Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

Incidence of COVID-19 recurrence among large cohort of healthcare employees

Fitzpatrick Veronica, DrPH[a,b,*], Rivelli Anne, MPH, MA[a,b], Blair Christopher, MS[a,b], Copeland Kenneth, PhD[a,c], Richards Jon, MD, PhD[a]

[a] Advocate Aurora Health, Downers Grove, IL
[b] Advocate Aurora Research Institute, Downers Grove, IL
[c] ACL Laboratories – Wisconsin and Illinois, Rosemont, IL West Allis, WI

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ABSTRACT

Purpose: To quantify COVID-19 recurrence among clinical and nonclinical healthcare employees with SARS-CoV-2 IgG antibodies or prior COVID-19 infection.

Methods: This prospective, cohort study collected and resulted SARS-CoV-2 IgG serum samples as positive or negative from June 8 to July 10, 2020 from a convenience sample of 16,233 adult participants employed by a large Midwestern healthcare system. Documented positive polymerase chain reaction test results representing COVID-19 infections were recorded up to four months prior to and post-IgG testing.

Results: Nine hundred and thirteen (6.12%) participants, including 45 (4.93%) IgG positive participants, experienced COVID-19 infections after study initiation, representing a 51% increased risk of COVID-19 infection among IgG positive participants (IRR = 1.51). Regressions adjusted for documented disparities showed no difference in COVID-19 infection by IgG status (OR=1.19; $P = .3117$) but significantly greater odds in COVID-19 recurrence among participants with a prior documented COVID-19 infection (OR=1.93; $P < .0001$).

Conclusions: SARS-CoV-2 IgG antibodies and prior COVID-19 infection do not appear to offer meaningful protection against COVID-19 recurrence in healthcare workers. Recurrence would impact decisions regarding ongoing healthcare resource utilization. This study can inform considerations for vaccine administration to vulnerable groups.

Introduction

COVID-19 was initially thought to be an immunizing, nonrelapsing disease, but current research is mounting to suggest this is not the case [1,2]. Currently, we have limited understanding of the innate and adaptive immunity to the novel SARS-CoV-2 virus [3,4,5]. Initial false assumptions of immunity, paired with a slew of treatment and prevention challenges, served to delay efforts to recognize and understand recurrence of COVID-19, the disease manifestation of the SARS-CoV-2 virus [2,5,6,7].

SARS-CoV-2 entered a highly-susceptible human population, resulting in its rapid and uncontrollable transmission [1]. The swift release of substandard polymerase chain reaction (PCR) tests to detect active SARS-CoV-2 ribonucleic acid (RNA) and concurrent widespread shortages of aforementioned tests contributed to misunderstanding recurrence potential [8]. Worldwide policies focused on disease containment also contributed to setbacks in documenting recurrence [1]. Evidence of recurrence of COVID-19, mostly as single or small-study case reports, are just beginning to emerge.

List of Abbreviations and Acronyms: EMR, Electronic Medical Records; IgG, Immunoglobulin G; IRR, Incidence Rate Ratio; OR, Odds Ratio; PCR, Polymerase Chain Reaction; RNA, Ribonucleic Acid.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

* Corresponding author at: Advocate Aurora Research Institute 3075 Highland Parkway Downers Grove, IL 60515
E-mail address: Veronica.fitzpatrick@aah.org (F. Veronica).

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Recurrence of disease

Detection of active SARS-CoV-2 RNA after clinical disease recovery could indicate a multitude of scenarios, including: persistent illness, prolonged viral RNA shedding, variation in collection technique, specimen handling or storage conditions affecting test performance, or, most alarming, genuine recurrence of disease [5]. Current research has raised two pathophysiological hypotheses underlying demonstrated COVID-19 recurrence: viral reactivation or viral reinfection [7]. Despite case studies offering preliminary evidence of COVID-19 recurrence from China, Korea, Italy, and the US [9-18]. circumstances have made it difficult to document recurrence.

First, the difference between viral reactivation and viral reinfection is not well-defined, convoluting this area of knowledge [7,9]. Additionally, PCR test shortages limited SARS-CoV-2 testing, discounting true prevalence of all infections and limiting capacity to understanding recurrence. Insufficient resources also reduced abilities to preserve or test samples for reinfection using genetic testing. Finally, experts have maintained that the immune system will function as it should, developing immunity to this virus as it has with prior viruses [19]. These circumstances have perpetuated beliefs that COVID-19 recurrence is very rare and natural herd immunity is possible [19]; however, contradictory evidence supports both the hypothesis of recurrence rarity and, in some studies, recurrence commonality [20].

Subsequently, there remains a prominent gap in COVID-19 recurrence knowledge and the role that SARS-CoV-2 antibodies may play in protection against COVID-19 recurrence [4,21]. The asymptomatic transmission of the virus has raised barriers to documenting recurrence using PCR testing for active SARS-CoV-2 RNA alone [5]. Research has asserted that serologic tests are alternative measures of exposure where difficult to isolate or is no longer present [18]. As COVID-19 continues to sweep the US, the use of PCR testing for COVID-19 following SARS-CoV-2 serologic test is an alternative approach to capturing incidence of recurrence after prior exposure to or infection with the SARS-CoV-2 virus [5,7].

Documenting SARS-CoV-2 recurrence

Serology, or antibody, tests are one method to assess proteins made by the body's immune system to fight antigens in response to a prior infection [22,23]. A positive IgG serology test result indicates prior exposure to the SARS-CoV-2 virus and subsequent response in the form of antibody development [24]. While antibody presence to SARS-CoV-2 has not been evidenced to suggest any length of protection from recurrence – a gap this study will attempt to address – it does indicate response and recovery of prior exposure [20].

Current study

The immune response to COVID-19 cannot fully be understood without more data on immunity and recurrence [5]. The primary objective of this study was to establish the incidence of COVID-19 infection, as measured by a documented positive PCR test result, among healthcare employees tested for SARS-CoV-2 IgG antibodies. This study will provide overall incidence of COVID-19 infection and incidence rate ratio (IRR) per 100 person-days among participants with positive IgG status relative to negative IgG status. This study will also determine adjusted odds ratios (AdjOR) of COVID-19 recurrence among healthcare employees using two definitions of prior exposure to SARS-CoV-2, including: 1) positive SARS-CoV-2 IgG status and 2) prior documented COVID-19 infection status. For the purposes of this study, *recurrence* refers to the larger umbrella term encompassing reactivation and reinfection. This study will not attempt to delineate between reactivation and reinfection, but instead will address SARS-CoV-2 recurrence, defined as documented COVID-19 infection after positive IgG status (primary analysis) or after prior documented COVID-19 infection (secondary analysis). This study builds off a prior study by the same authors that documented disparities in seroprevalence and determined the seroprevalence of SARS CoV-2 IgG antibodies was 3.83% among 16,233 healthcare employees [25].

Material and methods

This prospective cohort study recruited healthcare employees across a large Midwestern healthcare system, which consists of about 70,000 employees across 26-hospitals and over 500 sites of care in Illinois and Wisconsin. SARS-CoV-2 IgG was measured in serum specimens obtained from all participants at study initiation using the SARS-CoV-2 IgG Abbott Architect assay. Performance characteristics of the SARS-CoV-2 IgG assay were validated at ACL Laboratories, determining a sensitivity of 98.7% and specificity of 99.2% [26-29]. SARS-CoV-2 RNA, as detected by a positive PCR test representing COVID-19 infection, was measured from isolated and purified nasopharyngeal, oropharyngeal and nasal swab specimens and obtained from individuals who met COVID-19 clinical and/or epidemiological criteria and opted to undergo PCR testing within the healthcare system using the Aptima Panther SARS-CoV-2 assay [27]. Both assays were approved for use under Emergency Use Authorization in US laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 [29]. Prior to recruitment, this study obtained approval by the healthcare system's Institutional Review Board (#20–168E). This study was authorized to enroll up to 20,000 participants or complete SARS-CoV-2 IgG assays until July 10, 2020. Participants' positive SARS-CoV-2 RNA results were recorded by the healthcare system's Employee Health Department and collected by the research team until October 10, 2020.

Participants

This study enrolled and tested a convenience sample of 16,293 participants for SARS-CoV-2 IgG assay results between June 8, 2020 and July 10, 2020 and followed them until October 10, 2020 for positive PCR test results representing COVID-19 infection documented in the system's Electronic Medical Records (EMR). This study also recorded positive PCR results up to four months prior to and post-SARS-CoV-2 IgG testing, which established study initiation. For study inclusion, English- and Spanish-speaking adults ages $\geq$ 18 employed by the healthcare as of the study initiation date were eligible. Team members who met study inclusion criteria and completed a lab blood draw to test for SARS-CoV-2 IgG were participants in this study. Primary analysis (exposure is IgG status) excluded 1372 participants with a documented COVID-19 infection prior to study initiation (N = 14,921). It can be posited that participants with positive IgG status included in primary analysis experienced an asymptomatic COVID-19 infection or other exposure to COVID-19 that was undiagnosed or undocumented by the healthcare system. Due to the unknown relationship between prior documented COVID-19 infection and development (or sustainability) of SARS-CoV-2 IgG antibodies, these two exposures were explored separately. Secondary analysis (exposure is prior documented COVID-19 infection) included the entire sample (N = 16,293). See Figure 1 for flow diagram of study participants.

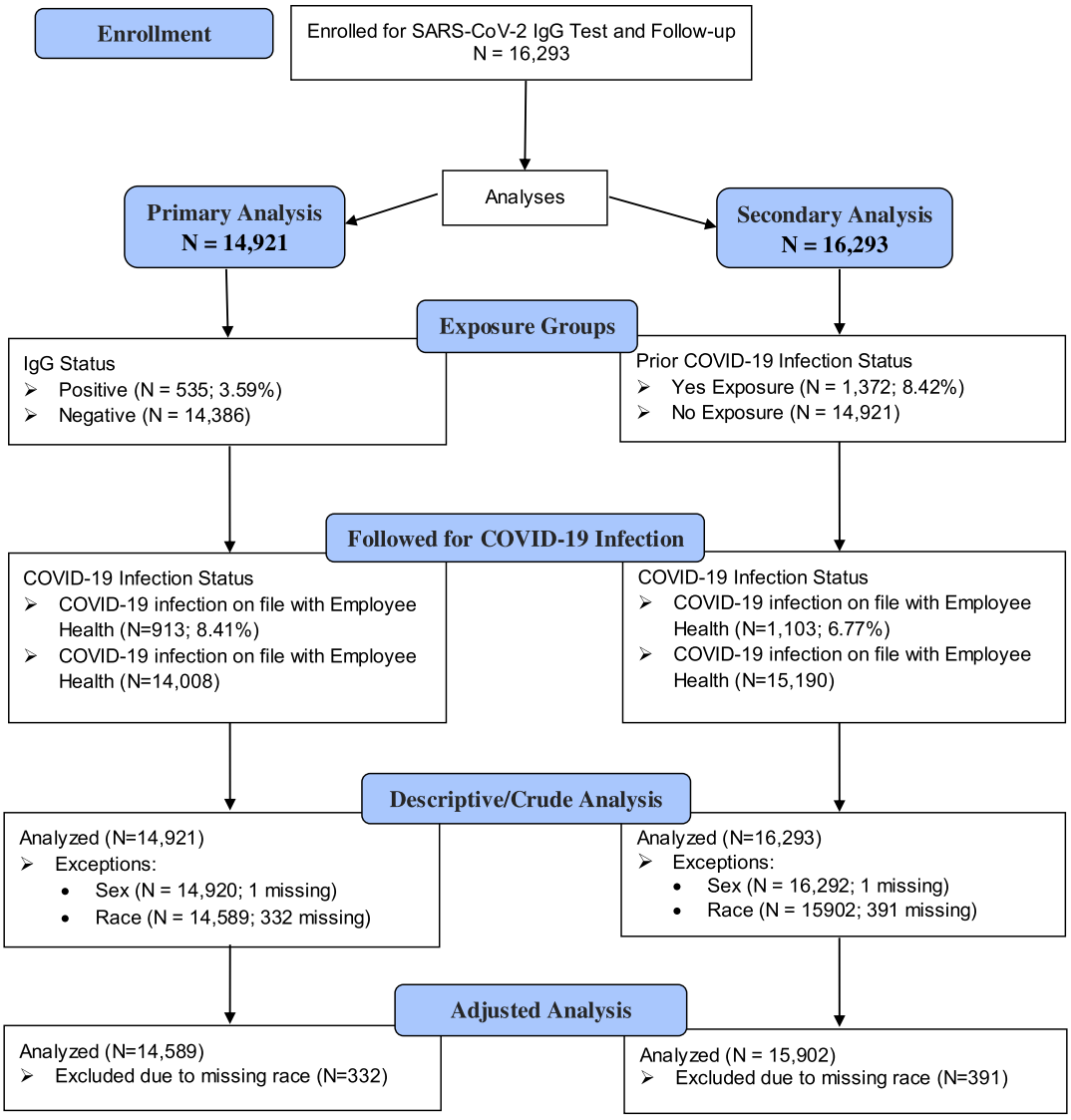

Fig. 1. Flow diagram of prospective cohort study.

Procedures

On June 6, 2020, a detailed recruitment email was sent to all team members' work email addresses. The email provided instructions for participation in the study, including an alteration of consent and a study-specific passcode required for study registration. Interested team members were instructed to register for a study-related IgG assay in their active online health portal. Team members became participants in this study once they voluntarily had their blood drawn for the IgG assay, not at registration.

Variables

Data gathered for this study included demographics, SARS-CoV-2 IgG assay result and any documented positive PCR test results for COVID-19 infection, documented in Epic, the healthcare system's EMR. Age was grouped into quantiles (ages 18–31; 32–41; 42–51; 52–82) for analysis to evaluate risk by increasing age and to avoid underrepresentation of the oldest-age participants. Race included White-, Black-, Asian-, or American Indian-only or Mixed-race (those who identified as two or more races), with 332 (2.23%) total missing values. Ethnicity included Hispanic and non-Hispanic. Sex included male and female, with one missing value. Clinical role category included COVID-clinical (participants working in a clinical capacity on COVID-19 designated units), clinical (participants working in a clinical capacity on a non-COVID-19 designated unit) or non-clinical (participants in non-clinical roles, both remote and on-site). Days to infection represented the number of days between participants' study initiation (i.e., day of IgG test) and their *first* documented COVID-19 infection after study initiation. It should be noted that participants could have had multiple documented COVID-19 infections.

The outcome of COVID-19 infection (yes/no) represents a documented COVID-19 infection after study initiation. Exposures include IgG status (positive/negative) in primary analysis and COVID-19 infection prior to study initiation (yes/no) in secondary analysis.

Statistical methods

Data management and analysis were performed by the study research team and conducted using SAS statistical software (Version 9.4; SAS Institute, Cary, NC).

Univariate analyses are reported as counts (%) or means (standard deviation) and median (interquartile range), as appropriate. Bivariate analyses highlight variables across IgG status (exposure). Corresponding measures of association represent differences in participants who were IgG positive status relative to IgG negative status and include mean differences for days to infection and age, and odds ratios (OR) for age quantiles, sex, race, ethnicity, and clinical role category. OR represents the ratio of odds of COVID-19 infection among those who were IgG positive relative to IgG negative at each variable level relative to the reference level of the same variable. Variable reference levels were chosen based on lowest presumed risk. Corresponding *P*-values were generated from Student's *t*-tests for continuous variables and Pearson X^2 (or Fisher's Exact Tests when any cell size(s) was < 5) to represent infection differences.

Incidence of COVID-19 infection after IgG test (outcome) was calculated as number of participants who experienced the outcome by person-days contributed to follow-up before outcome was experienced. Logistic regressions were performed to estimate adjusted odds of COVID-19 infection after exposure. Adjusted logistic regressions were adjusted for IgG status in primary analysis and documented COVID-19 infection prior to study initiation in secondary analysis, as well as age (as quantiles), race, ethnicity and clinical role category in both analyses. Due to a missing race variable, 332 and 391 participants were excluded from adjusted regressions in primary and secondary analyses, respectively.

Role of the funding source

This study was funded internally. The healthcare system had no influence over the study design, conduct, results, or dissemination of findings. The authors received no direct financial support for the research, authorship, and/or publication of this article. The authors have no competing interests to declare.

Results

Among all 14,921 total participants in the primary analyses, 535 (3.59%) were IgG positive and 14,386 (96.41%) were IgG negative. Overall, participants had a mean age of 42.13 (12.29), and the majority were female (85.54%), White (86.18%), Non-Hispanic (94.22%), and had a clinical role within the healthcare system (56.40%). This sample displayed a mean of 39.30 (26.65) days to COVID-19 infection after IgG test. See Table 1 for detailed univariate and bivariate results.

Bivariate analyses revealed statistically significant differences in age quantiles, race, ethnicity, clinical role category between IgG positive and negative participants, all at $P < .0001$. These variables were controlled for in primary and secondary adjusted analyses. Regarding days to COVID-19 infection, among the 913 participants that experienced a COVID-19 infection after study initiation, on average, those who were IgG positive experienced recurrence 9.11[−17.09,1.13] days sooner than those who were IgG negative ($P = .0253$).

Primary analysis

Incidence of COVID-19 infection (outcome) after IgG test (exposure)

Among all 14,921 total participants, 913 (6.12%) experienced COVID-19 infections after their IgG test, contributing 35,885 total days of follow-up. Of these 913 participants, 45 (4.93%) IgG positive participants and 868 (95.07%) IgG negative participants experienced COVID-19 infection. Incidence rate in 100 person-days was 2.52 for the overall sample, 3.26 for the IgG positive cohort and 2.16 for the IgG negative cohort. The IRR was 1.51, indicating 51% increased risk of COVID-19 infection among IgG positive participants relative to IgG negative participants.

COVID-19 infection (outcome) after IgG test (exposure)

Overall sample. Among the overall sample, adjusted analyses showed no difference in COVID-19 infection among positive and negative IgG participants (OR=1.19[0.85,1.67]; $P = .3117$). Age and clinical role category emerged as significant predictors of COVID-19 infection in adjusted analyses, both at $P < .0001$. Participants in the oldest age quantile demonstrating significantly lesser odds of COVID-19 infection relative to the youngest quantile (OR=0.58[0.47,0.71], $P = .0005$). COVID-clinical participants and clinical participants had 6.41[4.87,8.45]; $P < .0001$] times and 4.08[3.19,5.23; $P < .0001$] times greater odds of COVID-19 infection relative to non-clinical participants.

Among participants who were IgG negative, significant predictors and adjOR were similar, if not identical, to the overall adjusted model findings.

IgG positive cohort. Among participants who were IgG positive, the adjusted model demonstrated that clinical role category was the only remaining significant predictor of COVID-19 infection ($P = .0364$), driven by the difference in COVID-clinical and non-clinical participants. COVID-clinical participants showed 7.41[1.61,34.19; $P = .0201$] times greater odds of COVID-19 infection relative to nonclinical participants. Age was no longer a predictor of COVID-19 infection among IgG positive participants ($P = .1409$). See Table 2 for complete results of primary analyses.

Secondary analysis: COVID-19 recurrence (outcome) after COVID-19 infection (exposure)

Participants with a prior documented COVID-19 infection had 2.47[2.09,2.92] times greater crude odds and 1.93[1.62,2.29] times greater adjusted odds of recurrence of COVID-19 (both at $P < .0001$). Younger age and more exposure to COVID-19 via clinical role category were significant predictors of COVID-19 recurrence in adjusted analyses, both significant at $P < .0001$. See Table 3 for complete results of secondary analyses.

Conclusion

The results of this study contribute noteworthy data regarding recurrence of COVID-19 among individuals with evidence of prior exposure, defined by positive SARS-CoV-2 IgG antibodies or prior documented COVID-19 infection. These results have critical implications pertaining to immunity to the SARS-CoV-2 disease of COVID-19.

Regarding IgG positive status in primary analyses, findings show that crude incidence of COVID-19 recurrence is *greater* among those who are IgG positive, with an IRR showing 51% increased risk compared to those who are IgG negative. When adjusting for demographic factors and clinical role category, IgG status was not significant to the prediction of COVID-19 infection; instead, younger age and increased work-related exposure to COVID-19 was associated with significantly increased odds of COVID-19 infection, irrespective of IgG status.

In the secondary analysis, findings show that participants with a prior COVID-19 infection had 1.93–2.47 times greater odds of COVID-19 recurrence relative to those without a prior documented infection. After adjusting for demographic factors and clinical role, unlike positive IgG status, having a prior COVID-19 infection remained significant to the prediction of COVID-19 recurrence, reflecting nearly double the odds of recurrence. It is important to note that adjusted analyses with this exposure also showed younger age and increased work-related exposure was associated with increased odds of recurrence. *Findings reveal that neither prior*

Table 1
Demographics of sample of healthcare employees, overall and by SARS-CoV-2 IgG status

Variables of interest	Overall sample (N = 14,921)	IgG positive Status(N = 535; 3.59%)	IgG negative Status(N = 14,386)	Measure of association* (95% CI)	P-value
COVID-19 Infection	913 (6.12%)	45 (4.93%)	868 (95.07%)	1.43 (1.05, 1.96)‡	.0243‡
Days to Infection	39.30 (26.65);35.00 (33.00)	30.64 (21.35);28.00 (37.00)	39.75 (26.83);35.00 (33.00)	−9.11 (−17.09, −1.13)	.0253‡
Age, mean (SD);median (IQR)	42.13 (12.29);41.00 (20.00)	40.18 (12.64);39.00 (21.00)	42.20 (12.27);41.00 (21.00)	−2.02 (−3.11, −0.93)	.0002‡
18–31	3597 (24.11%)	183 (5.09%)	3414 (94.91%)	REF	<.0001†
32–41	4121 (27.62%)	115 (2.79%)	4006 (97.21%)	0.54 (0.42, 0.68)†	
42–51	3207 (21.49%)	114 (3.55%)	3093 (96.45%)	0.69 (0.54, 0.87)‡	
52–82	3996 (26.78%)	123 (3.08%)	3873 (96.92%)	0.59 (0.47, 0.75)†	
Sex (N = 14,920)					
Male	2157 (14.46%)	79 (3.66%)	2078 (96.34%)	REF	.8359
Female	12,763 (85.54%)	456 (3.57%)	12,307 (96.43%)	0.97 (0.76, 1.24)	
Race (N = 14,589)					
White only	12,573 (86.18%)	364 (2.90%)	12,209 (97.10%)	REF	<.0001†
Black only	548 (3.76%)	58 (10.58%)	490 (89.42%)	3.97 (2.97, 5.31)†	
Asian only	682 (4.67%)	40 (5.87%)	642 (94.13%)	2.09 (1.49, 2.92)†	
American Indian only	54 (0.37%)	2 (3.70%)	52 (96.30%)	1.29 (0.31, 5.32)	
Mixed	732 (5.02%)	44 (6.01%)	688 (93.99%)	2.15 (1.55, 2.96)†	
Ethnicity					
Not Hispanic	14,058 (94.22%)	480 (3.41%)	13,578 (96.59%)	REF	<.0001†
Hispanic	863 (5.78%)	55 (6.37%)	808 (93.63%)	1.93 (1.44, 2.57)†	
Clinical Role Category					
Non-clinical	4476 (30.00%)	135 (3.02%)	4341 (96.98%)	REF	<.0001†
Clinical	8416 (56.40%)	272 (3.23%)	8144 (96.77%)	1.07 (0.87, 1.32)	
COVID-clinical	2029 (13.60%)	128 (6.31%)	1901 (93.69%)	2.17 (1.69, 2.77)†	

* Statistical significance indicated in this column represents Wald test P-values for direct differences between the variable level relative to the reference level of the same variable.
† Statistically significant at $P < .0001$ for Pearson X^2 tests (or Fisher's Exact test) if categorical or Student's t-test if continuous.
‡ Statistically significant at $P < .05$ or Pearson X^2 tests (or Fisher's Exact test) if categorical or Student's t-test if continuous.

Table 2
Incidence and Adjusted (AdjOR) odds ratios of COVID-19 infection, overall and by SARS-CoV-2 IgG status

Incidence	Overall sample (N = 14,921) 913	Positive IgG status (N = 535) 45	Negative IgG status (N = 14.386) 868			
Person-Days of F/U	35,885	1379	34,506			
IR Per 100 Person-Days	2.52	3.26	2.16			
Rate Ratio	–	1.51	REF			
Variables of Interest for Adjusted Analysis	Overall Sample (N = 14,589)	Positive IgG Status (N = 508)	Negative IgG Status (N = 14.081)			
	AdjOR (95% CI)*	P-value	AdjOR (95% CI)*	P-value	AdjOR (95% CI)*	P-value
IgG Status						
Negative	REF	.3117	–	–	–	–
Positive	1.19 (0.85, 1.67)		–		–	
Age Category						
18–31	REF	<.0001†	REF	.1409	REF	<.0001†
32–41	0.77 (0.65, 0.92)		0.36 (0.13, 1.00)		0.79 (0.66, 0.95)	
42–51	0.68 (0.56, 0.83)		0.71 (0.30, 1.69)		0.68 (0.56, 0.84)	
52–82	0.58 (0.47, 0.71)‡		0.43 (0.15, 1.19)		0.59 (0.48, 0.73)‡	
Race						
White only	REF	.3389	REF	.7016	REF	.3824
Black only	0.68 (0.44, 1.04)‡		0.44 (0.10, 0.196)		0.70 (0.45, 1.10)‡	
Asian only	0.96 (0.70, 1.32)		0.57 (0.13, 2.59)		1.00 (0.72, 1.38)	
American Indian only	1.74 (0.68, 4.51)		–		1.87 (0.72, 4.86)	
Mixed Ethnicity	1.01 (0.75, 0.36)		0.57 (0.16, 2.00)		1.05 (0.77, 1.42)	
Not Hispanic	REF	.5776	REF	.5752	REF	.4419
Hispanic	0.92 (0.68, 1.24)		1.35 (0.48, 3.80)		0.88 (0.64, 1.22)	
Clinical Role Category						
Non-clinical	REF	<.0001†	REF	.0364‡	REF	<.0001†
Clinical	4.08 (3.19, 5.23)†		5.87 (1.35, 25.59)		4.04 (3.14, 5.19)†	
COVID-clinical	6.41 (4.87, 8.45)†		7.41 (1.61, 34.19)‡		6.44 (4.87, 8.53)†	

* Statistical significance indicated in this column represents Wald test p-values for direct differences between the variable level relative to the reference level of the same variable.
† Statistically significant at $P < .0001$.
‡ Statistically significant at $P < .05$.

Table 3
Crude and Adjusted (AdjOR) Odds Ratios of COVID-19 Infection by Prior COVID-19 Exposure.

Variables of Interest	Crude (N = 16,293) OR (95% CI)*	Adjusted (N = 15,902) P-value	AdjOR (95% CI)*	P-value
Prior COVID-19 Exposure				
No	REF	<.0001†	REF	<.0001†
Yes	2.47 (2.09, 2.92)†		1.93 (1.62, 2.29)†	
Age Category				
18–31	REF	<.0001†	REF	<.0001†
32–41	0.69 (0.59, 0.80)		0.80 (0.68, 0.93)	
42–51	0.54 (0.46, 0.65)‡		0.71 (0.59, 0.85)	
52–82	0.41 (0.34, 0.49)†		0.61 (0.50, 0.74)‡	
Race (N = 15,902)				
White only	REF	.0364‡	REF	.1629
Black only	0.66 (0.45, 0.98)‡		0.66 (0.45, 0.99)‡	
Asian only	1.14 (0.87, 1.50)		0.97 (0.73, 1.27)	
American Indian only	1.63 (0.70, 3.80)		1.80 (0.75, 4.32)	
Mixed	1.28 (0.99, 1.65)		1.10 (0.85, 1.42)	
Ethnicity				
Not Hispanic	REF	.2893	REF	.5254
Hispanic	1.14 (0.89, 1.46)		0.92 (0.70, 1.20)	
Clinical Role Category				
Non-clinical	REF	<.0001†	REF	<.0001†
Clinical	4.82 (3.82, 6.07)†		4.15 (3.27, 5.26)†	
COVID-clinical	7.49 (5.81, 9.64)†		5.90 (4.54, 7.68)†	

* Statistical significance indicated in this column represents Wald test P-values for direct differences between the variable level relative to the reference level of the same variable.
† Statistically significant at $P < .0001$.
‡ Statistically significant at $P < .05$.

exposure to SARS-CoV-2, as indicated by positive IgG status, nor prior infection with COVID-19 appear to be protective and, instead, are evidenced to increase likelihood of COVID-19 recurrence. This is especially true among healthcare workers who are younger and have more work-related exposure.

Discussion

Unexpectedly, this study demonstrated that prior SARS-CoV-2 exposure and antibody development did not result in decreased risk for subsequent COVID-19 infection. Conversely, the IRR of COVID-19 infection was 51% higher among participants who tested positive for SARS CoV-2 IgG in the prior four months. Due to the unexpected findings of our primary analysis, we sought to confirm this with a separate exposure. Because positive IgG status does not necessarily indicate prior COVID-19, our secondary analysis looked at documented history of COVID-19 infection within four months of study initiation. Participants with a prior documented COVID-19 infection, irrespective of IgG status, showed increased likelihood of COVID-19 recurrence, even when controlling for evidenced disparities in COVID-19 infection.

Our findings provide evidence of two things: first, COVID-19 infection is occurring among individuals with positive antibodies and a documented history of infection and second, immunity is short-lasting, if occurring at all. Incorporating results from both analyses, if there is a lingering assumption of immunity from COVID-19 after prior infection, this study negates this postulation. Furthermore, prior exposure or infection appears to increase likelihood of recurrence. This result corroborates the conclusion from the primary study endpoint – *prior infection by or exposure to SARS CoV-2 does not reduce the risk of subsequent COVID-19 infection.*

Strengths

This prospective study enrolled and followed a large cohort of individuals to determine incidence of recurrence of COVID-19, the largest cohort of individuals monitored for subsequent COVID-19 infection to date. This study offered free IgG testing, which eliminated a well-documented barrier to testing in vulnerable populations. This study utilized two objective exposure measures – IgG test status and prior COVID-19 infection status – to more comprehensively document potential for recurrence. The healthcare system-affiliated lab performed all IgG tests using the same assay and methods; furthermore, given the large size and breadth of the health system conducting this study, it is likely that most, if not all, assays for COVID-19 infection were performed within system-affiliated labs, resulting in performance and reporting consistency. All data was stored in the EMR and extracted by the system's Analytics Team, resulting in data collection consistency.

Limitations

There are several limitations to this study that could not be circumvented. This study's focus was on recurrence and, thus, did not address the relationship between documented prior COVID-19 infection and IgG status. It is important to note that individuals with no prior documented infection, and thus categorized as no exposure in secondary analysis, may not have a negative exposure history, but instead did not have RNA testing performed or documented, at all or at a system-affiliated lab.

Implications

Given the changing landscape of the COVID-19 outbreak, this paper provides much needed data to the emerging body of literature. This paper's COVID-19 recurrence findings may suggest a couple scenarios, one behavioral and one biological. First, it is possible that, after receiving antibody test results, individuals with positive IgG status behaved more recklessly by exposing themselves to potential infection sooner and more frequently, due to a misconception of immunity. Alternatively, individuals with positive IgG status may be more susceptible to COVID-19 infection due to their IgG status or a previous COVID-19 infection.

Considering these two potential scenarios, public health efforts should continue to widely disseminate the importance of infection-prevention measures, including but not limited to social distancing, mask-wearing, and hand hygiene. Furthermore, messaging should convey that previous exposure to SARS-CoV-2 or prior infection

with COVID-19 does not ensure immunity to subsequent COVID-19 infections. Without immunity, individuals are capable of spreading the disease and resource utilization still requires vigilance. Lastly, and perhaps most importantly, natural herd immunity appears unachievable, so policy efforts should challenge this narrative and advocate for universal vaccine uptake, when available.

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