Clinical Infectious Diseases

MAJOR ARTICLE

Severe Acute Respiratory Syndrome Coronavirus 2 Reinfection Associates With Unstable Housing and Occurs in the Presence of Antibodies

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Background. The factors associated with severe acute respiratory coronavirus 2 (SARS-CoV-2) reinfection remain poorly defined.

Methods. We identified patients with SARS-CoV-2 infection and at least 1 repeat reverse transcription polymerase chain reaction result a minimum of 90 days after the initial positive test and before 21 January 2021. Those with a repeat positive test were deemed to have reinfection (n = 75), and those with only negative tests were classified as convalescents (n = 1594). Demographics, coronavirus disease 2019 (COVID-19) severity, and treatment histories were obtained from the Boston Medical Center electronic medical record. Humoral responses were analyzed using SARS-CoV-2–specific enzyme-linked immunosorbent assays and pseudovirus neutralizations in a subset of reinfection (n = 16) and convalescent samples (n = 32). Univariate, multivariate, and time to event analyses were used to identify associations.

Results. Individuals with reinfection had more frequent testing at shorter intervals compared with the convalescents. Unstable housing was associated with more than 2-fold greater chance of reinfection. Preexisting comorbidities and COVID-19 severity after the initial infection were not associated with reinfection. SARS-CoV-2 immunoglobulin G levels and pseudovirus neutralization were not different within the early weeks after primary infection and at a timepoint at least 90 days later in the 2 groups. In the convalescents, but not in those with reinfection, the late as compared with early humoral responses were significantly higher.

Conclusions. Reinfection associates with unstable housing, which is likely a marker for virus exposure, and reinfection occurs in the presence of SARS-CoV-2 antibodies.

Keywords. SARS-CoV-2; reinfection; persistent shedding; homeless; antibody neutralization.

The majority of individuals develop a robust immune response after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1]. This immune response eventually extinguishes the ongoing virus replication. Furthermore, the initial infection establishes immune memory that may prevent reinfection. Despite this, there have been multiple reports of reinfection and prolonged shedding [2–14]. Although these investigations have suggested that persistent shedding is often observed among those immunosuppressed or pregnant, the demographic and immune characteristics that associate with reinfection are not known.

It can be difficult to distinguish between reinfection and prolonged shedding without serial longitudinal sampling and virus sequence analysis [15]. The Centers for Disease Control and Prevention (CDC) stipulates that asymptomatic patients with documented coronavirus disease 2019 (COVID-19) should not be retested before 90 days after the primary infection [16]. Repeat positive SARS-CoV-2 reverse transcription (RT) polymerase chain reaction (PCR) tests within 90 days of the original result may represent prolonged shedding rather than reinfection. Some cohort studies have also used serology to characterize patients with reinfection [17–19]. Retrospective and prospective cohort investigations suggest that reinfection occurs in less than 1% of healthcare workers [17, 20]. In the general population, prior infection may provide greater than 80% protection against reinfection, although it may be lower among individuals older than 65 years of age [18, 19, 21–23]. Besides age, other patient characteristics and immune factors that may associate with reinfection have not been identified.

In this retrospective cohort study, we examined the association of diverse demographic factors and antibody responses with reinfection. We found that unstable housing, but not other baseline characteristics or antibody levels, was associated with reinfection. Our study identifies modifiable factors that may be important in preventing SARS-CoV-2 reinfection.

Received 7 September 2021; editorial decision 27 October 2021; published online 10 November 2021.

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Clinical Infectious Diseases® 2022;75(1):e208–15

https://doi.org/10.1093/cid/ciab940

MATERIALS AND METHODS

Participants and Data Collection

Demographic and clinical information was extracted from the Boston Medical Center (BMC) electronic medical records (EMRs) for all patients that had a repeat SARS-CoV-2 RT-PCR result at least 90 days after primary infection between March 12, 2020, and January 21, 2021. Patients who had at least 1 repeat positive test 90 days after primary infection were deemed to have reinfection. Those with only negative tests after 90 days were classified as convalescents. A SARS-CoV-2 RT-PCR–positive result was required either 15 days before or during hospitalization for consideration as a "COVID-19–like illness." Data on housing were based on listed diagnoses or problems in the EMRs, and, in each case, the period of unstable housing was confirmed by reviewing provider notes. Patient plasma and residual nasal swab samples were obtained from the BMC COVID-19 biorepository or in some cases during a subsequent non-COVID-19 related visit.

Antibody Levels

SARS-CoV-2 antibody levels were quantified using a previously described enzyme-linked immunosorbent assay protocol [24]. CR3022 antibody (Abcam 273073) served as a positive control against SARS-CoV-2 receptor-binding domain (RBD). CR3022 binding was examined with each assay, and it was also used to calculate titers (relative units) for each sample by interpolating a 4-parameter logistic curve.

Cell Lines and Virus Stocks

Human epithelial kidney HEK293T cells and Vero E6 cells were acquired from the National Institutes of Health AIDS Reagent Program and American Type Culture Collection, respectively, and maintained per instructions. Vesicular stomatitis virus (VSV) pseudotyped with SARS-CoV-2 spike virus stocks were generated using previously described protocols [25]. Briefly, HEK293T cells were transfected with SARS-CoV-2 spike expression plasmid (BEI Resources, NR52310). After 24 hours, the transfected cells were infected with VSV-G pseudotyped virus (G*ΔG-VSV), which contains the firefly luciferase expression cassette substituted for G in the VSV genome. Twenty-four hours after infection, the cell culture supernatant was filtered, concentrated, aliquoted, and stored at -80°C for later use.

Neutralization Assay

All plasma samples were heat inactivated for 1 hour at 56°C. Protein G agarose (ThermoFisher, 20399) was used to isolate immunoglobulin G (IgG) from plasma per manufacturer's protocol. The neutralization assays were performed as described previously [25]. Briefly, virus stocks were incubated with 6 2-fold serially diluted plasma or an equivalent amount of isolated IgG starting with 1:5 highest dilution. Approximately 1.25×10^4 Vero E6 cells were added to each well. After 2 days, luciferase expression was assessed by the Promega Bright-Glo Luciferase Assay System (ThermoScientific). Relative light unit differences in the presence as compared with the absence of plasma and IgG were used to determine percent neutralization. Serial dilution curves were used to calculate area under the curve (AUC). Each neutralization assay was tested in triplicate a minimum of 2 independent times.

Virus Sequence Analysis

SARS-CoV-2 genomic fragments were amplified from discarded nasal swab sample–derived total RNA using a modified ARTIC-primer based protocol (ARTIC-V3) and sequenced on an Illumina platform. Nucleotide substitutions, insertions, and deletions were identified with LoFreq [26] following alignment to the Wuhan Hu-1 reference sequence (NC_045512.2) with Bowtie2 [27]. We used a quality threshold of ≥ 10 reads for determining a change from reference. Lineages of sequenced viruses were determined using the Pangolin algorithm (https://pangolin.cog-uk.io/).

Statistical Analysis

Univariate comparisons were done using Mann-Whitney *U* test for continuous variables and χ^2 or Fisher exact test for categorical variables. Kaplan-Meier analysis and Cox proportional hazard models were used for time to event analysis. Diverse demographic factors and hospitalization characteristics were used as covariates in the multivariate analysis. Multivariate linear regression analysis was conducted independently for RBD IgG, nucleocapsid IgG, and neutralization AUC with the predictors: (1) days from symptom onset for the early sample or days from first positive PCR result for the late sample; (2) sex; (3) age; and (4) reinfection or convalescent group categorical variable. All *P* values are 2-sided. All statistical analyses were performed using Stata v17 and GraphPad Prism 9.0.2.

Ethics Statement

The BMC institutional review board approved this study.

RESULTS

Subjects and Demographics

There were 67 688 unique patients with an available SARS-CoV-2 RT-PCR test result in the BMC EMRs from March 12, 2020, to January 21, 2021. Of these, 9910 (14.6%) unique patients had at least 1 positive SARS-CoV-2 RT-PCR–positive test. Of the patients with a positive test, 1669 (16.8%) had another SARS-CoV-2 RT-PCR result available at least 90 days after the initial positive result (Table 1). Of these patients, 75 (4.5%) had 2 positive test results at least 90 days apart. Forty-nine of these 75 individuals had at least 1 or more negative RT-PCR tests in the period between the first and the repeat positive RT-PCR result a minimum of 90 days later. Twenty-five individuals did not have another result between their first and last positive test,

Table 1. Demographics of the Reinfection and Convalescents Individuals at the Time of First Infection[a]

	Reinfection (n = 75)	Convalescents (n = 1594)	Univariate *P* Value
Age, median (IQR)	51 (37–61)	48 (34–60)	.81[b]
Male	39 (52)	713 (44.7)	.24
Race/ethnicity			.28[c]
Black	21 (28)	587 (36.8)	
White	10 (13.3)	258 (16.2)	
Hispanic/Latino	39 (52)	624 (39.1)	
Other or missing	5 (6.7)	124 (7.8)	
Body mass index (IQR)	28.0 (25.0–33.0)	29.1 (25.2–34.1)	.24[b]
Homeless	28 (37.3)	245 (15.4)	<.001
Pregnant	4 (5.3)	40 (2.5)	.13
Diabetes mellitus	13 (17.3)	376 (23.6)	.21
Heart disease[d]	9 (12)	125 (7.8)	.19
Lung disease[e]	9 (12)	269 (16.9)	.34
Chronic kidney disease	6 (8)	100 (6.3)	.47
End-stage renal disease	4 (5.3)	39 (2.4)	.13
Human immunodeficiency virus	4 (5.3)	30 (1.9)	.06
Cancer	4 (5.3)	63 (3.9)	.54
Smoking			.09[c]
Never smoker	40 (53.3)	1018 (63.9)	
Current smoker	14 (18.7)	247 (15.5)	
Former smoker	21 (28)	299 (18.8)	
Missing	0 (0)	30 (1.9)	
On immunosuppressive medication[f]	3 (4.0)	36 (2.2)	.42
Number of comorbidities[g]			.93[c]
0	41 (54.7)	904 (56.7)	
1	23 (30.7)	457 (28.7)	
≥2	11 (14.7)	233 (14.6)	

Abbreviation: IQR, interquartile range.

[a]Data are expressed as number (%) and *P* value was calculated using Fisher exact test unless otherwise indicated.

[b]Mann-Whitney *U* test.

[c]χ^2 test.

[d]Heart disease includes coronary artery disease and/or congestive heart failure.

[e]Lung disease includes chronic obstructive pulmonary disease and/or asthma.

[f]Immunosuppressive medication included chronic steroid use (> 10 mg daily prednisone or equivalent), chemotherapeutic, or immunomodulatory agents (bortezomib, infliximab, adalimumab, CellCept, tacrolimus, mercaptopurine, cyclosporine, methotrexate, atezolizumab).

[g]Number of comorbidities accounts for diabetes mellitus, heart disease, lung disease, kidney disease, human immunodeficiency virus, and cancer.

and 1 person had only intervening positive results. These 75 individuals were deemed to have reinfection. The remaining 1594 (95.5%) of the 1669 with only negative test results at least 90 days after a positive test were classified as convalescents.

Factors Associated With Reinfection

The number of unique SARS-CoV-2 tests were higher among those with reinfection (median 5, range 2–21) compared with the convalescents (median 3, range 2–25, $P < .0001$) group (Figure 1A). The days between the first and last positive test in the reinfection group (median 139, range 91–298) was shorter than the days between the first positive and last negative test in the convalescents group (median 172, range 90–317, $P = .0005$) (Figure 1B).

A greater proportion of the reinfection compared with the convalescent individuals had housing instability at the time of the first positive SARS-CoV-2 RT-PCR test (Table 1). Other demographics, including age, were not statistically different in the 2 groups. In time to event analysis, the percent of patients that had a repeat positive result at least 90 days after the first positive test was significantly higher in those with unstable housing compared with stable housing (hazard ratio [HR] 2.71; 95% confidence interval [95% CI], 1.69–4.36; $P < .001$; Figure 2 and Supplementary Table 1). After adjusting for demographics and other comorbidities, experiencing homelessness significantly predicted a repeat positive test 90 days later (adjusted HR [aHR] 3.26; 95% CI, 1.69–6.29; $P < .001$; Supplementary Table 1). In this multivariate analysis, the number of tests did not associate with reinfection (aHR 1.04; 95% CI. 0.99–1.10; $P = .12$).

The CDC's criteria for reinfection includes a repeat positive SARS-CoV-2 RT-PCR test separated by a minimum of 90 days. Presumably shorter intervals may incorporate more individuals that have prolonged shedding rather than reinfection. Decreasing the interval to 60 days between a positive SARS-CoV-2 RT-PCR results followed by a repeat positive ($\text{reinfection}_{60\text{days}}$) or a negative ($\text{convalescents}_{60\text{days}}$) test increased

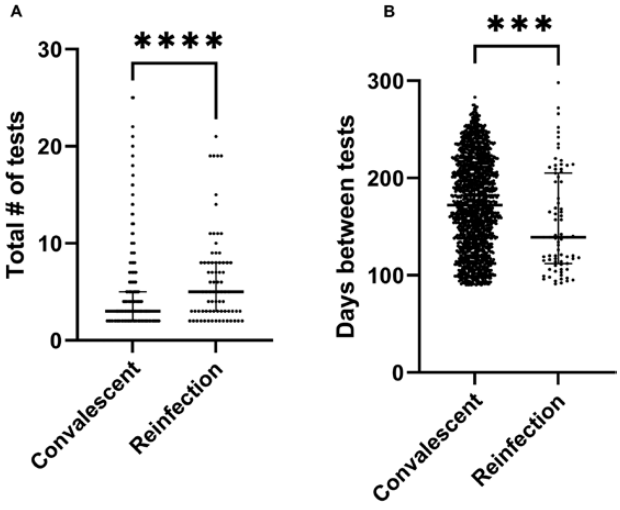

Figure 1. Reinfection associates with more frequent testing at shorter intervals. The total number of tests (*A*) and the interval in days between tests (*B*) among the reinfection and convalescent group. The interval is days from the first positive result to the next positive test at least 90 days later in those with reinfection, and from the first positive to the last negative test at least 90 days later in the convalescent. The box plots show median and interquartile range. *** and **** indicate $P \leq .001$ and $P \leq .0001$, respectively, by the Mann-Whitney *U* test.

the number of individuals in the 2 groups (Supplementary Table 2). With this shorter time span between the repeat tests, unstable housing remained significantly higher among those with repeat positive tests. Pregnancy and being on an immunosuppressive medication were also significantly higher in the reinfection$_{60days}$ compared with the convalescents$_{60days}$ group in univariate analysis.

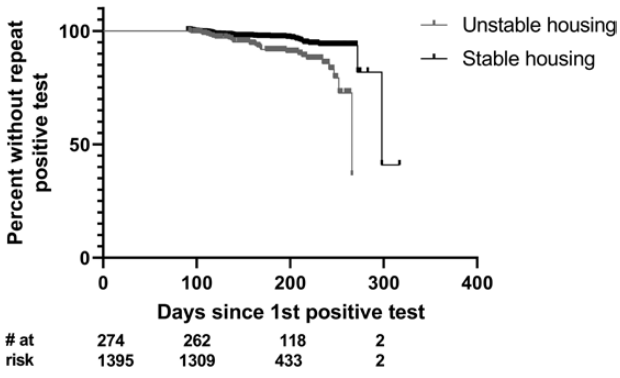

Figure 2. Unstable housing associates with reinfection. Kaplan-Meier survival curve for those with unstable housing and stable housing at the time of the first infection. The y-axis shows the percent without a repeat positive SARS-CoV-2 RT-PCR result, and the x-axis shows days after first SARS-CoV-2 positive RT-PCR result. The tick marks denote right censoring. Number of patients at risk at different time points is displayed below the x-axis. RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Hospitalization and Disease Severity

Individuals with mild COVID-19 after SARS-CoV-2 infection may develop lower antibody levels and thus, individuals with mild disease after initial infection may be at greater risk for reinfection [28]. The proportion of patients with hospitalization, with or without a COVID-19–like illness, intensive care unit stay, and need for mechanical ventilation was not different in the reinfection and the convalescent groups (Table 2). During the first COVID-19 surge, hydroxychloroquine, colchicine, and immune modulators, such as interleukin inhibitors were frequently used off-label or as part of clinical trials at BMC [29]. The use of these medications, especially hydroxychloroquine, was higher in the hospitalized convalescents compared with reinfection individuals (Table 2). Unstable housing remained predictive of having a repeat positive test 90 days later after adding use of any COVID-19 medications in the previous multivariate model (aHR 3.12; 95% CI, 1.62–6.00; $P = .001$). Use of a COVID-19 medication during the primary infection hospitalization was also associated a lower risk of reinfection (aHR 0.30; 95% CI, 0.11–0.79; $P = .02$), although in univariate analysis, the data violated the proportional hazard assumption (Supplementary Table 1).

Thirty-one of the 75 (41.3%) individuals in the reinfection group were hospitalized around the time of the repeat positive SARS-CoV-2 RT-PCR test. Three of these 31 (9.7%) individuals were deemed to have a COVID-19–like illness during their second hospitalization. Two of these 3 patients were treated with dexamethasone and 1 was treated with remdesivir. None of them required intensive care unit admission or mechanical ventilation. Two other patients required mechanical ventilation at the time of their second hospitalization, but both were deemed not to have an illness consistent with COVID-19.

Antibody Responses

A weakened humoral immune response to a primary SARS-CoV-2 infection could increase the probability of reinfection. Antibody levels within weeks after the first infection were compared between 10 and 20 reinfection and convalescent individuals, respectively. The samples were from individuals with similar age, sex distribution, day from symptom onset, and number of comorbidities (Supplementary Table 3). There were no significant differences between SARS-CoV-2 RBD and nucleocapsid IgG levels and ability to neutralize VSV-SARS-CoV-2-S pseudovirus between the convalescent and reinfection groups (Figure 3A–C).

Humoral responses at least 90 days after primary infection were also compared among 6 and 12 reinfection and convalescent individuals, respectively. For all the reinfection individuals, this late sample was collected after the second positive SARS-CoV-2 RT-PCR result. The individuals in the groups were well matched (Supplementary Table 3). Although median number of days from first positive SARS-CoV-2 test to

Table 2. Disease Severity Among Reinfection and Convalescents Individuals at the Time of First Infection[a]

	Reinfection (n = 75)	Convalescents (n = 1594)	*P* Value
Hospitalized	20 (26.7)	373 (23.4)	.49
Hospitalized with COVID-19–like illness	14 (18.7)	296 (18.6)	1.0
ICU (% of hospitalized)	1 (5.0)	52 (13.9)	.50
Mechanical ventilation (% of hospitalized)	1 (5.0)	43 (11.5)	.72
Any COVID-19–directed medications[b]	5 (35.7)	202 (68.2)	.01
Hydroxychloroquine	3 (21.4)	164 (55.4)	.01
Colchicine	0 (0)	10 (3.4)	1.0
Interleukin inhibitor[c]	2 (14.3)	72 (24.3)	.53
Dexamethasone	0 (0)	3 (1.0)	1.0
Remdesivir	0 (0)	14 (4.7)	1.0

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit.

[a]Data are expressed as number (%) and *P* value was calculated using Fisher exact test unless otherwise indicated.

[b](%) is of hospitalized with COVID-19–like illness. The numbers include individuals enrolled in randomized double-blind placebo-controlled trials.

[c]Interleukin inhibitors include tocilizumab, sarilumab, anakinra, or participation in clinical trial.

the late sample was around 55 days earlier in the reinfection group, this was not statistically different ($P = .37$). In the convalescent but not reinfection group, antibody levels and neutralization AUC were higher in the late compared with the early plasma sample (Figure 3A–C). In multivariate linear regression analysis, interval from primary infection to date of sample collection, but not reinfection compared with convalescent group, associated with higher RBD IgG levels, nucleocapsid IgG magnitude, and pseudovirus neutralization AUC (Table 3).

Sequence Analysis

Longitudinal early and late nasal swabs and after the repeat positive test only samples were available from 3 and 2 reinfection individuals, respectively. Only a late, without a matching early, and 3 early, without the matching late, nasal swab samples yielded quality sequences that covered the majority of the SARS-CoV-2 genome. Pangolin lineage assignment placed the 1 late and the 3 early samples into the B.1.2 and B.1 lineage, respectively. The B.1.2 lineage had very low incidence in the United States when the reinfection patient was first diagnosed on March 25, 2020, and high incidence at the time of the second positive RT-PCR test on December 22, 2020 [30]. The B.1 lineage, however, was highly prevalent when the 3 early samples were collected in April 2020. The 1 late sample had 10 of the 11 expected single nucleotide changes consistent with B.1.2, but it did not have extended mutations that would be associated with a long-term infection and prolonged shedding [15].

CONCLUSIONS

In this study, we identified factors associated with presumed SARS-CoV-2 reinfection. We compared demographics, disease

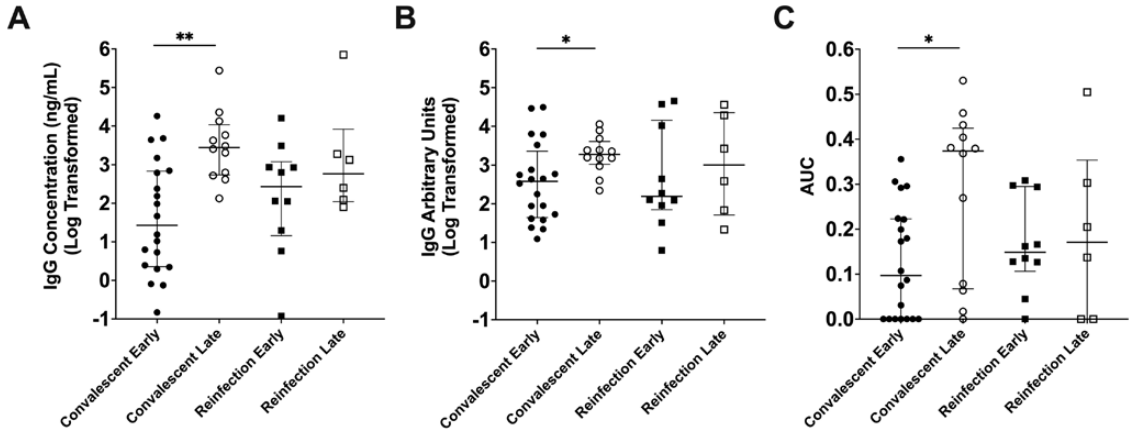

Figure 3. Antibody responses are not different among those with reinfection and the convalescents. Receptor-binding domain (RBD) (*A*), nucleocapsid (*B*) IgG levels, and pseudovirus neutralization area under the curve (*C*) among those with reinfection (squares) and the convalescent group (circles). The x-axis denotes the early (collected within weeks of primary infection, filled symbols) and late (obtained at least 90 days after first positive RT-PCR test, unfilled symbols) samples. * and ** denote $P \leq .05$ and $P \leq .01$, respectively, by Mann-Whitney *U* test. RT-PCR, reverse transcriptase polymerase chain reaction.

characteristics, and humoral responses among individuals believed to have reinfection. Reinfection was associated with unstable housing, but no other baseline demographic factor or comorbidity. Furthermore, antibody responses were not significantly different in a subset of individuals with reinfection. These observations suggest that socioenvironmental factors rather than preexisting comorbidities or immunologic deficits are associated with reinfection.

We defined reinfection based on the CDC criteria of 2 separate SARS-CoV-2 RT-PCR tests separated by at least 90 days. Virus sequence analysis confirmed reinfection in only 1 individual, primarily because of sample limitations. Quantitative PCR cycle threshold values were also not available for the majority of reinfection samples to potentially differentiate reinfection from prolonged shedding. Interestingly, by relaxing the criteria for reinfection as 2 separate positive tests separated by 60 as opposed to 90 days demonstrated that pregnancy and use of an immunosuppressive medication, along with unstable housing, were also associated with the reinfection group in univariate analysis. Pregnancy and use of immunosuppressive medications have been associated with prolonged virus shedding [7–10, 12–14]. This suggests that the 90- as opposed to 60-day criteria may exclude individuals that are more likely to have prolonged virus shedding rather than reinfection.

In this BMC cohort, individuals experiencing unstable housing had more reinfection. BMC is New England's largest safety net hospital that often serves people experiencing homelessness [31]. This finding may not be generalizable; association between unstable housing and SARS-CoV-2 incidence was not observed in another cohort [32]. Incomplete or inaccurate EMR documentation may also skew the findings. Studies found up to 36%–66% SARS-CoV-2 positivity rate among residents of large adult homeless shelters [33–35]. Unstable housing likely makes it difficult to maintain the physical distance known to reduce SARS-CoV-2 transmission, and it may present challenges for other measures such as mask usage and hand hygiene [36]. Thus, housing insecurity may be a surrogate marker for exposure to infectious SARS-CoV-2, although this was not directly measured in the study.

The reinfection compared with convalescents group were tested more frequently and at shorter intervals. The exact reason for every repeat test was not ascertained. SARS-CoV-2 testing is often done when patients present for any hospital-based medical care. It is possible that individuals in the reinfection compared with convalescent groups presented more frequently for medical care or were referred for SARS-CoV-2 testing more often. There was a significant effort put toward screening individuals living at homeless shelters in the Boston area, as recommended by the CDC [37]. Importantly, homelessness remained a significant predictor for reinfection after accounting for differential length of follow-up and number of SARS-CoV-2 RT-PCR tests. Thus, the association of unstable housing with reinfection does not merely reflect changes in testing frequency or interval. It is possible that the convalescents have a high incidence of asymptomatic reinfections that were not documented.

COVID-19 severity did not differ after primary infection among those with reinfection and the convalescent group. Less COVID-19 medication use during hospitalization was associated with higher incidence of reinfection although this association was based on a small sample size. A small minority had COVID-19–like illness that required hospitalization after reinfection. This suggests that the immune response after primary infection may not prevent infection, but it does ameliorate against severe disease, which is similar to previous reports [23] and observations from SARS-CoV-2 breakthrough infection after vaccination [38].

We also found that individuals with presumed reinfection did not have significantly lower antibody responses. Within the early weeks after SARS-CoV-2 infection, antibody levels and neutralization capacity were similar suggesting that individuals in the reinfection group did not have any obvious preexisting deficit that prevented this early antibody response. The convalescent, but not reinfection, group demonstrated a significant increase in antibody levels and neutralization in the sample collected at least 90 days after the first positive test. This is especially surprising because the late plasma sample from the reinfection group was collected after the second positive RT-PCR test. Presumably, reinfection should have boosted a preexisting immune response as has been observed with vaccination among previously infected individuals [39]. The lack of both higher antibody levels and greater neutralization

Table 3. Predictors of Humoral Responses in Multi-variable Linear Regression Analyses

	RBD IgG β (95% CI, *P*-value)	Nucleocapsid IgG β (95% CI, *P*-value)	Neutralization AUC β (95% CI, *P*-value)
(Intercept)	1.18 (–.52 to 2.88, .17)	2.47 (1.05 to 3.90, .001)	–0.02 (.24 to .21, .88)
Reinfection	0.63 (–.10 to 1.36, .09)	0.19 (–.42 to .80, .53)	0.01 (–.08 to .11, .83)
Interval (days)[a]	0.007 (.004 to .01, <.0001)	0.003 (0.0005 to .005, .02)	0.0004 (1.9×10^{-5} –.0008, .04)
Age (y)	0.02 (–.01 to .04, .14)	0.01 (–.01 to .03, .46)	0.003 (–.003 to .006, .08)
Male	–1.09 (–1.84 to –.34, .005)	–0.65 (–1.28 to –.022, .04)	–0.009 (–.109 to .09, .86)

Abbreviations: CI, confidence interval; RBD, receptor binding domain.

[a]Interval is days from symptom onset for the early sample and days from first positive RT-PCR test for the late sample.

responses in the late compared with the early plasma possibly may suggest that those with reinfection have a lower peak and/or faster decay in their antibodies over time. The data, however, were based on evaluating a small number of individuals at 2 timepoints only. There could be selection bias in the samples available in the BMC biorepository. More intensive longitudinal examination of the immune responses from a larger number of individuals will be required to understand the frequency of reinfection in relation to changes in immunity along with virus exposure.

The end date for the data acquisition in this study occurred before both the vaccine rollout in the city of Boston and emergence of the highly infectious delta (B.1.617.2) variant. Demographic and immunologic factors associated with repeat infections may be different with these changes. Vaccination reduces the chance of reinfection, but our data suggest that high levels of exposure can overcome prevalent immune responses [40]. In this regard, policies aimed at reducing homelessness, along with increasing vaccination, may be helpful in reducing subsequent infections.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. The authors thank all the participants who contributed samples for these studies.

Financial support. This study was supported by K24-AI145661 and P30-AI042853. D. J. B. was supported by National Institutes of Health (NIH) T32-5T32AI00730928. The funders had no role in the study design, data collection, and interpretation or the decision to submit this work for publication.

Potential conflicts of interest. J. H. C. reports support for the present manuscript from NIH/National Center for Advancing Translational Sciences (NCATS; UL1TR001430) and Boston University School of Medicine (Genome Sciences Institute seed funding); grants or contracts outside of the submitted work from NIH (AI151559, AI135517, AI121933, HL157790), Department of Defense (FA8649-20-C-0231), and Defense Threat Reduction Agency (21-85620-01); antibody creation consulting fees from Cell Signaling Technologies; and payment for expert testimony from Massachusetts Attorney General's Office for consulting on antiviral efficacy. M. S. reports consulting fees paid to self not related to this study from Sigilon Therapeutics, Guidepoint Consulting, and Gehrson Lehrman Group. J. T. reports support for the present manuscript from NIH/NCATS (UL1TR001430) and Boston University School of Medicine (Genome Sciences Institute seed funding) and registration fee for conference waived from American Society of Virology. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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