of both COVID-19 symptoms and neurologic symptoms.



RR, relative risk