Determinants and Dynamics of SARS-CoV-2 Infection in a Diverse Population: 6-Month Evaluation of a Prospective Cohort Study

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Background. We studied risk factors, antibodies, and symptoms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in a diverse, ambulatory population.

Methods. A prospective cohort (n = 831) previously undiagnosed with SARS-CoV-2 infection underwent serial testing (SARS-CoV-2 polymerase chain reaction, immunoglobulin G [IgG]) for 6 months.

Results. Ninety-three participants (11.2%) tested SARS-CoV-2-positive: 14 (15.1%) asymptomatic, 24 (25.8%) severely symptomatic. Healthcare workers (n = 548) were more likely to become infected (14.2% vs 5.3%; adjusted odds ratio, 2.1; 95% confidence interval, 1.4–3.3) and severely symptomatic (29.5% vs 6.7%). IgG antibodies were detected after 79% of asymptomatic infections, 89% with mild-moderate symptoms, and 96% with severe symptoms. IgG trajectories after asymptomatic infections (slow increases) differed from symptomatic infections (early peaks within 2 months). Most participants (92%) had persistent IgG responses (median 171 days). In multivariable models, IgG titers were positively associated with symptom severity, certain comorbidities, and hospital work. Dyspnea and neurologic changes (including altered smell/taste) lasted ≥ 120 days in ≥ 10% of affected participants. Prolonged symptoms (frequently more severe) corresponded to higher antibody levels.

Conclusions. In a prospective, ethnically diverse cohort, symptom severity correlated with the magnitude and trajectory of IgG production. Symptoms frequently persisted for many months after infection.

Clinical Trials Registration. NCT04336215.

Keywords. COVID-19; humoral immunity; longitudinal data analysis; postacute sequelae of COVID-19; prospective cohort; risk factors; SARS-CoV-2 infection; symptoms.

As the coronavirus disease 2019 (COVID-19) pandemic continues to surge, as of early May 2021, the United States has recorded the most cases (>32 million) and deaths (>580 000) of any country [1]. Approximately one-third of infections are estimated to be asymptomatic [2–4] and are considered important drivers of viral transmission [5]. Nonetheless, asymptomatic infections may be accompanied by subclinical abnormalities in laboratory tests and lung imaging [6]. Important questions remain about long-term clinical and immunologic consequences of asymptomatic infections.

Most persons infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) develop antibodies against the virus [7]. However, immune responses vary considerably, with a minority of infected people not producing detectable antibodies [8]. The magnitude of humoral immune responses may be proportional to illness severity [9, 10]. The duration and trajectory of humoral immunity also remain unclear; some studies report substantial declines in antibody responses within a few months [11, 12] while others report persistent responses over many months [8, 13, 14]. One challenge in interpreting these studies is differences in study populations: most studies have focused on hospitalized, convalescent, and

referred patients previously diagnosed with SARS-CoV-2 infection, raising questions about selection bias and generalizability. Few prospective studies have systematically evaluated long-term antibody trends and associated factors among diverse, previously undiagnosed populations of individuals across a spectrum of illness severity, including asymptomatic infections [15].

We characterized the incidence of and risk factors for SARS-CoV-2 infection in a prospective cohort of ambulatory, previously undiagnosed healthcare workers (HCWs) and non-HCWs recruited early in the US pandemic and followed over 6 months. The study was conducted in New Jersey (NJ), an ethnically diverse state hit particularly hard by the spring 2020 COVID-19 surge [1, 16]. We further examined dynamics and correlates of anti-SARS-CoV-2 antibodies and persistence of symptoms up to 6 months postinfection.

METHODS

Study Design and Population

As described [17], the Rutgers Corona Cohort is a prospective, university-based observational cohort of HCWs and non-HCW comparators recruited and consented 24 March to 7 April 2020, across 2 campuses (Newark and New Brunswick/Piscataway). Eligibility criteria included: (1) age ≥ 20 years; (2) not pregnant or breastfeeding; (3) no recent (prior 30 days) urgent care or emergency department visits, hospitalizations, operations, or changes in prescribed medicines; (4) no previously diagnosed SARS-CoV-2 infection/COVID-19; and (5) no fever at the baseline visit. Eligibility for HCWs required: (1) ≥ 20 hours of weekly hospital work; (2) roles with regular patient exposure (eg, physicians, nurses, technicians, respiratory therapists); and (3) regular direct patient contact (≥3 patients/shift). Eligibility for a comparator group of non-HCWs required: (1) work as faculty, staff, or students at Rutgers for ≥ 20 hours weekly; and (2) no patient contact. Hospital-based employees without direct patient care responsibilities were not eligible for enrollment. All study activities were approved by the Rutgers Institutional Review Board (Pro2020000679) and all participants provided electronic informed consent prior to engaging in study activities.

Study Activities and Data

Study visits took place at baseline, 2, 4, 8, 16, and 26 weeks. At each visit, study staff in personal protective equipment (PPE) measured body temperature and collected oropharyngeal swabs immersed in phosphate-buffered saline [18] and blood using serum separator tubes. For the first 2 study months, participants recorded an early evening body temperature using a study-issued oral thermometer. Participants completed questionnaires at baseline, weekly for 2 months, then every other week. Questionnaire items included demographics, comorbidities, lifestyle, occupation, COVID-19 exposures and diagnoses, recent symptoms, and, for HCWs, unit locations, patient contacts, and PPE use. Participant zip code was used to classify residence in areas with high COVID-19 rates, defined as > 2% of residents with confirmed infections as of 20 August 2020.

Additional information about SARS-CoV-2–positive participants was obtained through follow-up surveys, telephone calls, and medical chart review; symptoms were assessed using all available data sources. Among symptomatic participants, overall symptom severity was assessed using the question: "Please consider any past or present COVID-19 symptoms when answering the following question: Overall, when these symptoms were at their worst, how bad or bothersome were they?" Responses options were: mild, moderate, severe, and very severe. Based on the distribution of responses, we categorized symptom severity as asymptomatic, mild-moderate, or severe. All study data were managed using REDCap electronic data capture tools hosted at Rutgers Robert Wood Johnson Medical School [19].

SARS-CoV-2 Assays

SARS-CoV-2 assays were conducted at all study visits under Food and Drug Administration-approved Emergency Use Authorization number 200090 at Infinity Biologix (Piscataway, NJ), as described [17, 18]. In brief, total RNA was extracted from oropharyngeal swabs using nucleic acid-binding paramagnetic beads (Chemagic Viral DNA/RNA 300 Kit H96). Reverse transcriptase-polymerase chain reaction (RT-PCR) was performed in triplicate for 3 SARS-CoV-2 genomic regions: nucleocapsid (N), spike protein (S), and ORF1ab. Positive and negative assay controls were used.

SARS-CoV-2 Antibody Testing

We used an in-house developed enzyme-linked immunosorbent assay (ELISA) platform for antibody binding to 2 portions of SARS-CoV-2 spike protein (S1 subunit receptor-binding domain [RBD], full-length S2 subunit) [20]. Detection of antigen-bound antibodies used combined alkaline phosphatase-conjugated anti-human immunoglobulin A (IgA), IgM, and IgG secondary antibodies, or anti-human IgG antibody alone, at 1:2000 dilution (Supplementary Methods and Supplementary Table 1). For participants with optical density 450 (OD_{405}) ≥1 positive IgM/G/A (total) antibody test and/or positive PCR, anti-RBD IgG titers were determined. Seropositivity was defined as total antibody levels OD_{405} ≥0.7 across ≥ 2 time points or ≥ 1.0 once; or IgG titers ≥ 1:80 across ≥ 2 time points or ≥ 1:320 once. We chose RBD as our solid-phase antigen in our assay because it is a preferred target of neutralizing antibodies [21].

Routine Chemistries and Blood Counts

Comprehensive metabolic panels were analyzed on baseline plasma samples, and cell counts were analyzed on whole-blood samples from all visits, using standard clinical assays (Beckman Coulter).

Statistical Analyses

Study outcomes were defined by SARS-CoV-2 positivity with PCR and/or antibody testing (IgM/G/A or IgG only). Comparisons of characteristics between SARS-CoV-2–infected and –uninfected participants and between HCWs and non-HCWs used χ^2 or Fisher exact testing (categorical data) and t tests or Wilcoxon rank sum testing (continuous data), as appropriate. Trends were evaluated across levels of symptom severity using Cochran-Armitage tests (categorical data) and Jonckheere-Terpstra tests (continuous data).

To identify explanatory baseline and early exposure characteristics associated with likelihood of SARS-CoV-2 infection, multivariable logistic regression models were fitted with elastic net penalty for regularization, permitting selection from many variables (Table 1) while avoiding overfitting due to penalties on regression coefficients. Separate models were applied to all participants and to HCWs, the latter including HCW-specific variables (eg, role, PPE use) (Table 1). Models accounted for time-varying exposures (eg, sick contacts, patient care metrics) over the first study month, during the first surge's peak [22]; data after SARS-CoV-2 diagnosis were excluded to limit bias from factors resulting from infection.

Antibody curves were estimated for (1) different levels of symptom severity and (2) different durations of symptoms, with spline for time and random effects set to 0. To identify factors associated with IgG titers at each visit, we fitted generalized additive mixed effects models. We included all SARS-CoV-2–positive participants (PCR positive or antibody positive) except individuals newly positive by PCR at the final (26-week) visit (n = 2), who had not yet mounted an antibody response. Time of positivity was anchored by the date of the first positive test (PCR or antibody), defined as time 0. Given the nonlinear changes in antibody levels expected over time, models included a spline function for time. A random intercept accounted for within-subject correlation over time. Model variables included symptom severity (none, mild-moderate, severe), preselected baseline chemistries (glomerular filtration rate, alanine aminotransferase, albumin), time-updating cell counts (lymphocytes, neutrophils, platelets, hemoglobin), and variables listed in Table 1. Missing data were imputed using multiple imputation with chained equations based on 50 imputed data sets [23]. Presence and persistence of symptoms over time was graphed using Kaplan-Meier plots and summarized by the median, 75th and 90th percentiles. Analyses were performed using SAS 9.4, R 4.0.3, and Stata 16.1.

RESULTS

We enrolled 831 participants (548 HCWs, 283 non-HCWs; Supplementary Figure 1); 722 (86.9%) completed a 26-week visit and 758 (91.2%) completed at least 5 of 6 study visits. Overall, 71% of participants completed at least 12 of 16 follow-up questionnaires. Two-thirds of participants were female, and half were < 40 years old (Table 1). The cohort was racially and ethnically diverse (58.6% white, 20.8% Asian, 10.9% black, 9.7% other race, and 12.2% Hispanic/Latino). Nearly half (45.3%) of participants had at least 1 comorbidity, most commonly obesity (22.8%). Within 1 month after enrollment, 23.8% reported exposure to someone outside of home/work suspected or confirmed to have COVID-19. Most HCWs (91.8%) reported close contact with ≥ 1 patient with suspected or confirmed COVID-19 within 1 month of enrollment. Compared to non-HCWs, HCWs were younger, more racially diverse, more likely Newark-based, and more likely to report unprotected COVID-19 exposures at and outside work before diagnosis (Supplementary Table 2). Compared to eligible persons who did not enroll, enrolled participants were more likely to be of Hispanic/Latino ethnicity, have certain comorbidities (eg, respiratory, autoimmune), be a HCW, and be recruited at the Newark campus, and less likely to be female and a HCW caring for patients with COVID-19 (Supplementary Table 3).

Ultimately, 93 participants (11.2%) tested positive for virus and/or antibodies, 86 (92.5%) within the first 2 months of the study, echoing trends more broadly in NJ and participating hospitals (Supplementary Figure 2). Five participants tested positive at the final visit (3 by PCR, 2 by antibody), during the second COVID-19 surge in NJ in late 2020. These included 1 late asymptomatic PCR-positive infection following early asymptomatic infection in April, with sustained low-titer IgG and 5 negative PCRs until late September.

Among infected participants, 62 (66.7%) tested positive by both PCR and antibodies, 12 (12.9%) tested positive by PCR only, and 19 (20.4%) tested positive by antibody only. Of infected participants, 24 (25.8%) reported severe symptoms (including the 5 hospitalized participants, none in intensive care units [ICUs]), 55 (59.1%) reported mild to moderate symptoms, and 14 (15.1%) reported no symptoms. Only 13 (14.0%) infected participants received pharmacologic treatment. Despite being less likely to live in high-risk zip codes (10.3% vs 17.1%, P = .02), HCWs were significantly more likely to test positive for virus or antibodies (14.2% vs 5.3%, P < .001). Among infected individuals, HCWs were more likely to have severe symptoms (29.5% vs 6.7%, P = .04) and require hospitalization (6.4% vs 0%, P = .31). Self-reported severity correlated with symptom burden, settings of care, treatments received, and laboratory values (Supplementary Table 4 and Supplementary Figure 3). More-symptomatic participants had lower hemoglobin and absolute lymphocyte and neutrophil counts during follow-up, especially while infected (Supplementary Figure 4).

Among all participants, the factors most strongly associated with infection were HCW status (adjusted odds ratio [aOR], 2.13; 95% confidence interval [CI], 1.36–3.33) and Newark affiliation (aOR, 1.55; 95% CI, 1.06–2.25) (Figure 1A). Among HCWs, nursing role and Newark affiliation were most positively associated with infection, whereas work in ICUs or COVID-19

Table 1. Characteristics of Rutgers Corona Cohort Study Participants Stratified by SARS-CoV-2 Test Results[a]

Characteristics	All (n = 831)	Ever Positive (n = 93, 11.2%)	Never Positive (n = 738, 88.8%)	P Value[b]
Female	533 (64.1)	66 (71.0)	467 (63.3)	.15
Age, y				.52
20–39	430 (51.7)	50 (53.8)	380 (51.5)	
40–59	315 (37.9)	31 (33.3)	284 (38.5)	
≥60	86 (10.3)	12 (12.9)	74 (10.0)	
Race				.03
White	483 (58.6)	53 (58.9)	430 (58.6)	
Asian	171 (20.8)	10 (11.1)	161 (21.9)	
Black	90 (10.9)	15 (16.7)	75 (10.2)	
Other	80 (9.71)	12 (13.3)	68 (9.26)	
Hispanic/Latino ethnicity	101 (12.2)	19 (20.4)	82 (11.1)	.01
Residence in high-risk zip code[c]	101 (12.6)	6 (6.59)	95 (13.3)	.18
Child < 18 y in the home	326 (39.2)	36 (38.7)	290 (39.3)	.91
Smoking				.21
Current	37 (4.47)	4 (4.30)	33 (4.49)	
Former	230 (27.8)	33 (35.5)	197 (26.8)	
Chronic illness	376 (45.2)	51 (54.8)	325 (44.0)	.05
Obesity	188 (22.8)	31 (33.3)	157 (21.5)	.01
Diabetes mellitus	48 (5.84)	2 (2.15)	46 (6.31)	.11
Hypertension	125 (15.2)	20 (21.7)	105 (14.3)	.06
Cardio/cerebrovascular disease	20 (2.41)	3 (3.23)	17 (2.30)	.58
Chronic respiratory disorder[d]	113 (13.6)	10 (10.8)	103 (14.0)	.40
Autoimmune disease or immunosuppressant use	40 (4.81)	5 (5.38)	35 (4.74)	.79
HCW	548 (65.9)	78 (83.9)	470 (63.7)	<.001
Attending physician	113 (13.6)	8 (8.60)	105 (14.2)	<.001
Resident or fellow physician	98 (11.8)	8 (8.60)	90 (12.2)	
Nurse	225 (27.1)	45 (48.4)	180 (24.4)	
Other role	112 (13.5)	17 (18.3)	95 (12.9)	
Work location				<.001
Newark	342 (41.2)	54 (58.1)	288 (39.0)	
New Brunswick/Piscataway	489 (58.8)	39 (41.9)	450 (61.0)	
Exposure over the first month[e]				
Worked on site, ever	752 (90.8)	86 (95.6)	666 (90.2)	.10
Stayed home as much as possible when not working	502 (60.5)	63 (68.5)	439 (59.5)	.10
Avoided others as much as possible when not at work	514 (61.9)	67 (72.0)	447 (60.6)	.03
Mask use outside the home[f]				.51
None	510 (61.4)	52 (55.9)	458 (62.1)	
Sometimes	225 (27.1)	29 (31.2)	196 (26.6)	
Always	95 (11.4)	12 (12.9)	83 (11.3)	
Unprotected COVID-19 exposure at home	112 (14.4)	16 (42.1)	96 (13.0)	<.001
Unprotected COVID-19 exposure at work	543 (67.0)	66 (90.4)	477 (64.6)	<.001
Unprotected COVID-19 exposure outside home/work	103 (13.3)	12 (34.3)	91 (12.3)	<.001
Unprotected COVID-19 exposure at home or outside home/work	188 (24.1)	25 (61.0)	163 (22.1)	<.001
Average level of patient contact				<.001
Non-HCW	283 (34.2)	15 (16.3)	268 (36.4)	
Patient contact below median	268 (32.4)	60 (65.2)	208 (28.3)	
Patient contact at or above median	277 (33.5)	17 (18.5)	260 (35.3)	
HCWs only				
Worked in emergency department	311 (38.9)	43 (69.4)	268 (36.3)	<.001
Worked on medical floor	246 (31.5)	22 (50.0)	224 (30.4)	.01
Worked in operating room	147 (18.8)	24 (52.2)	123 (16.7)	<.001
Worked in intensive care unit	262 (33.7)	19 (47.5)	243 (32.9)	.06
Worked in designated COVID-19 unit	242 (31.2)	17 (44.7)	225 (30.5)	.06
Average % patients for whom used PPE per shift				.86
<25%	42 (7.79)	6 (7.89)	36 (7.78)	
25%–49%	48 (8.91)	8 (10.5)	40 (8.64)	
≥50%	449 (83.3)	62 (81.6)	387 (83.6)	

Table 1. Continued

Characteristics	All (n = 831)	Ever Positive (n = 93, 11.2%)	Never Positive (n = 738, 88.8%)	P Value[b]
Average % time in PPE using N95 mask per shift				<.001
<25%	75 (14.0)	22 (28.9)	53 (11.5)	
25%–49%	51 (9.51)	8 (10.5)	43 (9.35)	
≥50%	410 (76.5)	46 (60.5)	364 (79.1)	
Average number of patients with COVID-19 per shift				.12
0	41 (8.17)	10 (13.3)	31 (7.26)	
1–4	170 (33.9)	20 (26.7)	150 (35.1)	
≥5	291 (58.0)	45 (60.0)	246 (57.6)	

Data are No. (%).

Abbreviations: COVID-19, coronavirus disease 2019; HCW, healthcare worker; PPE, personal protective equipment; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]PCR- or antibody-positive for SARS-CoV-2 were classified as positive.

[b]P values were computed using χ^2 or Fisher exact testing, as appropriate.

[c]High-risk zip code defined as having confirmed SARS-CoV-2 infections in > 2% of residents as of 20 August 2020.

[d]Asthma, chronic obstructive pulmonary disease, or other chronic lung disease.

[e]Excluding any values after diagnosis of SARS-CoV-2 infection.

[f]Lowest reported value in the first month of participation.

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units was negatively associated with infection (Figure 1B). More-extensive N95 use was reported among SARS-CoV-2–negative participants (Table 1).

Median follow-up after diagnosis was 171 days (interquartile range, 158–180). Not including 2 participants newly PCR-positive at week 26, overall seropositivity was lower among asymptomatic participants (IgG 79%) compared to mildly-moderately symptomatic (IgG 89%) and severely symptomatic participants (IgG 96%) (Supplementary Table 4). At the final visit, IgG antibody prevalences among previously infected participants were: asymptomatic, IgG 69%; mildly-moderately symptomatic, IgG 83%; severely symptomatic, IgG 91%. Among antibody-positive participants (by total Ig or IgG) infected in the first wave with available samples at month 6, detectable antibodies persisted in most (67/73, 92%) participants, irrespective of symptom severity. Severe symptomatic illness was most strongly associated with higher IgG titers over time (coefficient 1.03; 95% CI, .71–1.36; Figure 2, Figure 3, Supplementary Table 4, and Supplementary Figure 5). Other factors associated with higher IgG titers included several comorbidities and HCW status; factors associated with lower IgG titers included Asian race, smoking, and working on site within 1 month after enrollment (Figure 3).

Among symptomatic infected participants, the median duration of most symptoms was ≤ 2 weeks except for neurologic changes besides altered smell and taste (eg, brain fog, memory problems, visual disturbances; median 45 days), which were least prevalent among 15 symptoms measured (changes reported in 12% of participants) (Figure 4 and Supplementary Figure 6). Nonetheless, multiple symptoms were reported in ≥ 25% of affected individuals for ≥ 30 days, and ≥ 10% of affected individuals reported having ≥ 120 days of shortness of breath, chest congestion, loss of small and/or taste, and other neurologic changes (Figure 4 and Supplementary Figure 6). About one-third (33/93, 35%) reported symptoms lasting 30 days or longer. Not surprisingly, symptom duration was correlated with symptom severity ($r = 0.26$, $P = .03$) and antibody titer ($P = .03$; Figure 5).

DISCUSSION

This study represents a 6-month prospective cohort study of risk factors, humoral responses, and symptoms in ambulatory, previously undiagnosed, at-risk individuals, recruited from a diverse professional community affected early in the US pandemic. Over 1 in 10 participants were SARS-CoV-2 infected, and most were followed for 5–6 months with excellent cohort retention. HCWs were more likely to become infected and have more severe illness. Among hospital workers, nurses were at greater risk for infection, whereas ICU and COVID-19 unit workers were at lower risk. Symptom severity and duration were associated with magnitude and trajectory of antibody responses. In contrast, most demographic characteristics, comorbidities (except hypertension), and laboratory criteria were not associated with antibody responses. Persons with asymptomatic infections had few changes in cell counts, lower seroconversion rates, and lower antibody levels. Multiple symptoms lasted 1 month or longer in at least 25% of participants; neurologic changes besides altered smell or taste were less frequent (approximately 1/8) but generally long lasting in those reporting them.

We and others have reported increased risks of SARS-CoV-2 among HCWs [17, 22, 24]. In our cohort, professional role (eg, nursing) was associated with greater risk. We also observed differences in illness severity between HCWs and others: HCWs were more likely to have severe symptoms and more robust antibody responses, consistent with other research suggesting higher risk of hospitalization among infected HCWs, particularly those with patient-facing roles, including nurses [25, 26]. In contrast to some [26] but consistent with other [27] studies, we observed lower infection rates among ICU workers and even those on COVID-19 units, which may have related to more

rigorous N95-mask usage. Unlike in other studies [28], HCWs in our cohort were less likely to live in areas with higher rates of local transmission, and the increased rates observed were not well explained by outside exposures. The excess rates of infection in Newark may have resulted from later implementation of universal masking in that hospital versus in New Brunswick [29].

Our longitudinal cohort study contributes new insights into several aspects of the humoral response to SARS-CoV-2

infection. One is the correlation between rates of seropositivity and presence or severity of symptoms. Some studies have reported high rates of seropositivity after even asymptomatic or mild infections [6, 13], while others have found a correlation between illness severity and seropositivity [9, 30]. Such distinctions may relate to differences in recruitment, because studies that recruited previously diagnosed or self-referred infected volunteers are subject to selection bias by excluding those with asymptomatic or milder, undiagnosed infection. This was not
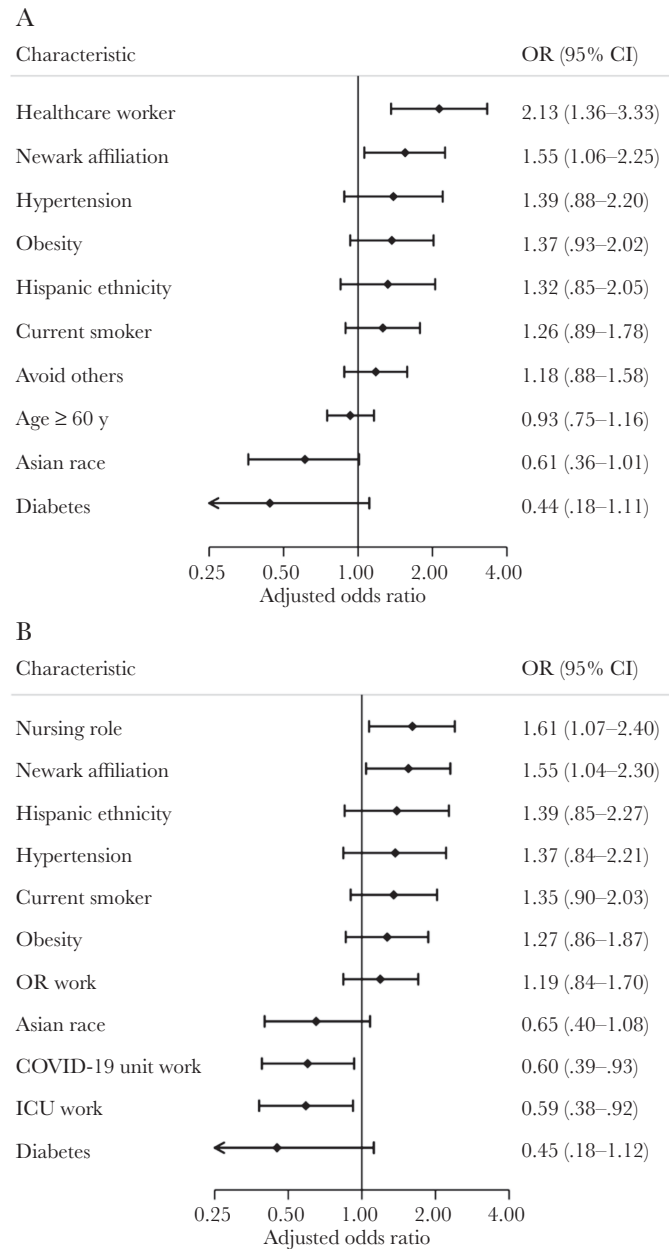
Figure 1. Factors associated with SARS-CoV-2 infection. Forest plots show factors associated with infection in (*A*) Rutgers Corona Cohort participants (n = 831) and (*B*) the subset of healthcare workers (n = 548) as measured by positive SARS-CoV-2 PCR or antibody testing. Results reflect aORs from multivariable logistic regression models fitted with elastic net penalty for regularization and variable selection from among variables listed in Table 1. Reference groups included: age < 40 years (versus ≥ 60 years), white race (versus Asian race), and attending physician (vs nursing). Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit; OR, operating room; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

an issue with our prospective cohort study design, which minimized the influence of selection bias and enhanced the internal validity of our findings. Second, we observed a strong positive correlation between antibody levels and symptom severity, which might be explained by stronger B-cell activation in the context of excessive inflammation typically associated with severe COVID-19 [31]. Because our cohort comprised an ambulatory population with mostly mild infections not requiring hospitalization, our work expands on previous observations of positive correlations between strength of antibody
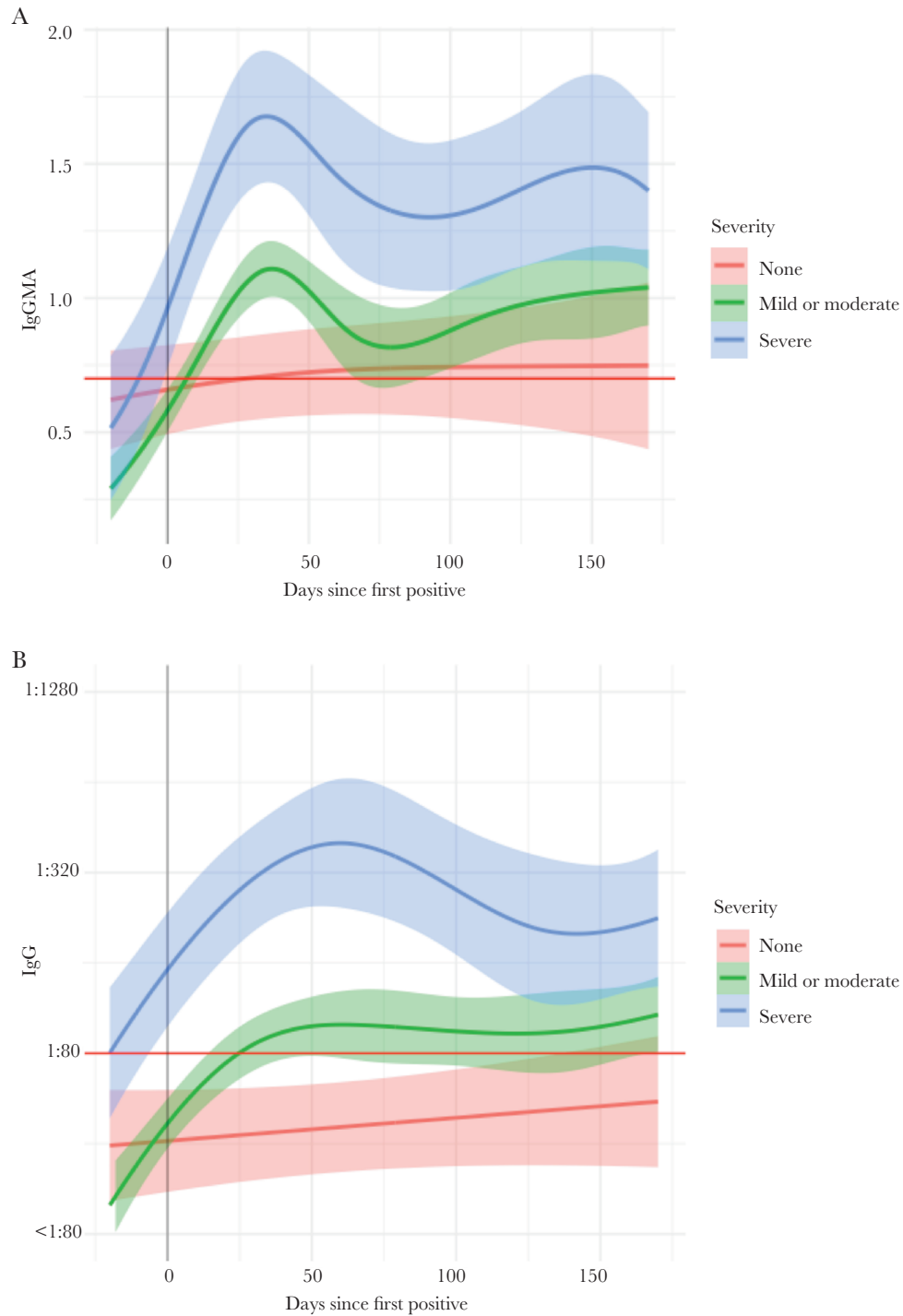
Figure 2. Average antibody levels over time among SARS-CoV-2–infected Rutgers Corona Cohort participants, stratified by symptom severity. Plots show estimated average levels of (*A*) total antibody and (*B*) IgG over time with 95% confidence intervals based on symptom severity. Curves and 95% confidence bands were estimated for different levels of symptom severity by fitting a model with a spline function for time and a random intercept to account for repeated measures. Abbreviations: Ig, immunoglobulin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
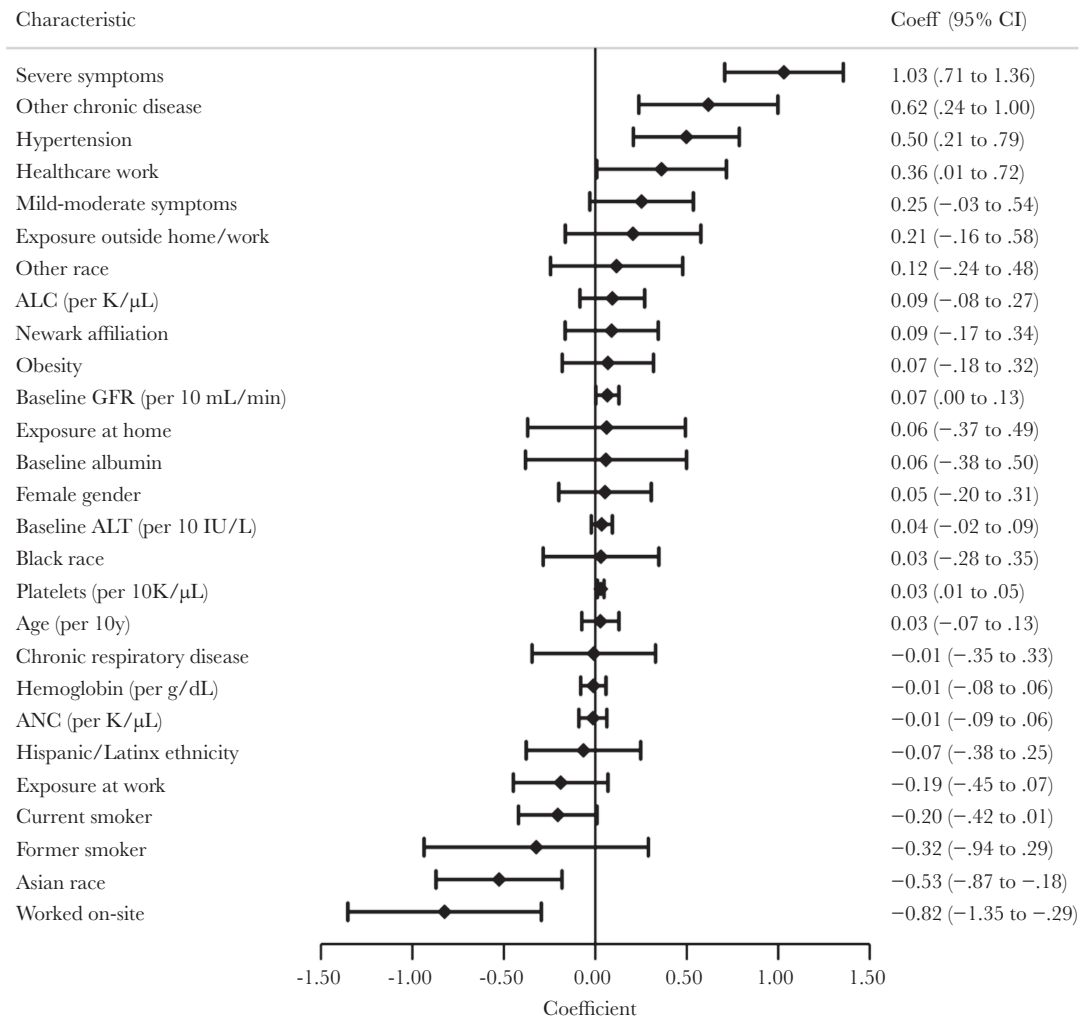
Characteristic	Coeff (95% CI)
Severe symptoms	1.03 (.71 to 1.36)
Other chronic disease	0.62 (.24 to 1.00)
Hypertension	0.50 (.21 to .79)
Healthcare work	0.36 (.01 to .72)
Mild-moderate symptoms	0.25 (−.03 to .54)
Exposure outside home/work	0.21 (−.16 to .58)
Other race	0.12 (−.24 to .48)
ALC (per K/µL)	0.09 (−.08 to .27)
Newark affiliation	0.09 (−.17 to .34)
Obesity	0.07 (−.18 to .32)
Baseline GFR (per 10 mL/min)	0.07 (.00 to .13)
Exposure at home	0.06 (−.37 to .49)
Baseline albumin	0.06 (−.38 to .50)
Female gender	0.05 (−.20 to .31)
Baseline ALT (per 10 IU/L)	0.04 (−.02 to .09)
Black race	0.03 (−.28 to .35)
Platelets (per 10K/µL)	0.03 (.01 to .05)
Age (per 10y)	0.03 (−.07 to .13)
Chronic respiratory disease	−0.01 (−.35 to .33)
Hemoglobin (per g/dL)	−0.01 (−.08 to .06)
ANC (per K/µL)	−0.01 (−.09 to .06)
Hispanic/Latinx ethnicity	−0.07 (−.38 to .25)
Exposure at work	−0.19 (−.45 to .07)
Current smoker	−0.20 (−.42 to .01)
Former smoker	−0.32 (−.94 to .29)
Asian race	−0.53 (−.87 to −.18)
Worked on-site	−0.82 (−1.35 to −.29)

Coefficient axis: -1.50, -1.00, -0.50, 0.00, 0.50, 1.00, 1.50

Figure 3. Factors associated with IgG titer among SARS-CoV-2–infected Rutgers Cohort participants (n = 81). Estimates reflect coefficients for factors in association with log-transformed IgG titer over time from a generalized additive mixed model, fitted with a spline for time. Factors reflect baseline values except disease severity (global assessment), cell counts (updated over time), and selected variables reflecting exposure in the first month of follow-up but excluding any values after SARS-CoV-2–positive testing (unprotected exposures to infected persons, worked on site). See "Methods" for details. Reference groups not shown are no symptoms, white race, and never smoker. Other chronic disease includes diabetes mellitus, cardio/cerebrovascular disease, cancer, chronic kidney disease, autoimmune disease, or immunosuppressant use. Chronic respiratory disease includes asthma, chronic obstructive pulmonary disease, or other chronic lung disease. Abbreviations: ALC, absolute lymphocyte count; ALT, alanine transaminase; ANC, absolute neutrophil count; CI, confidence interval; GFR, glomerular filtration rate; IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

responses and COVID-19 severity, which were obtained in studies including only hospitalized patients or clinically diagnosed convalescent cases [32–34]. Moreover, while our study does not address cellular immunity, it allows for indirect inferences about immune status, because no or weak anti-SARS-CoV-2 antibody responses are accompanied by low frequencies of antigen-specific T cells [35]. Third, prior reports of anti-SARS-CoV-2 antibody trajectories have been conflicting, with some studies reporting antibody declines and loss of detectable antibodies, particularly following asymptomatic infections [6, 11, 12], and others showing antibody responses persisting for several months [8, 13, 14, 36]. In our study, most participants had sustained IgG up to 6 months after infection, irrespective of symptom severity. We also found severity-related differences in antibody trajectories, with slow, steady increases following asymptomatic infections compared to sharper rises and declines after symptomatic infections. These findings echo previous findings of sustained, nondeclining antibody responses in those with milder infections [36].

We cannot extrapolate our results to SARS-CoV-2 variants of concern (VOCs) because our cohort was recruited and followed in 2020 during earlier phases of the pandemic, prior to the emergence of several VOCs, including the highly transmissible Delta variant [37, 38]. Furthermore, given the relative reduction of protective immune responses against the Delta variant among previously infected persons [39, 40], our data do not
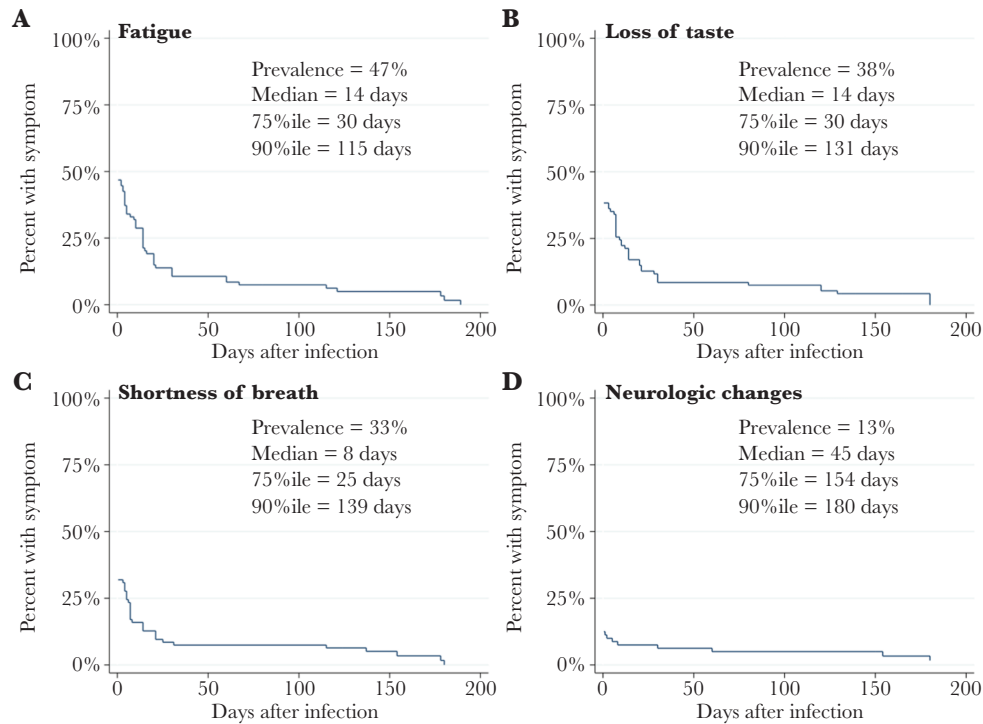
Figure 4. Duration of selected symptoms in infected RCC participants. Kaplan-Meier plots show prevalence and time course (in days) of 4 selected symptoms among infected RCC participants from infection to resolution: (*A*) fatigue; (*B*) loss of taste; (*C*) shortness of breath; and (*D*) neurologic changes besides altered taste or smell, eg, altered cognition or visual changes. Symptoms are shown in decreasing order of overall prevalence (*A–D*). Median, 75th, and 90th percentiles are indicated for each symptom among those who reported the symptom. Abbreviations: %ile, percentile; RCC, Rutgers Corona Cohort.
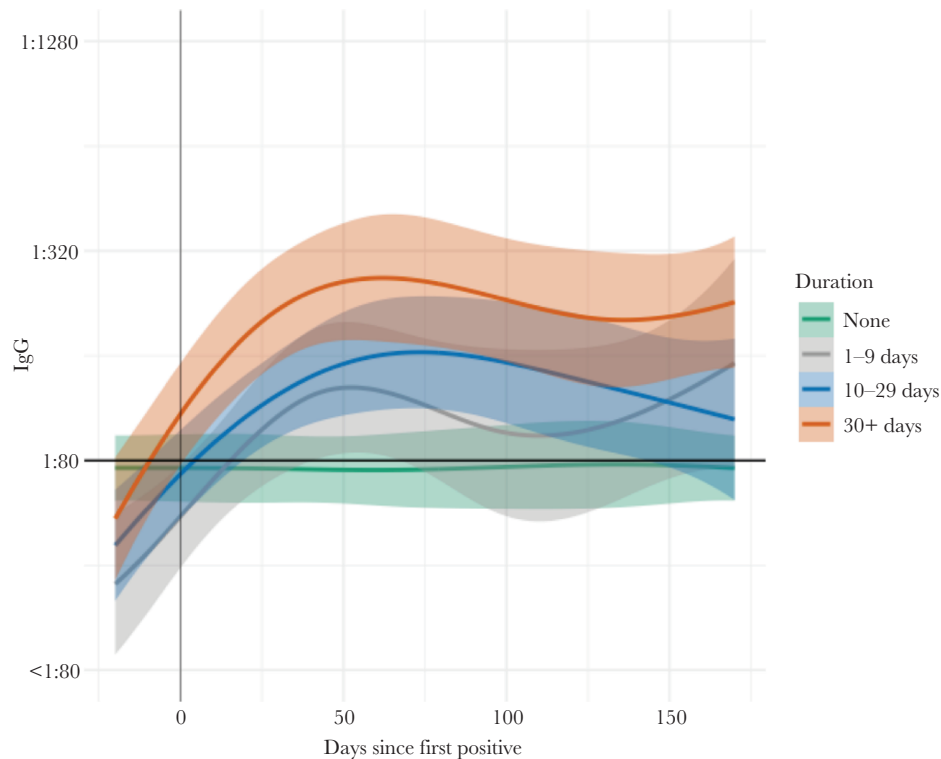
Figure 5. Average antibody levels over time among SARS-CoV-2–infected Rutgers Corona Cohort participants, stratified by symptom duration. Plots show estimated average levels of IgG over time with 95% confidence intervals based on symptom duration. Curves and 95% confidence bands were estimated for different durations of symptoms by fitting a model with a spline function for time and a random intercept to account for repeated measures. Abbreviations: IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

support changes in current recommendations for vaccinating those with history of prior infection.

Our data on the duration of symptoms complement other reports of prolonged abnormalities in studies of previously infected subjects [41–44]. Notably, we studied an ambulatory population with generally mild illnesses, most not requiring hospitalization, over a 6-month timeframe that bracketed 2 infection surges in NJ. Of infected participants, about one-third reported symptoms lasting at least 30 days, and greater than 10% had persistent symptoms lasting for months, including fatigue, altered smell and taste, and shortness of breath. Notably, in contrast to other research [45], we found that participants with longer duration of symptoms also had higher levels of antibodies over time, perhaps reflecting the correlation between symptom duration and symptom severity, although further study is warranted on the immune profiles among those with prolonged symptoms. Nonetheless, because mild illnesses are much more common than illnesses that required hospitalization, the frequency of prolonged symptoms in our cohort raises a cautionary note about post–SARS-CoV-2 sequelae.

Our study had multiple strengths. The prospective inclusion of generally healthy, ethnically diverse, previously undiagnosed participants followed longitudinally from the early phases of the US pandemic, with exceptional retention, captured a range of clinical responses, including asymptomatic infections. Most participants received no medical intervention for their illness (86%), allowing us to characterize the natural history of disease and biomarker trajectories in a predominantly untreated cohort. Compared to results from hospitalized or convalescent cohorts, our findings may be more generalizable to the broader population of people with mild or asymptomatic infections [3, 4], often undiagnosed and contributing to viral transmission [5]. Following participants at 6 time points over 6 months, with ≥ 5 months of follow-up data for most SARS-CoV-2–infected participants, enabled study of antibody responses and symptoms longitudinally in relation to disease severity and other factors. The high levels of subject participation and retention increased confidence in the validity of our findings.

This study also had limitations. The rapid enrollment of a highly motivated convenience cohort may have preferentially enriched the study population with persons who perceived themselves at higher risk for infection, such as people with underlying respiratory diseases (although not itself a risk factor in our analysis). Enrolled participants and eligible participants who did not enroll also differed in certain respects related to the populations recruited at each campus location (eg, more HCWs and Hispanic/Latino participants in Newark). Nonetheless, the enrollment of persons not previously diagnosed with infection remains a strength of this study, and we do not believe that the enrollment procedures substantially affected the internal validity of our findings. Certain analyses were limited in statistical power due to smaller sample sizes of infected individuals. Less-frequent sampling during periods of lower transmission may have missed some asymptomatic infections without seroconversion. Disease severity was based on self-report, but this classification correlated well with symptom burden, levels of care and treatments received, and antibody responses. Sources of infectious exposure among participants could not be known with certainty; some infected participants who reported infected household members before their diagnosis may still have been the source of infections for other household members. Finally, given the differences in infection risk and severity between HCWs and non-HCWs, findings from our study population may not fully generalize to all populations.

In summary, in our prospective, ethnically diverse cohort of ambulatory, previously undiagnosed participants recruited early in the COVID-19 pandemic in the United States, levels and trajectories of antibody responses correlated with disease severity more so than any other factor. Asymptomatic infections led to lower seroconversion rates and antibody levels. One-third of infected participants had symptoms lasting 1 month or longer. Fatigue, respiratory, and neurologic symptoms lasted for months in at least 10% of affected individuals. Participants with prolonged symptoms, who were generally more severely symptomatic, also tended to have higher antibody levels over time. Going forward, this cohort of uninfected and infected, seropositive and seronegative, participants will allow further investigation of postacute sequelae of SARS-CoV-2 infection, risks factors for reinfection, and relationships between infection and vaccine responses.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. 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.

Notes

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