Occupational Risk Factors for SARS-CoV-2 Seropositivity in Healthcare Workers

Results of a Longitudinal Cohort

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Objective: The aim of the study is to evaluate COVID-19 risk factors among healthcare workers (HCWs) before vaccine-induced immunity. **Methods:** We conducted a longitudinal cohort study of HCWs (N = 1233) with SARS-CoV-2 immunoglobulin G quantification by ELISA and repeated surveys over 9 months. Risk factors were assessed by multivariable-adjusted logistic regression and Cox proportional hazards models. **Results:** SARS-CoV-2 immunoglobulin G was associated with work in internal medicine (odds ratio [OR], 2.77; 95% confidence interval [CI], 1.05–8.26) and role of physician-in-training (OR, 2.55; 95% CI, 1.08–6.43), including interns (OR, 4.22; 95% CI, 1.20–14.00) and resident physicians (OR, 3.14; 95% CI, 1.24–8.33). Odds were lower among staff confident in N95 use (OR, 0.55; 95% CI, 0.31–0.96) and decreased over the follow-up. **Conclusions:** Excess COVID-19 risk observed among physicians-in-training early in the COVID-19 pandemic was reduced with improved occupational health interventions before vaccinations.

Keywords: COVID-19, SARS-CoV-2, healthcare personnel, healthcare worker, occupational risk factors, infection prevention, prospective cohort

LEARNING OUTCOMES

- In this large prospective, longitudinal cohort study of healthcare workers (HCWs) in a single metropolitan hospital system, role as a physician-in-training was associated with increased odds of COVID-19 immunoglobulin G antibodies (odds ratio [OR], 2.55; 95% confidence interval [CI], 1.08–6.43) during the early pandemic period from March to May 2020.
- Among physicians-in-training, prevalence of COVID-19 immunoglobulin G antibodies exhibited an inverse dose-response relationship to level of training, with highest odds among interns (OR, 4.22; 95% CI, 1.20–14.00), followed by resident physicians (OR, 3.14; 95% CI, 1.24–8.33) and clinical fellows (OR, 1.19; 95% CI, 0.30–4.03) after multivariable adjustment.
- Excess risk among physicians-in-training in this cohort was eliminated through standard occupational health interventions, including increased training and access to personal protective equipment, during the first year of the pandemic, before the widespread distribution of vaccines.

The US healthcare workforce experienced more COVID-19–related mortality than that of any other nation in the early pandemic period.[1,2] Approximately 40,000 to 60,000 US healthcare workers (HCWs) died from COVID-related illnesses in the first 18 months of the pandemic, according to estimates from the World Health Organization and the Institute for Health Metrics and Evaluation.[1,2] During this same period, the Occupational Safety and Health Administration received more than 10,000 COVID-related complaints from the health services sector alone—more than any other sector of the US economy, and an average of one new Occupational Safety and Health Administration complaint per hour through the entire first year of the pandemic.[3]

Despite these concerns, many recent studies on SARS-CoV-2 risk factors have attributed most HCW infections to community rather than occupational exposures.[4–11] In the midst of a pandemic, this conclusion is in fact an expected result, based on the prolonged duration, close proximity, low ventilation rates, and lack of personal protective equipment (PPE) characteristic of most household and community-based exposures. Occupational hazards may persist in healthcare settings irrespective of the population attributable risk, however, and ongoing assessment, communication, and mitigation of modifiable risk factors are critical for infection control and occupational health in the healthcare setting.[12]

There is substantial evidence that occupational transmission has contributed to the spread of COVID among HCWs,[13–17] but recognizing and reducing risk factors for infection in healthcare settings have been challenging because of concomitant community-based transmission. A recent systemic review of HCW risk factors concluded that SARS-CoV-2 infection was associated with direct care of COVID-19 patients and participation in high-risk procedures and mitigated by education and training in infection control, mask use, and use of appropriate PPE. Despite the large number of studies (N > 150) and participants (>200,000 HCWs) summarized in this analysis, however, the quality of the evidence was considered low to moderate because of methodological limitations, heterogeneity, and imprecision.[18,19] Most research has also been cross-sectional and insufficient for causal inference, with relatively few longitudinal studies of evolving HCW risk factors and incident infections in the United States.[6]

In particular, the effect of job role has been inconsistent across studies, with early research showing physicians at higher risk and subsequent studies demonstrating elevated risk among nurses.[19] Although research on job role has many challenges—including missing data,[20] exposure misclassification, and heterogeneity of job roles[19]—point estimates for SARS-CoV-2 infection among physicians-in-training have been consistently observed to be higher than attending physicians in the United States.[13,21–23] Physicians-in-training may experience elevated occupational risk of SARS-CoV-2 infection due to their level of training as well as their close contact in caring for patients.

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To address these gaps in the literature, we sought to provide a more granular analysis of HCW risk factors in a single metropolitan hospital system, including more detailed job classifications that account for physicians-in-training, and longitudinal follow-up to characterize both prevalent and incident infections. This study uses repeated measures of SARS-CoV-2 immunoglobulin G (IgG) and surveys of infectious exposures and health behaviors in a large workforce ($N > 1200$) to characterize occupational and community risk factors as they evolved during the first year of the pandemic from March 2020 through January 2021. This period also serves as a natural experiment for assessing the effectiveness of occupational health interventions on emerging infections before the development of vaccines, and strategies for reducing occupational infections and improving pandemic preparedness are discussed.

METHODS

Human Subjects

Human subjects older than 18 years who worked at a single, metropolitan academic hospital in Northeastern, United States, were recruited through announcements at regularly scheduled staff meetings and via email beginning in March 2020 with baseline survey and serum collection. Follow-up continued with repeat serology and surveys through January 2021. Recruitment of this volunteer sample and all study methods were approved by the Yale Institutional Review Board and Human Investigations Committee.

Individual and Community Data Sources

Surveys were collected from enrolled participants at 4 time points using the online Qualtrics survey platform, and data were aggregated in a MySQL database (https://www.qualtrics.com). Survey questionnaires captured demographic information and potential occupational and community risk factors associated with COVID-19 transmission. Daily COVID-19 incidence rates per 100,000 individuals for each town were obtained from the Connecticut Department of Health,[24] using the standardized case definition of probable and confirmed cases from the Council of State and Territorial Epidemiologists.[25] For each participant, community exposure to COVID-19 was calculated as the mean incidence in the participant's town of residence during the interval between each date of serum collection.

Enzyme-Linked Immunosorbent Assay

Peripheral blood samples were obtained by venipuncture using vacutainer tubes (Becton Dickinson, Falcon Lakes, NJ) with a serum separator, aliquoted and stored at −80°C before use in enzyme-linked immunosorbent assays (ELISAs). All blood samples were handled under biosafety level 2+.

Nunc band Maxisorp™ 96-well microtiter plates from Life Technologies (Grand Island, NY) were coated with 50 μL/well of a 1 μg/mL solution of spike antigen (S1+S2 ECD, YP_009724390.1), extracellular domain (Val-16 to Pro-1213) from Sino Biological (Wayne, PA) in 0.1 M sodium carbonate buffer with pH 9.6, overnight at 4°C. After blocking with 200 μL/well of 3% dry milk/omniblok™ from AmericanBio (Canton, MA) in phosphate-buffered saline, pH 7.4, for 1 hour at room temperature, and 1 hour incubation with 100 μL/well of 1:100 serum, the plates were developed with 75 μL/well of 1:2000 dilution of anti-human IgG-peroxidase, conjugated from Pharmingen (San Diego, CA), clone G18-145 for 1 hour, followed by 100 μL/well 3,3′,5,5′-tetramethylbenzidine substrate as previously described.[26–28] Optical density was read at 450 nm, with reference at 650 nm after addition of 2 M HCL.

Optimal cutoffs for binary classification of the continuous optical density scale were established after a receiver operating characteristic analysis with positive control samples obtained from patients documented to have COVID-19 by clinical symptomatology and a positive polymerase chain reaction (PCR) test, and negative controls obtained from prepandemic blood samples. A subset of samples was compared with commercially available serologic assays from EuroImmun, Abbot Architect, and Vitros, with similar results.[27] The sensitivity and specificity of the Laboratory Diagnostic Test were estimated to be 96% and 98%, respectively, with an optical density value of 0.345, which was used as the cutoff for this analysis.

Statistical Analysis

Descriptive statistics for categorical and continuous variables were calculated using Fisher exact and Mann-Whitney U tests as appropriate (Table 1). A multivariable-adjusted logistic regression model was constructed for analysis of risk factors of prevalent infections from baseline serologic testing. Department, which was correlated with job position and resulted in models with higher residual deviance, was excluded from adjustment in multivariable models. All other variables included for adjustment exhibited no significant evidence of collinearity. Emergency medicine and nurses were selected as reference categories for department and occupation, respectively, because of diversity of patient exposure, the large sample sizes present in this study, and the low prevalence of infection at baseline.

A mixed effects Cox proportional hazards model with the individual subject included as a random effect[29] was used to evaluate risk factors for seroconversion in repeated observations during the follow-up period. For missing data, we used a last observation carried forward method. Independent interval-censored data, which can result in biased estimates for time-varying covariates as intervals increase in length,[30] was accounted for by multiple imputation[31,32] as extended to mixed effects Cox models in R Statistical Software (https://www.r-project.org).[33] Community incidence rates and covariates from individual survey data were derived from data corresponding to the imputed survival time; surveys that occurred more than 28 days after the imputed survival time were considered at risk of bias and excluded from analysis for that assessment interval.

Kaplan-Meier curves (Figs. 1, 2) include baseline and follow-up data and illustrate the changing hazards across these 2 periods. All statistical analyses were conducted using R statistical software (version 4.1.3). [34,35]

RESULTS

Information on the HCWs ($N = 1233$) enrolled in the present study is summarized in Table 1, including demographic, environmental, and occupational data relevant to SARS-CoV-2 exposure. The participants were from a large metropolitan hospital in Northeastern, United States, and included hospital staff from general internal medicine (20.2%); emergency medicine (18.5%); internal medicine subspecialties such as pulmonology and infectious disease (22.7%); other specialties such as pediatrics and neurology (17.1%); and anesthesiology (13.1%) and other surgical specialties (8.4%). The population was predominately White (74.5%) and female (65.7%), with a median age of 35, and resided in the vicinity of New Haven, Connecticut (85%). The large majority of participants were house staff officers (29.8%), attending physicians (27.3%), or nurses (21.5%) who were involved in direct patient care more than once a week (87.2%), including exposure to aerosol-generating procedures (40.1%), and reported concern for COVID-19 exposure at work more than once a week (86.3%). Initial enrollment began after the first case of COVID-19 infection was detected in Connecticut on March 8, 2020, and 1223 (99.2%) had baseline serology performed by May 8, 2020. Follow-up with both serology and surveys continued over a 9-month period through January 2021.

SARS-CoV-2 Seroprevalence

Baseline prevalence of SARS-CoV-2 spike antigen-specific IgG detected by ELISA was 72 of participants (5.8%). Prevalence of

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TABLE 1. Baseline Characteristics of Study Participants

	Total (N = 1,233)	Seronegative (n = 1,161)	Seropositive (n = 72)	
	n (%) or Median (IQR)	n (%) or Median (IQR)	n (%) or Median (IQR)	P
Demographics				
Sex	1232 (100)	1160 (100)	72 (100)	<0.01
Female	810 (65.7)	775 (66.8)	35 (48.6)	
Male	422 (34.3)	385 (33.2)	37 (51.4)	
Age	35 (31.0–45.0)	35 (31.0–44.2)	35.5 (31.0–48.5)	0.41
Race				
White	918 (74.5)	863 (74.4)	55 (76.4)	0.78
Asian	219 (17.8)	206 (17.8)	13 (18.1)	1.00
Black	48 (3.9)	45 (3.9)	3 (4.2)	0.76
Ethnicity	1232 (100)	1160 (100)	72 (100)	0.43
Latinx	71 (5.8)	69 (5.9)	2 (2.8)	
History of COVID				
History of COVID symptoms	196 (15.9)	163 (14.0)	33 (45.8)	<0.0001
Missed work due to illness, d	0 (0.0–0.0)	0 (0.0–0.0)	0 (0.0–5.0)	<0.0001
COVID PCR+	27 (2.2)	3 (0.3)	24 (33.3)	<0.0001
Serology result (optical density)	0.11 (0.1–0.2)	0.1 (0.1–0.1)	0.56 (0.4–0.9)	<0.0001
Date of enrollment, wk	5.14 (4.1–6.4)	5.14 (4.1–6.1)	5.29 (4.5–6.6)	0.03
Environmental exposures				
Population density (1000 people/mi^2)	2.6 (1.1–9.0)	2.84 (1.1–9.0)	1.51 (0.9–9.0)	0.61
Household size	958 (100)	894 (100)	64 (100)	0.61
1 person	189 (19.7)	174 (19.5)	15 (23.4)	
2 people	331 (34.6)	308 (34.5)	23 (35.9)	
3 or more people	438 (45.7)	412 (46.1)	26 (40.6)	
Adults working outside of home	958 (100)	894 (100)	64 (100)	0.52
1 or none	542 (56.6)	503 (56.3)	39 (60.9)	
2 or more	416 (43.4)	391 (43.7)	25 (39.1)	
Community COVID incidence	3 (1.0–4.0)	3 (1.0–4.0)	3 (1.8–3.2)	0.89
COVID exposure outside of work	346 (28.1)	326 (28.1)	20 (27.8)	1.00
Occupational exposures				
Department	1232 (100)	1160 (100)	72 (100)	0.15
Emergency medicine	228 (18.5)	222 (19.1)	6 (8.3)	
Anesthesiology	161 (13.1)	150 (12.9)	11 (15.3)	
General internal medicine	249 (20.2)	232 (20.0)	17 (23.6)	
Internal medicine subspecialty	280 (22.7)	266 (22.9)	14 (19.4)	
Other specialty	211 (17.1)	195 (16.8)	16 (22.2)	
Surgical specialty	103 (8.4)	95 (8.2)	8 (11.1)	
Position	1232 (100)	1160 (100)	72 (100)	0.29
Nursing	265 (21.5)	255 (22.0)	10 (13.9)	
Attending physician	336 (27.3)	314 (27.1)	22 (30.6)	
House staff	367 (29.8)	340 (29.3)	27 (37.5)	
Other clinical (eg, APRN, PA)	172 (14.0)	165 (14.2)	7 (9.7)	
Other staff (eg, administrator, medical assistant, technician)	92 (7.5)	6 (8.3)		
Direct patient care	1231 (100)	1159 (100)	72 (100)	0.28
Less than once a week	157 (12.8)	145 (12.5)	12 (16.7)	
More than once a week	1074 (87.2)	1014 (87.5)	60 (83.3)	
Worked with COVID+ coworker	187 (15.2)	177 (15.2)	10 (13.9)	0.87
Exposure to aerosol procedures	494 (40.1)	467 (40.2)	27 (37.5)	0.71
Health knowledge and behaviors				
Confidence in using an N95	485 (39.4)	465 (40.1)	20 (27.8)	0.05
Endorse feeling overworked	459 (37.3)	443 (38.2)	16 (22.2)	<0.01
Endorse feeling burnout	913 (74.0)	870 (74.9)	43 (59.7)	<0.01
Concern for COVID at work	1233 (100)	1161 (100)	72 (100)	<0.01
Less than once a week	169 (13.7)	150 (12.9)	19 (26.4)	
More than once a week	1064 (86.3)	1011 (87.1)	53 (73.6)	

APRN, Advanced Practice Registered Nurse; IQR, interquartile range; PA, Physician Assistant; PCR, polymerase chain reaction.

SARS-CoV-2 IgG was significantly ($P < 0.0001$) higher in subjects who reported prior positive COVID-19 PCR test result and subjects who reported a history of COVID-19 symptoms. Of those who were seropositive at baseline, 39 individuals (54.2%) reported no history of COVID-19 symptoms. Individuals who used a higher number of sick days and those who enrolled in the study later were also significantly more likely to be seropositive ($P < 0.0001$ and $P = 0.03$, respectively). Higher rates of seropositivity at baseline were observed among males, house staff officers, individuals employed in general internal medicine, and those who had less concern for COVID at work and did not report burnout or overwork. Baseline seropositivity was not associated with community-based exposures or other demographic characteristics such as age, race or ethnicity.

Risk Factors for Prevalent Infections

Unadjusted analysis (Table 2) demonstrated significant associations of baseline seropositivity with male gender (odds ratio [OR],

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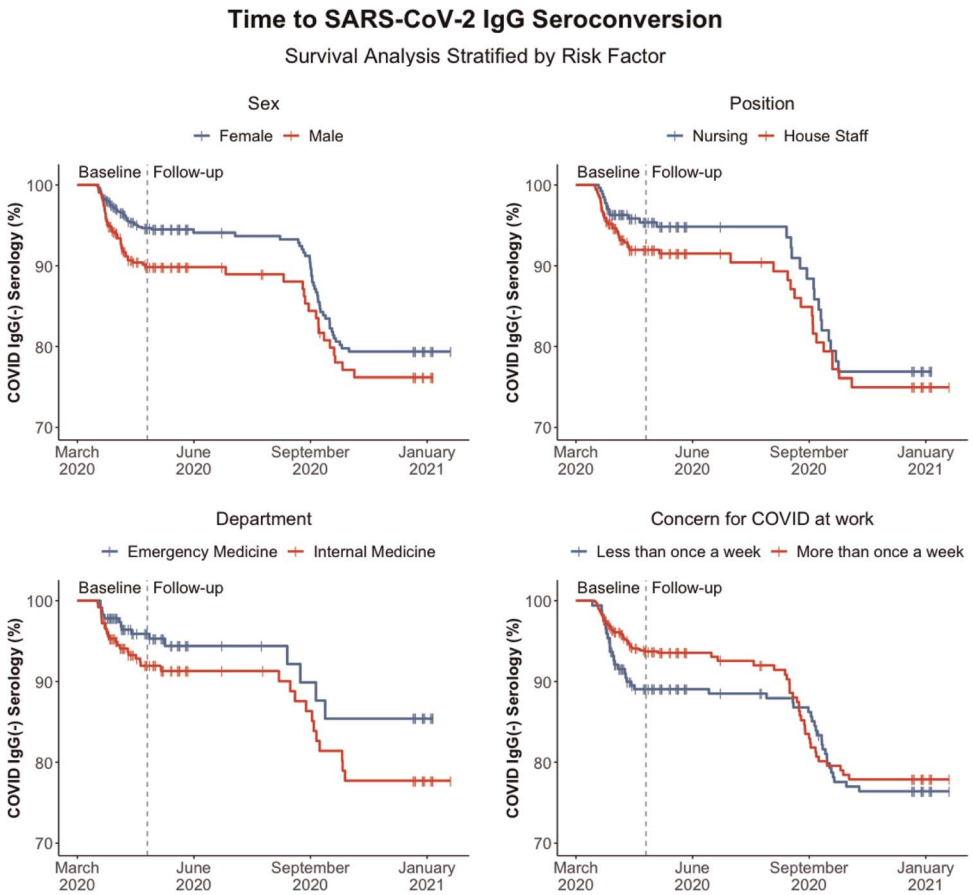

FIGURE 1. Kaplan-Meier curves for time to SARS-CoV-2 spike antigen-specific IgG seroconversion as stratified by gender, job position, department, and concern for COVID-19 at work, respectively. Prevalent infections recorded during the baseline period of enrollment are designated to the left of vertical dotted line, and incident infections observed during the 9 months of follow-up are designated to the right of the vertical dotted line.

2.13; 95% confidence interval [CI], 1.32–3.44) and departmental affiliation, with higher rates in anesthesiology, general internal medicine, as well as surgical and other specialties when compared with emergency medicine. Analysis of job position demonstrated higher rates among house staff (OR, 2.02; 95% CI, 0.99–4.46) compared with all nurses. The elevated odds among physicians-in-training was attributable to higher odds of seropositivity among residents (OR, 2.44; 95% CI, 1.11–5.64) and interns (OR, 2.51; 95% CI, 0.83–7.02). Odds of seropositivity were not elevated among fellows and chief residents (OR, 1.01; 95% CI, 0.27–3.10).

Several measures of health knowledge and behaviors were associated with lower odds of SARS-CoV-2 seropositivity, including confidence in using an N95 respirator (OR, 0.57; 95% CI, 0.33–0.96), increased concern for COVID exposure at work (OR, 0.41; 95% CI, 0.24–0.73), endorsement of feeling overworked (OR, 0.46; 95% CI, 0.25–0.80), and experience of burnout (OR, 0.50; 95% CI, 0.31–0.82). Community risk factors, including COVID-19 incidence rates in the town of residence, population density of town of residence, self-reported COVID-19, exposure outside of work, household size, and number of cohabitating adults working outside the household, were not significantly associated with SARS-CoV-2 seropositivity at baseline.

After adjustment for major demographic variables and suspected risk factors—including age, sex, race, ethnicity, date of enrollment, COVID-19 incidence in the town of residence, self-reported COVID-19, exposure outside of work, job position, frequency of direct patient care, exposure to aerosol-generating procedures, and work with coworker who was known or suspected to have COVID—male gender remained highly associated with anti-SARS-CoV-2 IgG with an OR of 1.91 (95% CI, 1.13–3.24). After adjustment, house staff physicians exhibited higher odds of seropositivity (OR, 2.55; 95% CI, 1.08–6.43); the highest odds were observed among interns (OR, 4.22; 95% CI, 1.20–14.00), followed by residents (OR, 3.14; 95% CI, 1.24–8.33). Prevalence of SARS-CoV-2 antibodies were not significantly elevated in fellows and chief residents (OR, 1.19; 95% CI, 0.30–4.03). Subgroup analysis of nurses (not shown) also demonstrated that in comparison with non–intensive care unit nurses, critical care registered nurses (RNs) were also at increased risk of COVID-19 seropositivity (OR, 4.41; 95% CI, 1.16–16.84). Using emergency medicine as a reference, employment in general internal medicine was also associated with an elevated risk of seropositivity (OR, 2.77; 95% CI, 1.05–8.26).

Several measures of health knowledge and behavior remained significantly associated with decreased seropositivity after adjustment, including confidence in using an N95 respirator (OR, 0.55; 95% CI, 0.31–0.96), increased concern for COVID exposure at work (OR, 0.53; 95% CI, 0.30–0.98), and endorsement of feeling overworked (OR, 0.47; 95% CI, 0.25–0.83). Date of enrollment in the study also remained significant after adjustment (OR, 1.26; 95% CI, 1.09–1.44).

Risk Factors for Incident Infections

Of the 1161 individuals who did not test positive at baseline, 939 (81%) returned for antibody testing over a 9-month follow-up,

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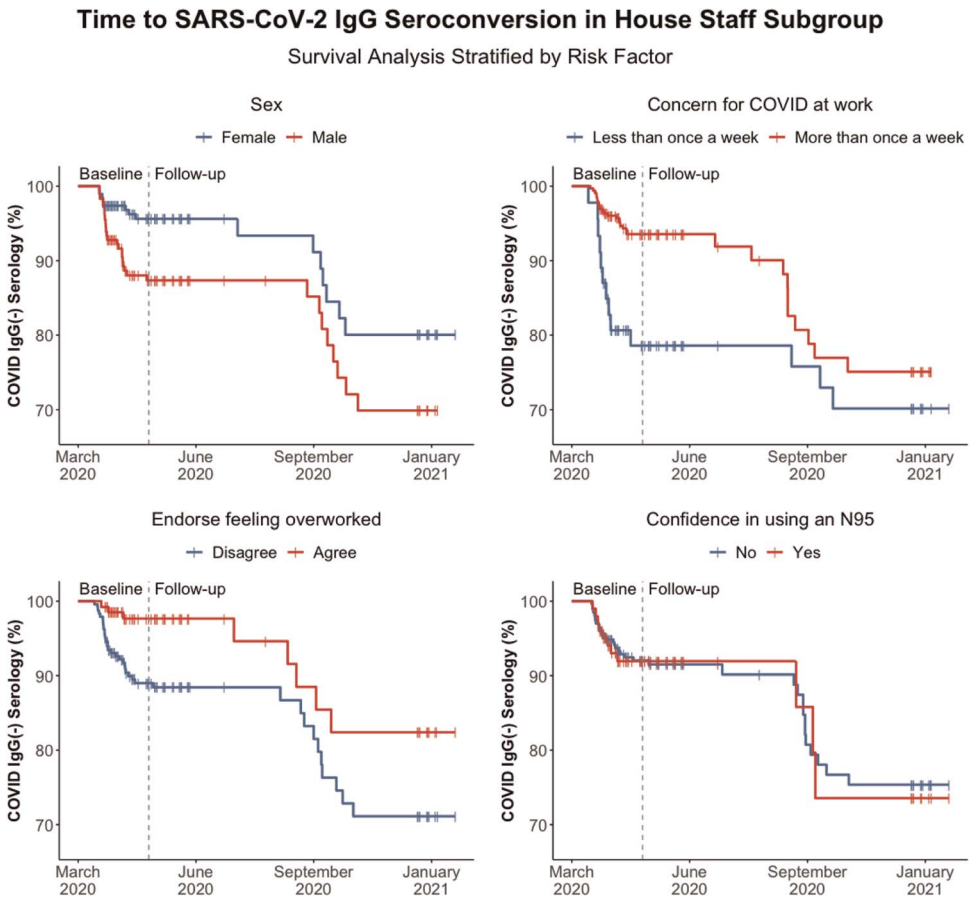

FIGURE 2. Kaplan-Meier curves for time to SARS-CoV-2 spike antigen-specific IgG seroconversion in a subgroup analysis of house staff physicians as stratified by gender, concern for COVID-19 at work, endorsement of feeling overworked, and confidence in using an N95 respirator, respectively. Prevalent infections recorded during the baseline period of enrollment are designated to the left of vertical dotted line, and incident infections observed during the 9 months of follow-up are designated to the right of the vertical dotted line.

period from April 2020 through January 2021 (302 total person-years of follow-up). Serology demonstrated SARS-CoV-2 IgG in 65 of participants (6.92%) during follow-up, giving an incidence rate of 21.5 new infections per 100 person-years of follow-up.

During the follow-up period, none of the suspected demographic, occupational, and community risk factors were associated with significantly elevated hazard ratios in a mixed effects Cox proportional hazards model. This null finding was unchanged after multivariable adjustment for age, sex, race, ethnicity, COVID-19 incidence in the town of residence, self-reported COVID-19, exposure outside of work, job position, frequency of direct patient care, exposure to aerosol-generating procedures, and work with coworker who was known or suspected to have COVID-19. Date of study enrollment was associated with a lower hazard ratio for seroconversion, which was an expected finding of the study design discussed hereinafter.

Kaplan-Meier curves of time to seropositivity (Fig. 1) include both the prevalent infections detected through the baseline testing period (left of vertical line) and the incident cases detected during 9 months of follow-up (right of vertical line), as stratified by gender, job position, department, and concern for COVID-19. Although offset by the separation observed during the early pandemic period, survival curves are parallel or convergent for incident infections in the follow-up period and reflect nonsignificant differences in hazard ratios between groups.

Kaplan-Meier curves in a subgroup analysis of house staff physicians (Fig. 2) reflect increased rates of seropositivity among males at baseline, but the effect was not sustained during follow-up. Increased concern for COVID-19 at work and endorsement of feeling overworked were both associated with lower rates of seropositivity at baseline, although this effect was attenuated during the follow-up period. Confidence in using an N95 respirator did not seem to have a significant association with COVID-19 seropositivity among house staff at any time point.

DISCUSSION

This report details prevalent and incident SARS-CoV-2 infections from a large longitudinal cohort of HCWs ($N = 1233$) at a major academic hospital during the first year of the SARS-CoV-2 pandemic. The results demonstrated that a strong association between SARS-CoV-2 seropositivity and occupation during the initial wave of the local pandemic, from March 2020 to May 2020, was ultimately reduced during the follow-up period from May 2020 to January 2021.

Most notably, house staff physicians exhibited a 2- to 3-fold increase in odds (OR, 2.55; 95% CI, 1.08–6.43) of seropositivity that was inversely associated with training. Interns exhibited the highest odds (OR, 4.22; 95% CI, 1.20–14.0), followed by resident physicians (OR, 3.14; 95% CI, 1.24–8.33), and clinical fellows and chief residents (OR, 1.19; 95% CI, 0.30–4.03) after multivariable adjustment. This result is consistent with prior research that disaggregated physicians-in-training from attending physicians[13,21–23] but is, to our knowledge, the first report of an inverse dose-response relationship

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TABLE 2. Association of SARS-CoV-2 IgG Serology With HCW Risk Factors for Prevalent and Incident Infections

	Prevalent Infections	Incident Infections		
	Total at baseline (n = 1,233)	Total With Follow-up (n = 939)		
	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)
Demographics				
Sex				
Female	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Male	2.13 (1.32–3.44)	1.91 (1.13–3.24)	1.42 (0.39–5.23)	0.89 (0.38–2.07)
Age	1.01 (0.99–1.04)	1.02 (0.99–1.05)	1.01 (0.97–1.05)	1.01 (0.97–1.05)
Race				
White	1.11 (0.65–2.00)	1.34 (0.29–5.70)	0.54 (0.17–1.72)	0.25 (0.03–2.41)
Asian	1.02 (0.53–1.84)	1.18 (0.24–5.09)	1.52 (0.52–4.48)	0.50 (0.05–5.15)
Black	1.08 (0.26–3.05)	1.42 (0.20–7.76)	0.89 (0.12–6.63)	0.17 (0.01–4.31)
Ethnicity				
Latinx	0.45 (0.07–1.48)	0.55 (0.07–2.53)	1.66 (0.46–5.93)	0.55 (0.05–5.62)
History of COVID				
History of COVID symptoms	5.18 (3.15–8.47)	5.47 (3.22–9.28)	1.96 (0.59–6.52)	1.39 (0.38–5.09)
Missed work due to illness, d	1.18 (1.13–1.24)	1.20 (1.14–1.26)	1.04 (0.90–1.21)	1.02 (0.89–1.16)
Date of enrollment, wk	1.09 (0.99–1.20)	1.26 (1.09–1.44)	0.67 (0.55–0.82)	0.67 (0.53–0.85)
Environmental exposures				
Population density (1000 ppL/mi^2)	0.99 (0.94–1.04)	0.99 (0.91–1.08)	1.00 (0.91–1.10)	0.99 (0.87–1.13)
Household size				
1 person	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
2 people	0.87 (0.44–1.74)	0.81 (0.40–1.66)	0.82 (0.26–2.59)	0.88 (0.31–2.51)
3 or more people	0.73 (0.38–1.45)	0.62 (0.30–1.32)	0.58 (0.18–1.85)	0.61 (0.21–1.80)
Adults working outside of home				
1 or none	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
2 or more	0.82 (0.49–1.38)	0.81 (0.47–1.38)	0.76 (0.31–1.84)	0.97 (0.45–2.10)
Community COVID incidence	0.99 (0.80–1.22)	0.89 (0.71–1.12)	0.82 (0.54–1.25)	0.89 (0.57–1.39)
COVID exposure outside of work	0.99 (0.57–1.65)	0.93 (0.53–1.58)	0.55 (0.20–1.49)	0.67 (0.30–1.49)
Occupational exposures				
Department				
Emergency medicine	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Anesthesiology	2.71 (1.01–8.02)	2.69 (0.95–8.39)	0.82 (0.23–2.87)	0.83 (0.21–3.28)
General internal medicine	2.71 (1.10–7.63)	2.77 (1.05–8.26)	0.82 (0.26–2.56)	0.86 (0.24–3.13)
Internal medicine subspecialty	1.95 (0.77–5.58)	1.67 (0.63–4.96)	0.73 (0.23–2.30)	0.86 (0.26–2.80)
Surgical specialty	3.12 (1.06–9.70)	2.80 (0.88–9.32)	0.38 (0.05–2.74)	0.57 (0.08–4.02)
Other specialty	3.04 (1.22–8.60)	2.69 (1.00–8.14)	0.73 (0.20–2.61)	0.95 (0.24–3.72)
Position				
Nursing	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Attending physician	1.79 (0.85–4.01)	1.39 (0.59–3.42)	1.42 (0.47–4.27)	0.62 (0.20–1.90)
House staff	2.02 (0.99–4.46)	2.55 (1.08–6.43)	1.32 (0.42–4.14)	0.59 (0.17–2.07)
Interns	2.51 (0.83–7.02)	4.22 (1.20–14.0)	2.61 (0.56–12.2)	1.55 (0.31–7.70)
Residents	2.44 (1.11–5.64)	3.14 (1.24–8.33)	0.39 (0.06–2.62)	0.24 (0.04–1.54)
Fellows and chiefs	1.01 (0.27–3.10)	1.19 (0.30–4.03)	2.40 (0.59–9.81)	0.87 (0.17–4.47)
Other clinical (eg, APRN, PA)	1.08 (0.39–2.87)	1.09 (0.38–3.01)	1.05 (0.28–4.00)	0.67 (0.19–2.34)
Other staff (eg, administrator, medical assistant, technician)	1.78 (0.59–4.94)	1.38 (0.45–3.91)	1.60 (0.35–7.25)	0.96 (0.21–4.41)
Direct patient care				
Less than once a week	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
More than once a week	0.71 (0.39–1.42)	0.93 (0.48–1.92)	2.44 (0.94–6.31)	1.72 (0.71–4.17)
Worked with COVID+ coworker	0.90 (0.43–1.71)	1.14 (0.53–2.26)	0.64 (0.16–2.56)	0.35 (0.07–1.82)
Exposure to aerosol procedures	0.89 (0.54–1.45)	1.08 (0.62–1.86)	1.23 (0.61–2.49)	0.90 (0.42–1.92)
Health knowledge and behaviors				
Confidence in using an N95	0.57 (0.33–0.96)	0.55 (0.31–0.96)	0.63 (0.25–1.59)	0.68 (0.30–1.53)
Endorse feeling overworked	0.46 (0.25–0.80)	0.47 (0.25–0.83)	0.81 (0.28–2.38)	0.67 (0.31–1.47)
Endorse feeling burnout	0.50 (0.31–0.82)	0.60 (0.36–1.03)	1.17 (0.43–3.19)	1.39 (0.57–3.38)
Concern for COVID at work				
Less than once a week	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
More than once a week	0.41 (0.24–0.73)	0.53 (0.30–0.98)	2.09 (0.71–6.12)	1.58 (0.67–3.70)

CI, confidence interval; HR, hazard ratio; OR, odds ratio.

*All hazard and odds ratios have been adjusted for age, sex, race, ethnicity, community COVID incidence, high-risk COVID exposure outside of work, job position using house staff as a combined category, frequency of direct patient care, exposure to aerosol-generating procedures, and work with coworker who was known or suspected to be COVID+. Baseline odds ratios have also been adjusted for date of enrollment in the study.

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between year of training and COVID-19 seroprevalence among physicians-in-training.

Increased odds of seropositivity was also observed among employees in general internal medicine (OR, 2.77; 95% CI, 1.05–8.26), who staffed both COVID-19 inpatient wards, including intensive care and step-down units, as well as general medicine floors and primary care clinics in the period before widespread availability of COVID-19 PCR testing. In a separate subgroup analysis (data not shown in table because of a different reference level), critical care nurses (CCRNs) who staffed the same intensive care unit and step-down units also exhibited a higher odds of prevalent infections when compared with other nursing staff (OR, 4.41; 95% CI, 1.16–16.84), consistent with prior reseach.[36]

Increased risk among interns, residents, and CCRNs, especially those affiliated with general internal medicine, likely reflects a common source of exposure or inadequate access to or use of appropriate PPE. In particular, these individuals experienced high contact with patients on both the general medicine floors and the medical intensive care units during a time before the introduction of universal masking for source control and respiratory protection. Interns, residents, and CCRNs are also the most likely to be in close contact with patients during cardiopulmonary resuscitation, a risk factor for viral exposure[37–40] that can persist despite N95 respirator use.[41–43] The absence of association between seropositivity and aerosol-generating procedures is notable and suggests that most occupational SARS-CoV-2 transmission resulted from unrecognized sources of SARS-CoV-2 exposure, such as unmasked contact with patients not known to have COVID-19 or coworkers sharing workspaces,[15,16,44] rather than aerosol-generating procedures performed on known COVID-19 patients. These results are consistent with prior research that demonstrated increased risk among healthcare workers,[45] including those HCW who reported no known exposure to COVID-19 patients,[14] with the primary risk attributable to the lack of PPE.[14,45,46]

The current investigation also observed a strong association between SARS-CoV-2 IgG seroprevalence and health knowledge and behaviors during the first wave of the pandemic from March to May 2020. Confidence in using an N95 respirator and concern for occupational transmission of COVID-19 were both associated with reduced odds of SARS-CoV-2 seropositivity and likely reflect the protective effects of a worker's preventive health knowledge or adherence to PPE use, which is consistent with prior research[14,17,19,45,46] Lower odds of seropositivity among those experiencing burnout and endorsing overwork may be related to individual behavioral practices or reflective of lower cumulative occupational exposures, as such workers may be less likely to volunteer for additional shifts. Taken together, the association between training level, and health knowledge and behaviors on COVID-19 prevalence suggests that improved training and awareness of occupational transmission could significantly reduce infections in future pandemics.

The basis for the association between male sex and SARS-CoV-2 IgG seropositivity is uncertain and has been attributed to both behavioral as well as biological differences, such as viral susceptibility and immunogenicity.[47,48] In this longitudinal study, the narrowing of seropositivity disparities between sexes over time suggests that sex variation is context sensitive and likely attributable to behavioral differences in the early pandemic period. Gendered differences in preventive behaviors, such as compliance with mask wearing and social distancing, have been previously observed in both the United States[49,50] and international contexts.[51] The finding from the current study is consistent with a comprehensive longitudinal analysis of sex disparities in COVID-19 outcomes in the United States[52] and suggests that public health interventions targeting risk reduction among male HCWs may be beneficial.

The current study did not find a significant relationship between SARS-CoV-2 IgG and demographic risk factors such as race, ethnicity, age, or town of residence. These null findings have been observed in other studies of community risk factors[53] and may indicate that community-transmission may have been more limited in the setting of widespread business and school closures that characterized the early pandemic in this area.

In contrast to occupational risk factors identified at baseline, no significant associations were observed for incident infections in mixed-effects Cox proportional hazard models. Resolution of risk over time among house staff physicians, including interns and residents, in a single hospital system may reflect the success of intervening occupational health strategies, which included greater availability of PPE such as N95 respirators; the introduction of universal masking for all patients and hospital staff; greater access to PCR testing in the hospital and the surrounding community; greater knowledge of modes of transmission; and increased awareness of the prevalence of asymptomatic infections. To our knowledge, this is one of the few granular longitudinal studies of HCWs to show that excess risk identified in the early pandemic was successfully controlled with occupational health interventions even before the introduction of COVID-19 vaccinations.

The strengths and weakness of the present study should be recognized when interpreting the findings. The strengths include the research design as a prospective cohort study, the active participation of HCWs, the ability to screen large numbers of participants through high-throughput serology, and the duration of follow-up throughout the first year of the pandemic. A limitation is the focus on a single hospital system, which, although similar to other large academic medical centers, may differ substantially from rural and community hospital settings. Because of differences in the modality and availability of community-based COVID-19, testing, this study could also not determine whether risk of HCW infection during the follow-up period remained in excess of risk in the general population.

CONCLUSIONS

This large-scale prospective cohort study of HCWs at a major academic hospital in the northeast US observed that COVID-19 infection was associated with health knowledge and behaviors consistent with prior research but is the first to identify an inverse dose-response relationship between level of training and COVID-19 seroprevalence among physicians-in-training. Longitudinal analysis demonstrated that this excess risk from the early phase of the pandemic was effectively eliminated with existing occupational health interventions before the introduction of COVID-19 vaccinations. This study indicates that reliable availability and improved training on the use of PPE among healthcare workers, especially those with the least experience and the greatest exposures, can effectively reduce excess infection risk among HCWs in future emerging infections.

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