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Association of Messenger RNA Coronavirus Disease 2019 (COVID-19) Vaccination and Reductions in Post COVID Conditions Following Severe Acute Respiratory Syndrome Coronavirus 2 Infection in a US Prospective Cohort of Essential Workers

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Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (<http://jid.oxfordjournals.org/>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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Abstract

Background.—Data are limited on whether vaccination reduces post COVID conditions (PCCs) risk after less severe nonhospitalized coronavirus disease 2019 (COVID-19). This study assessed whether COVID-19 vaccination protected against PCCs in persons with mild initial infections during Delta and Omicron variant predominance.

Methods.—This study utilized a case-control design, nested within the HEROES-RECOVER cohort. Participants aged ≥ 18 years with test-confirmed severe acute respiratory syndrome coronavirus disease 2 (SARS-CoV-2) between 28 June 2021 and 14 September 2022 were surveyed for PCCs, defined by symptoms lasting >4 weeks after initial infection. Cases self-reported PCCs and controls self-reported no PCCs. The exposure was messenger RNA (mRNA) COVID-19 vaccination (2 or 3 monovalent doses). Odds of PCCs among vaccinated and unvaccinated persons were compared with logistic regression.

Results.—Of 936 participants, 23.6% reported PCCs and 83.2% were vaccinated. Participants who received 3 vaccine doses had lower odds of PCC-related gastrointestinal, neurological, and other symptoms compared to unvaccinated participants (adjusted odds ratio [95% confidence interval]: 0.37 [.16–.85], 0.56 [.32–.97], and 0.48 [.25–.91], respectively).

Conclusions.—COVID-19 vaccination protected against development of PCCs among persons with mild infection during both Delta and Omicron variant predominance, supporting vaccination as an important PCCs prevention tool.

Keywords

post-COVID conditions; COVID-19 vaccines; mRNA vaccines; Long COVID; COVID-19

Post COVID conditions (PCCs), also referred to as long COVID, are estimated to impact millions of Americans [1, 2]. A study analyzing prevalence of long COVID, using the Household Pulse Survey data, among United States (US) adults reporting previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection found that 11.0% of adults who self-reported SARS-CoV-2 infection describe having symptoms lasting 3 months or longer [3]. The Centers for Disease Control and Prevention defines PCCs as physical and mental health symptoms and conditions that persist ≥ 4 weeks after SARS-CoV-2 infection.

PCCs may occur regardless of initial disease severity and may present as persistent symptoms that do not resolve after initial infection, symptoms that recur after a period of improvement, or symptoms that newly occur after the acute infection resolves [4]. The most common symptoms associated with PCCs are fatigue, memory problems, dyspnea, sleep problems, and joint pain [5]. Some symptoms may reflect development of new medical conditions including diseases affecting the cardiovascular system (eg, myocarditis, heart failure, cardiac dysrhythmias, stroke), chronic kidney disease, neurologic conditions, and diabetes [5–8]. When assessing symptom clusters in both vaccinated and unvaccinated persons who tested positive for SARS-CoV-2, cardiorespiratory, central neurological, and multiorgan systemic inflammatory symptom clusters were most commonly detected among self-reported symptoms lasting >28 days after acute infection [9].

Among persons who have had acute SARS-CoV-2 infection that did not require hospitalization, several risk factors for subsequent development of PCCs have been identified, including female sex, smoking, obesity, and presence of comorbidities [7]. Less is understood about factors that may reduce risk of developing PCCs. While there is growing evidence that coronavirus disease 2019 (COVID-19) vaccines reduce the frequency and symptoms of PCCs following infection, most studies have focused on persons with severe initial infection caused by ancestral and early SARS-CoV-2 variants [7, 8, 10–16]. While there is some evidence that earlier variants were associated with higher likelihood of PCCs, even when controlling for time since vaccination, this finding has not been consistent and factors that reduce risk of PCCs during predominance of the SARS-CoV-2 Omicron variant and sublineages after nonsevere COVID-19 illness, which represent the majority of ongoing infections in the US, remain less well understood [10, 17, 18].

Using a multisite prospective cohort of frontline and essential workers, a substudy was performed to assess the odds of developing PCCs after an acute SARS-CoV-2 infection during SARS-CoV-2 Delta and Omicron variant predominance among persons who had received 2 or 3 doses of a monovalent messenger RNA (mRNA) COVID-19 vaccine compared to persons who were unvaccinated at the time of infection. By focusing on persons with predominantly nonsevere initial infection during Delta and Omicron variant predominance, this study addresses an important gap in the understanding of the role of COVID-19 vaccines in preventing or mitigating PCCs and postinfection medical care.

METHODS

Study Design and Population

A retrospective nested case-control analysis was performed among participants enrolled in the preexisting HEROES-RECOVER longitudinal cohort study who tested positive for SARS-CoV-2 and completed an online survey asking about self-report of PCCs. The HEROES-RECOVER network consists of 2 jointly run prospective cohorts: the Arizona Healthcare, Emergency Response, and Other Essential Workers Surveillance Study (HEROES) and Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel (RECOVER) [19, 20]. This network is comprised of healthcare workers, first responders, and other essential workers (such as persons working in hospitality, food service, education, and other essential infrastructure operations) across 6 US states:

Arizona (Phoenix, Tucson, and other areas), Florida (Miami), Minnesota (Duluth), Oregon (Portland), Texas (Temple), and Utah (Salt Lake City). The network began data collection in July 2020 and followed participants weekly through April 2023 for HEROES and May 2023 for RECOVER to collect exposure and infection information. Participants self-collected mid-turbinate nasal swabs weekly, regardless of symptoms, and an additional nasal and saliva swab at the onset of any illness symptoms. Sociodemographic information, prescribed daily medication use, COVID-19 vaccination status, worker knowledge and perceptions of COVID-19 infections and vaccines, and COVID-19 exposure and personal protective equipment use were collected through electronic surveys. History of prior SARS-CoV-2 infection was determined based on self-report of infection at enrollment and/or presence of antibodies at enrollment blood draw. Serum was collected at enrollment, approximately every 3 months during the study, and after vaccination.

The present analysis was conducted among cohort participants following an in-study SARS-CoV-2 infection occurring between 28 June 2021 and 14 September 2022. Participants with documented infection in this timeframe were sent an online survey (“Long COVID” survey) asking them to report symptoms of PCCs, defined as any symptoms persisting 1 month or longer after the initial illness; surveys were distributed between May and December 2022. To ensure at least 1 month had elapsed since initial infection, surveys were distributed at least 60 days after the illness start date, defined as the earliest of either the initial infection symptom onset date or date of positive qualitative reverse-transcription polymerase chain reaction (RT-PCR) SARS-CoV-2 specimen collection.

Actively enrolled participants in Arizona, Florida, Minnesota, Texas, and Utah were eligible to receive the survey. The analysis excluded participants with a history of SARS-CoV-2 infection prior to study enrollment (determined through self-report at enrollment or evidence of infection-induced SARS-CoV-2 antibodies on enrollment blood draw). Participants were also excluded who (1) had an in-study infection with a SARS-CoV-2 variant other than the Delta or Omicron variant, (2) had an incomplete survey or completed the survey <60 days after infection, (3) completed the survey for an infection other than their first, (4) received a non-mRNA COVID-19 vaccine, (5) had indeterminate or partial vaccination status, (6) had an infection that occurred after ≥ 4 doses of COVID-19 vaccination, (7) received an mRNA COVID-19 vaccination after infection but before survey completion, or (8) had a first in-study infection that occurred between a first and second dose of mRNA COVID-19 vaccine (Figure 1).

All participants provided written informed consent, and their common protocols and procedures were approved by the institutional review boards at participating sites.

Respiratory Specimen Testing

Nasal swab specimens were tested by RT-PCR assay at the Marshfield Clinic Research Institute (Marshfield, Wisconsin). Whole genome sequencing was conducted on eligible samples to determine virus lineage. For ineligible specimens (cycle threshold value ≥ 30), virus sequence was presumptively assigned as the Delta variant when Delta accounted for $\geq 50\%$ of viruses sequenced from other specimens at each site; specimens were presumed to

be the Omicron variant when $\geq 50\%$ of viruses sequenced were Omicron for each site. The detailed specimen collection and testing procedure is outlined in Supplementary Table 3.

Exposures

COVID-19 vaccination status was the primary exposure of interest. Participants self-reported vaccination dates and manufacturers through electronic or phone surveys; self-report was verified via uploaded images of vaccination cards in all sites. This was further verified by electronic medical records and state immunization registries from sites in Arizona, Minnesota, Texas, and Utah. Vaccination status was defined in relation to initial infection date: vaccinated with 2 doses if 2 doses were received ≥ 14 days prior to initial infection, vaccinated with 3 doses if 3 doses were received ≥ 7 days prior to initial infection, or unvaccinated (no doses received prior to infection). Only monovalent COVID-19 mRNA vaccines were considered in the analysis.

Outcomes

The outcome of interest was PCCs, defined as self-reported symptoms persisting ≥ 4 weeks after acute infection on self-report during survey. Cases were defined as participants who reported at least 1 symptom persisting for longer than a month when asked, “Since your COVID-19 illness ... have you had any of the below symptoms lasting over 4 consecutive weeks?” Controls were defined as those who completed the PCC survey and did not report at least 1 symptom persisting for at least a month or longer. The full list of symptoms defining PCCs is provided in Supplementary Table 1. Symptoms could have been continuous since initial infection or relapsing/remitting since initial infection. PCCs were further subcategorized by number of symptoms (≥ 1 or ≥ 2) and by symptom category: cardiovascular/respiratory (shortness of breath, palpitations, chest pain/tightness, and runny nose/congestion), gastrointestinal (loss of appetite, nausea, vomiting, abdominal/stomach pain, constipation, and diarrhea), general (worsening of symptoms following minor mental or physical activity, fatigue, joint pain, joint swelling, and muscle pain), neurological (dizziness/lightheadedness/fainting, numbness/tingling, fogginess in thinking, change in sleeping, headache, difficulty speaking/communicating, difficulty swallowing/chewing, problems with balance/movement), and other (weight loss, hair loss, change in color of toes/fingers, rash, bruising/bleeding easily, change in menstrual cycle, change in sexual drive, and erectile dysfunction).

Statistical Analysis

Pearson χ^2 tests were used to examine differences in sociodemographic characteristics and previous/current health conditions by report of PCCs and vaccination status; Fisher’s exact test was used to assess differences when frequencies were < 5 . Normality was assessed and t test was used to assess difference in means. The association of vaccination with PCCs was estimated using logistic regression comparing the odds of vaccination among persons with and without PCCs. Separate multivariable logistic models were conducted for PCCs with ≥ 1 symptom, ≥ 2 symptoms, and each PCC symptom category. All models were adjusted for gender, presence of chronic conditions (categorized by none or ≥ 1 chronic condition), age (< 40 years or ≥ 40 years), number of symptoms experienced during acute infection (≤ 3 or > 3), interval between initial infection and survey completion (60–119 days, 120–179 days,

or ≥ 180 days), and the variant of infection (Delta or Omicron). Covariates of interest were selected a priori for inclusion based on literature review. Standardized mean differences were calculated to evaluate those who completed and did not complete or did not respond to the PCC survey. Analyses were conducted using SAS software (version 9.4, SAS Institute, Cary, North Carolina) and R software (version 4.3, R Foundation for Statistical Computing). The 5% level of significance was used in all statistical tests and confidence intervals (CIs).

RESULTS

A total of 2584 HEROES-RECOVER participants had a documented SARS-CoV-2 infection during the study period and were initially eligible for study inclusion and received the PCC survey. Among those who received the survey, 733 (28.4%) were excluded due to infection with a non-Delta or non-Omicron variant, 275 (10.6%) for infection prior to study enrollment, 305 (11.8%) for early survey response (defined as survey received < 60 days from date of acute infection), incomplete survey response, or survey nonresponse, and 110 (4.3%) for receipt of a vaccine dose after acute infection but before the survey was received (Figure 1). The remaining 936 (36.2%) participants comprised the final analytic sample. Mean age of included participants was 44.2 years (standard deviation, 10.5 years); 571 (61.0%) were female, 826 (88.2%) were White, and 742 (79.3%) were non-Hispanic; 406 (43.4%) were healthcare personnel, 224 (23.9%) essential frontline workers, and 306 (32.7%) other frontline workers. Most participants did not report comorbidities (73.6%), were nonsmokers (76.9%), and self-reported their health as “very good” or “excellent” (70.0%) upon enrollment; 102 (10.9%) were infected during Delta variant predominance and 834 (89.1%) during Omicron predominance (Table 1). Comparing those who did and did not respond to the survey/incompletely responded to the survey, responders were more likely to be frontline workers compared to other occupations and symptomatic versus asymptomatic during acute infection (Supplementary Table 2).

In total, 779 (83.2%) participants received at least 2 doses of the mRNA COVID-19 vaccine ≥ 14 days prior to infection, including 478 (51.1%) who also received a third monovalent mRNA vaccine dose ≥ 7 days prior to their infection (Table 2). Among all vaccinated persons, 460 (59.1%) received the Pfizer-BioNTech (BNT162b2) vaccine for all doses and 285 (36.6%) received the Moderna (mRNA-1273) vaccine for all doses; 34 (4.4%) participants received a combination of these 2 products. The median time since most recent dose to infection among those who received 2 monovalent dose was 324 days (interquartile range [IQR], 249.0–419.0 days); among those who received 3 monovalent doses, the median time between the most recent dose and infection was 112 days (IQR, 76.0–214.0 days) (Table 2).

Overall, 221 (23.6%) participants reported experiencing ≥ 1 PCC symptom, with 158 (16.5%) reporting ≥ 2 symptoms. Of these, 158 (71.5%) were female, 139 (62.9%) self-rated their enrollment health as “excellent” or “very good,” and 126 (57.0%) self-reported using 1 or more physician-prescribed daily medications at enrollment (Table 1). The most reported category of symptoms was general symptoms including pain/fatigue (16.2%), followed by neurological (13.7%), cardiovascular/respiratory (11.4%), and other (8.5%); gastrointestinal symptoms were least common (4.9%) (Table 3). Persons reporting PCC

symptoms compared with those who did not report PCCs were more frequently symptomatic during acute infection (97.7% vs 89.4%, $P < 0.0001$). Those who reported PCC symptoms also more frequently reported >3 symptoms during acute infection compared to individuals who did not report PCC symptoms (82.8% vs 69.4%, $P < 0.0001$, respectively) (Table 1).

After adjustment for gender, age, presence of chronic conditions, number of symptoms during acute infection, interval between infection and survey completion, and variant type, and stratified by symptom category, receipt of 3 vaccine doses ≥ 14 days prior to acute infection compared to being unvaccinated was associated with lower odds of PCC gastrointestinal symptoms (adjusted odds ratio [aOR], 0.37 [95% CI, .16–.85]), neurological symptoms (aOR, 0.56 [95% CI, .32–.97]), and other symptoms (aOR, 0.48 [95% CI, .25–.91]) compared to being unvaccinated (Table 3). No significant associations were found between 3 doses of vaccine and the odds of number of symptoms, cardiovascular/respiratory symptoms, and general symptoms (Table 3). Comparing receipt of 2 doses ≥ 14 days prior to acute infection to unvaccinated, the odds of PCCs with at least 1 symptom was 0.84 (95% CI, .53–1.32). The odds were lower compared to unvaccinated but not statistically significant. Assessing specific PCC symptom categories among those receiving 2 doses compared to unvaccinated, odds ratios were as follows: cardiovascular/respiratory symptoms (aOR, 1.12 [95% CI, .62–2.05]), gastrointestinal symptoms (aOR, 0.69 [95% CI, .31–1.53]), general symptoms (aOR, 1.08 [95% CI, .64–1.84]), neurological symptoms (aOR, 0.80 [95% CI, .46–1.40]), and other symptoms (aOR, 0.77 [95% CI, .41–1.46]) (Table 3).

DISCUSSION

In this analysis of the HEROES-RECOVER cohort of US frontline and essential workers, the odds of developing PCC-specific symptom categories (gastrointestinal, neurological, and other symptoms) after acute SARS-CoV-2 infection during circulation of both SARS-CoV-2 Omicron and Delta variants were lower among persons who received 3 doses of monovalent mRNA COVID-19 vaccine prior to acute infection compared to those who were unvaccinated at the time of acute infection. This report demonstrates the effect of COVID-19 vaccination in reducing progression to PCCs during circulation of the SARS-CoV-2 Omicron variant in the US and highlights that COVID-19 vaccination can serve as an important additional tool to prevent PCCs. Furthermore, the HEROES-RECOVER cohort is unique in that it consists of predominantly younger, healthy adult participants and almost all infections captured represented nonsevere disease. In total, approximately 28% of participants included in the analysis had 3 or fewer symptoms during their initial infection, 8.7% were asymptomatic, and only 6 of 936 (0.6%) had a hospitalization related to their infection. The findings of this report demonstrate that even among young healthy adults in whom the vaccine may not prevent infection, there is still a protective benefit offered by vaccines, which is an important potential consideration for ongoing vaccine policy.

This analysis found that receipt of 3 doses of an mRNA COVID-19 vaccine was associated with lower odds of experiencing specific categories of PCC symptoms following infection, including reducing the odds of other symptoms (weight loss, hair loss, and skin, menstrual, and sexual symptoms) by 52%, gastrointestinal symptoms by 63%, and neurological symptoms by 44%. The differential effect on the development of PCC symptoms has been

identified elsewhere in the literature. For example, in a recent meta-analysis, Gao et al. identified vaccination to only be protective against some, but not all, PCC symptoms [14].

There was no association observed between development of PCCs and receipt of 2 doses of mRNA COVID-19 vaccine. This is in contrast to other studies that have demonstrated a protective effect from 2 doses, including in similar cohorts of nonsevere COVID-19 infections in the United Kingdom and in Italy [21, 22]. However, the median time between receipt of a second vaccine dose and acute infection was 324 days in the HEROES-RECOVER cohort. It is therefore possible that the lack of an association observed here is the result of waning vaccine protection against development of PCCs after infection, similar to what is observed against infection itself; smaller sample size in the 2-dose group may also have played a role, limiting power to detect an association. Although further research is needed, the potential that protection against development of PCCs after infection may wane, just as it does for other outcomes, highlights the importance of staying up to date with COVID-19 vaccination recommendations, including updated doses.

Lastly, this analysis focused on the reduction in odds of developing PCCs only among persons who had SARS-CoV-2 infection. Because these estimates do not account for PCCs averted by protection against infection, the findings here likely underestimate the overall reduction in PCCs that vaccinated persons experience compared to unvaccinated persons.

This analysis is subject to at least 6 limitations. First, only participants with a documented SARS-CoV-2 infection received the PCC survey and baseline rates of PCC-like symptoms among persons without SARS-CoV-2 infection were unknown, which meant that incidence of PCCs could not be calculated in this cohort. Second, participants were asked to report symptoms occurring after an illness that may have happened up to 2 years prior, leading to potential recall bias and under- or overreporting of PCC symptoms. To try to ensure that reported PCC symptoms were associated with the first in-study infection, individuals with any subsequent SARS-CoV-2 infections after the first in-study infection were excluded. Third, analyses rely solely on multiple regression to account for any confounding, and unmeasured confounding may have remained. Fourth, those who experienced asymptomatic acute infections were less likely to complete the survey; if acute infection symptom severity is related to likelihood of developing PCCs, excluded individuals may have had a lower likelihood of PCCs regardless of vaccination status. Fifth, this survey was voluntary and while survey nonrespondents were generally similar to respondents in observable characteristics, if nonresponse was associated both with likelihood of developing PCCs and likelihood of vaccination, estimates could be biased. Sixth, this cohort had high vaccine uptake and consisted predominantly of younger, healthier adults and frontline healthcare and essential workers. This group has a higher level of exposure to SARS-CoV-2 infection, which may limit generalizability of these results.

CONCLUSIONS

In this analysis of the HEROES-RECOVER frontline worker cohort, individuals who received 3 doses of monovalent mRNA COVID-19 vaccine prior to SARS-CoV-2 infection had a reduction in the odds of developing PCCs, specifically neurological, gastrointestinal,

and general symptoms (including weight loss, hair/skin issues, and menstrual/sexual symptoms). These results confirm that COVID-19 vaccination can play an important role in protecting individuals against PCCs, including among patients who have mild initial infection during Delta and Omicron variant predominance. Further research is needed to evaluate whether this effect is even greater with additional vaccine doses and the improved variant–vaccine match of updated COVID-19 vaccines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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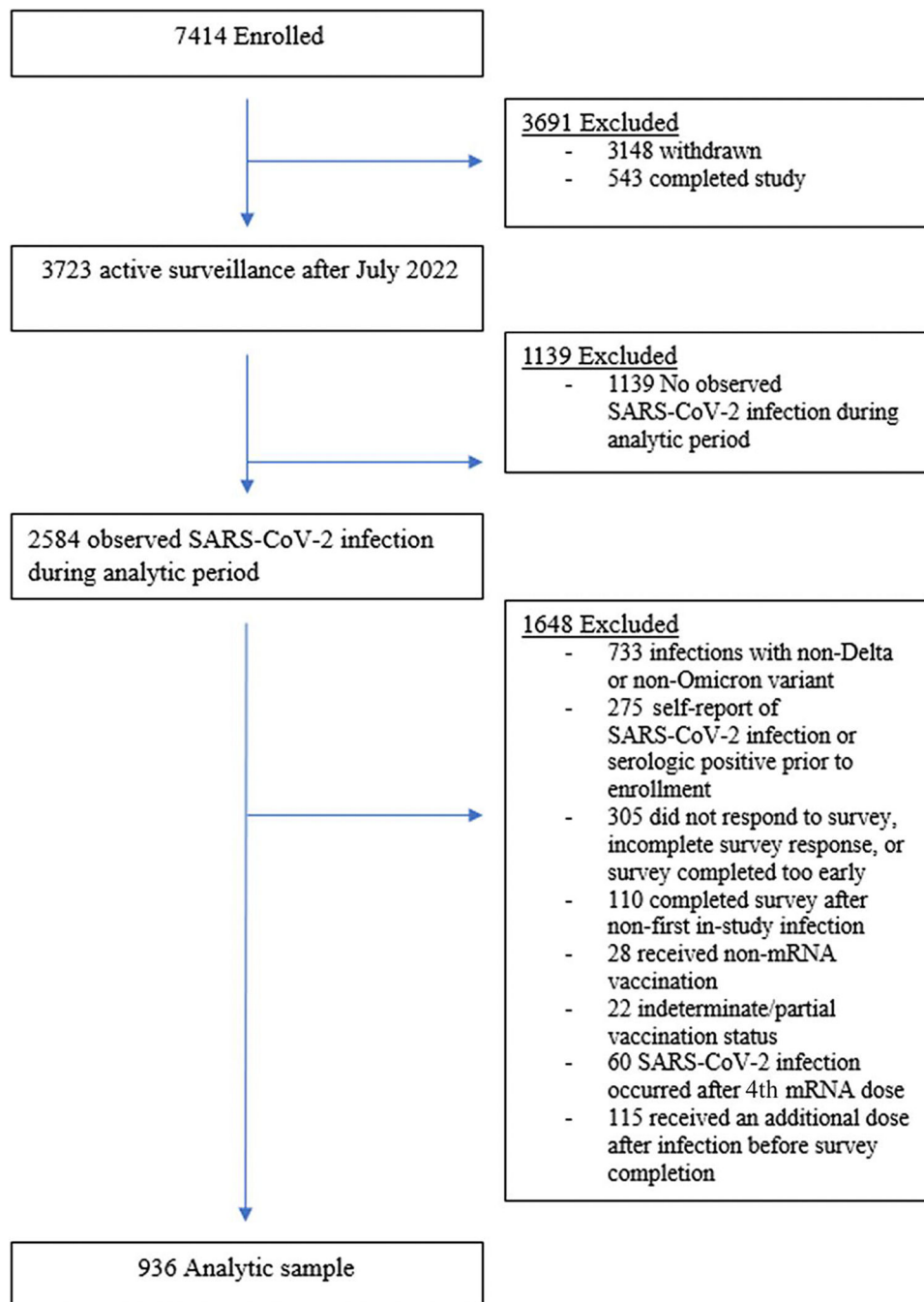


Figure 1.

Consolidated Standards of Reporting Trials (CONSORT) diagram of HEROES-RECOVER cohort participants included in an analysis of association of messenger RNA (mRNA) coronavirus disease 2019 vaccination and occurrence of post-COVID conditions after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Table 1.

Characteristics of HEROES-RECOVER Cohort Participants With Severe Acute Respiratory Syndrome Coronavirus 2 Infection Included in Analysis of Post-COVID Conditions (PCCs), by Whether They Did or Did Not Report PCCs on Postinfection Survey Between 5 May 2022 and 26 November 2022

Characteristic	Total		Did Not Report PCCs ^a		Reported PCCs ^a		P Value ^b
	No.	(Col %)	No.	(Col %)	No.	(Col %)	
No. of participants	936	...	715	(76.4)	221	(23.6)	
Sociodemographic characteristics							
Age, y, mean (SD)	44.2	(10.5)	44.1	(10.4)	44.8	(10.7)	.413
Gender							.000
Female	571	(61.0)	413	(57.8)	158	(71.5)	
Male	363	(38.8)	300	(42.0)	63	(28.5)	
Did not disclose ^c	2	...	2	...	0	...	
Race							.297
American Indian/Alaska Native	8	(0.9)	7	(1.0)	1	(0.5)	
Asian ^d	26	(2.8)	22	(3.1)	4	(1.8)	
Black or African American	16	(1.7)	11	(1.5)	5	(2.3)	
White	826	(88.2)	628	(87.8)	198	(89.6)	
Multiracial	8	(0.9)	4	(0.6)	4	(1.8)	
Did not disclose	52	...	43	...	9	...	.640
Ethnicity							
Hispanic	174	(18.6)	131	(18.3)	43	(19.5)	
Non-Hispanic	742	(79.3)	571	(79.9)	171	(77.4)	
Did not disclose	20	...	13	...	7	...	.308
Cohort location							
Phoenix, Arizona	152	(16.2)	105	(14.7)	47	(21.3)	
Tucson, Arizona	391	(41.8)	298	(41.7)	93	(42.1)	
Other, Arizona	107	(11.4)	83	(11.6)	24	(10.9)	
Miami, Florida	63	(6.7)	52	(7.3)	11	(5.0)	
Duluth, Minnesota	81	(8.7)	65	(9.1)	16	(7.2)	
Temple, Texas	31	(3.3)	25	(3.5)	6	(2.7)	

Characteristic	Total		Did Not Report PCCs ^d		Reported PCCs ^d		P Value ^b
	No.	(Col %)	No.	(Col %)	No.	(Col %)	
Salt Lake City, Utah	111	(11.9)	87	(12.2)	24	(10.9)	.001
Occupation ^e							
Primary HCP	148	(15.8)	124	(17.3)	24	(10.9)	
Secondary HCP	258	(27.6)	186	(26.0)	72	(32.6)	
First responder	224	(23.9)	187	(26.2)	37	(16.7)	
Frontline worker	306	(32.7)	218	(30.5)	88	(39.8)	<.0001
SARS-CoV-2 infection characteristics							
Infection type							
Symptomatic	855	(91.3)	639	(89.4)	216	(97.7)	
Asymptomatic	81	(8.7)	76	(10.6)	5	(2.3)	
No. of symptoms reported during infection							<.0001
0–3	257	(27.5)	219	(30.6)	38	(17.2)	
≥4	679	(72.5)	496	(69.4)	183	(82.8)	
Infection severity							.150
Nonhospitalized	897	(95.8)	685	(95.8)	212	(95.2)	
Hospitalized	6	(0.6)	3	(0.4)	3	(1.4)	
Did not respond	33	...	27	...	6	...	
SARS-CoV-2 lineage ^f							.144
Delta variant	102	(10.9)	72	(10.1)	30	(13.6)	
Omicron variant	834	(89.1)	643	(89.9)	191	(86.4)	
Medical history prior to SARS-CoV-2 infection							.077
No. of chronic conditions							
None	689	(73.6)	538	(73.6)	151	(68.3)	
≥1	232	(24.8)	168	(24.8)	64	(29.0)	
Did not disclose	15	...	9	...	6	...	
Daily medication use							.004
None	458	(48.9)	369	(48.9)	89	(40.3)	
≥1	459	(49.0)	333	(49.0)	126	(57.0)	
Did not disclose	19	...	13	...	6	...	

Characteristic	Total		Did Not Report PCCs ^a		Reported PCCs ^a		P Value ^b
	No.	(Col %)	No.	(Col %)	No.	(Col %)	
Smoking history							.137
Not current smoker	720	(76.9)	560	(76.9)	160	(72.4)	
Smoke tobacco products	198	(21.2)	144	(21.2)	54	(24.4)	
Did not disclose	18	...	11	...	7	...	
Self-rated health							.009
Excellent/very good	655	(70.0)	516	(70.0)	139	(62.9)	
Good/fair/poor	281	(30.0)	199	(30.0)	82	(37.1)	

Abbreviations: Col, column; HCP, healthcare personnel; PCC, post-COVID condition; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

^a PCC was defined as self-reported symptoms persisting >4 weeks after acute SARS-CoV-2 infection. Symptoms could have been continuous since initial infection or relapsing/remitting since initial infection.

^b P values calculated using Pearson χ^2 test (cells with ≥ 5 observations), Fisher's exact test (cells with <5 observations), or *t* test to assess difference in means.

^c Includes 2 individuals who reported "none of these."

^d Includes individuals who responded as native Hawaiian or other Pacific Islander.

^e Occupation categories: primary HCP (physicians, physician assistants, nurse practitioners, dentists), other allied HCP (nurses, therapists, technicians, medical assistants, orderlies, and all others providing clinical support in inpatient or outpatient settings), first responders (firefighters, law enforcement, corrections, emergency medical technicians), and essential and frontline workers (workers in hospitality, delivery, and retail; teachers; all other occupations that require contact within 3 feet of the public, customers, or coworkers as a routine part of their job).

^f SARS-CoV-2 lineage was determined through whole genome sequencing on eligible samples. For ineligible specimens (cycle threshold value ≥ 30), virus sequence was presumptively assigned as the Delta variant when Delta accounted for $\geq 50\%$ of viruses sequenced from other specimens at each site location; specimens were presumed to be the Omicron variant when $\geq 50\%$ of viruses sequenced were Omicron for each site.

Characteristics of HEROES-RECOVER Cohort Participants With Severe Acute Respiratory Syndrome Coronavirus 2 Infection Included in Analysis of Post-COVID Conditions, by Vaccination Status

Characteristic	Total		Unvaccinated		Vaccinated 2 Monovalent Doses (≥14 d Prior to Initial Infection)			Vaccinated 3 Monovalent Doses (≥7 d Prior to Initial Infection)		
	No.	(Col %)	No.	(Col %)	No.	(Col %)	P Value ^a	No.	(Row %)	P Value ^a
No. of participants	936	...	157	(16.8)	301	(32.2)		478	(51.1)	
Sociodemographic characteristics										
Age, y, mean (SD)	44.2	(10.5)	45.1	(11.0)	44.6	(10.9)	.684	43.7	(10.0)	.150
Gender							.647			.001
Female	571	(61.0)	82	(52.2)	165	(54.8)		324	(67.8)	
Male	363	(38.8)	74	(47.1)	136	(45.2)		153	(32.0)	
Did not disclose ^b	2	...	1	...	0	...		1	...	
Race										
American Indian/Alaska Native	8	(0.9)	0	(0.0)	3	(1.0)	.085	5	(1.0)	.141
Asian ^c	26	(2.8)	5	(3.2)	4	(1.3)		17	(3.6)	
Black or African American	16	(1.7)	0	(0.0)	8	(2.7)		8	(1.7)	
White	826	(88.2)	142	(90.4)	261	(86.7)		423	(88.5)	
Multiracial	8	(0.9)	2	(1.3)	5	(1.7)		1	(0.2)	
Did not disclose	52	...	8	...	20	...		24	...	
Ethnicity										
Hispanic	174	(18.6)	30	(19.1)	66	(21.9)	.589	78	(16.3)	.311
Non-Hispanic	742	(79.3)	119	(75.8)	229	(76.1)		394	(82.4)	
Did not disclose	20	...	8	...	6	...		6	...	
Cohort location										
Phoenix, Arizona	152	(16.2)	22	(14.0)	49	(16.3)	.364	81	(16.9)	.014
Tucson, Arizona	391	(41.8)	70	(44.6)	121	(40.2)		200	(41.8)	
Other, Arizona	107	(11.4)	19	(12.1)	28	(9.3)		60	(12.6)	
Miami, Florida	63	(6.7)	13	(8.3)	30	(10.0)		20	(4.2)	
Duluth, Minnesota	81	(8.7)	7	(4.5)	16	(5.3)		58	(12.1)	
Temple, Texas	31	(3.3)	2	(1.3)	16	(5.3)		13	(2.7)	

Characteristic	Total		Unvaccinated		Vaccinated 2 Monovalent Doses (≥14 d Prior to Initial Infection)			Vaccinated 3 Monovalent Doses (≥7 d Prior to Initial Infection)		
	No.	(Col %)	No.	(Col %)	No.	(Col %)	P Value ^a	No.	(Row %)	P Value ^a
Salt Lake City, Utah	111	(11.9)	24	(15.3)	41	(13.6)		46	(9.6)	
Occupation ^d							.061			<.001
Primary HCP	148	(15.8)	5	(3.2)	31	(10.3)		112	(23.4)	
Secondary HCP	258	(27.6)	40	(25.5)	75	(24.9)		143	(29.9)	
First responder	224	(23.9)	56	(35.7)	100	(33.2)		68	(14.2)	
Frontline worker	306	(32.7)	56	(35.7)	95	(31.6)		155	(32.4)	
SARS-CoV-2 infection characteristics										
Infection type							.001			.000
Symptomatic	855	(91.3)	131	(83.4)	280	(93.0)		444	(92.9)	
Asymptomatic	81	(8.7)	26	(16.6)	21	(7.0)		34	(7.1)	
No. of symptoms reported during infection							.097			.845
0–3	257	(27.5)	46	(29.3)	67	(22.3)		144	(30.1)	
≥4	679	(72.5)	111	(70.7)	234	(77.7)		334	(69.9)	
Infection severity							.607			.2586
Nonhospitalized	897	(95.8)	149	(94.9)	293	(97.3)		455	(95.2)	
Hospitalized	6	(0.6)	2	(1.3)	2	(0.7)		2	(0.4)	
Did not disclose	33	...	6	...	6	...		21	...	
SARS-CoV-2 lineage ^e							.071			<.0001
Delta variant	102	(10.9)	41	(26.1)	56	(18.6)		5	(1.0)	
Omicron variant	834	(89.1)	116	(73.9)	245	(81.4)		473	(99.0)	
Days since most recent vaccine dose, median (IQR)	198.0	(96.0–301.0)	...	...	324.0	(249.0–419.0)		112.0	(76.0–214.0)	
Medical history prior to SARS-CoV-2 infection										
No. of chronic conditions							.877			.883
None	689	(73.6)	113	(72.0)	221	(73.4)		355	(74.3)	
≥1	232	(24.8)	37	(23.6)	75	(24.9)		120	(25.1)	
Did not disclose	15		7		5			3		
Daily medication use							.528			.050
None	458	(48.9)	83	(52.9)	155	(51.5)		220	(46.0)	
≥1	459	(49.0)	66	(42.0)	140	(46.5)		253	(52.9)	

Characteristic	Total		Unvaccinated		Vaccinated 2 Monovalent Doses (≥14 d Prior to Initial Infection)			Vaccinated 3 Monovalent Doses (≥7 d Prior to Initial Infection)		
	No.	(Col %)	No.	(Col %)	No.	(Col %)	P Value ^a	No.	(Row %)	P Value ^a
Did not disclose	19	...	8	...	6	...		5	...	
Smoking history							.229			.551
Not current smoker	720	(76.9)	121	(77.1)	224	(74.4)		375	(78.5)	
Smoke tobacco products	198	(21.2)	28	(17.8)	70	(23.3)		100	(20.9)	
Did not disclose	18	...	8	...	7	...		3	...	
Self-rated health							.728			.363
Excellent/very good	655	(70.0)	106	(67.5)	208	(69.1)		341	(71.3)	
Good/fair/poor	281	(30.0)	51	(32.5)	93	(30.9)		137	(28.7)	
Vaccine product										
BNT162b2 (Pfizer-BioNTech)	460	(49.1)	...	...	166	(55.1)		294	(61.5)	
mRNA-1273 (Moderna)	285	(30.4)	...	...	133	(44.2)		152	(31.8)	
Mixed dosing ^f	34	(3.6)	...	...	2	(0.7)		32	(6.7)	

Abbreviations: Col, column; HCP, healthcare personnel; IQR, interquartile range; mRNA, messenger RNA; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

^aP values calculated using Pearson χ^2 test (cells with ≥5 observations), Fisher's exact test (cells with <5 observations), or *t* test to assess difference in means.

^bIncludes 2 individuals who reported "none of these."

^cIncludes individuals who responded as native Hawaiian or other Pacific Islander.

^dOccupation categories: primary HCP (physicians, physician assistants, nurse practitioners, dentists), other allied HCP (nurses, therapists, technicians, medical assistants, orderlies, and all others providing clinical support in inpatient or outpatient settings), first responders (firefighters, law enforcement, corrections, emergency medical technicians), and essential and frontline workers (workers in hospitality, delivery, and retail; teachers; all other occupations that require contact within 3 feet of the public, customers, or coworkers as a routine part of their job).

^eSARS-CoV-2 lineage was determined through whole genome sequencing on eligible samples. For ineligible specimens (cycle threshold value ≥30), virus sequence was presumptively assigned as the Delta variant when Delta accounted for ≥50% of viruses sequenced from other specimens at each site location; specimens were presumed to be the Omicron variant when ≥50% of viruses sequenced were Omicron for each site.

^fMixed dosing defined as receiving at least 1 dose of each mRNA vaccine.

Table 3.

Odds of Reporting Post-COVID Conditions After Severe Acute Respiratory Syndrome Coronavirus 2 Infection Among Vaccinated Versus Unvaccinated Study Participants

Outcome	Total		Unvaccinated		Vaccinated 2 Monovalent Doses (≥14 d Prior to Initial Infection)		Vaccinated 3 Monovalent Doses (≥7 d Prior to Initial Infection)	
	No.	(Col %)	No.	(Row %)	No.	(Row %)	No.	(Row %)
All participants	936	...	157	(16.8)	301	(32.2)	478	(51.1)
No PCC (no symptoms)	715	(76.3)	115	(16.3)	227	(32.2)	373	(52.8)
PCC by No. of symptoms								
≥1 symptom ^b	221	(23.6)	42	(19.0)	74	(33.5)	105	(47.5)
≥2 symptoms ^b	158	(16.5)	27	(17.1)	62	(39.2)	69	(43.7)
PCC by symptom category								
Cardiovascular/respiratory ^c	107	(11.4)	19	(17.8)	44	(41.1)	44	(41.1)
Gastrointestinal ^d	46	(4.9)	12	(26.1)	17	(37.0)	17	(37.0)
General ^e	152	(16.2)	26	(17.1)	58	(38.2)	68	(44.7)
Neurological ^f	128	(13.7)	26	(20.3)	44	(34.4)	58	(45.3)
Other ^g	80	(8.5)	19	(23.8)	29	(36.3)	32	(40.0)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; Col, column; PCC, post-COVID condition.

^a Odds ratio estimated using logistic regression with no PCC (no symptoms) as referent group. All models were adjusted for gender, presence of chronic conditions (categorized by none or ≥1 chronic condition), age (categorized as <40 or ≥40 years), number of symptoms experienced during acute infection (categorized as ≤3 or >3), interval between initial infection and survey completion (categorized as 60–119 days, 120–179 days, and ≥180 days), and variant of infection (Delta or Omicron).

^b Symptoms include shortness of breath, palpitations, chest pain/tightness, runny nose/congestion, loss of appetite, nausea, vomiting, abdominal/stomach pain, constipation, diarrhea, worsening of symptoms following minor mental or physical activity, fatigue, joint pain, joint swelling, muscle pain, dizziness/lightheadedness/fainting, numbness/tingling, foggy in thinking, change in sleeping, headache, difficulty speaking/communicating, difficulty swallowing/chewing, problems with balance/movement.

^c Cardiovascular/respiratory symptoms include shortness of breath, palpitations, chest pain/tightness, and runny nose/congestion.

^d Gastrointestinal symptoms include loss of appetite, nausea, vomiting, abdominal/stomach pain, constipation, and diarrhea.

^e General symptoms include worsening of symptoms following minor mental or physical activity, fatigue, joint pain, joint swelling, and muscle pain.

^f Neurological symptoms include dizziness/lightheadedness/fainting, numbness/tingling, foggy in thinking, change in sleeping, headache, difficulty speaking/communicating, difficulty swallowing/chewing, and problems with balance/movement.

^gOther symptoms include weight loss, hair loss, change in color of toes/fingers, rash, bruising/bleeding easily, change in menstrual cycle, change in sexual drive, and erectile dysfunction.

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