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SARS-CoV-2 antibody seroprevalence after the first wave among workers at a community healthcare system in the Greater Boston area

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ABSTRACT

SARS-CoV-2 antibody seroprevalence among health-care workers (HCW) can assess past exposure and possible immunity, which varies across different regions, populations and times. We investigated the seroprevalence among HCW in Massachusetts (a region suffering high COVID-19 mortality) at the end of first wave of the SARS-CoV-2 pandemic. All HCW at Cambridge Health Alliance were invited to participate in this cross-sectional survey in June 2020. Those who volunteered, consented and provided a blood sample were included. Dried blood specimens from finger-prick sampling collected either at home by each HCW or onsite by the study team were analyzed for anti-SARS-CoV-2 IgM and IgG to the virus' receptor binding domain, using an enzyme-linked immunosorbent assay. IgM and IgG antibody abundance were categorized based on the number of standard deviations above the cross-reacting levels found in existing, pre-pandemic blood samples previously obtained by the Ragon Institute and analyzed by the Broad Institute (Cambridge, MA). Seroprevalence estimates were made based on 'positive' IgM or IgG using 'low' (>6 SD), 'medium' (>4.5 SD), and 'high' prevalence cutoffs (>3 SD).

A total of 433 out of 5,204 eligible HCWs consented and provided samples. Participating HCWs had a lower cumulative incidence (from the start of the pandemic up to the bloodspot collections) of SARS-CoV-2 RT-PCR positivity (1.85%) compared to non-participants (3.29%). The low, medium, and high seroprevalence estimates were 8.1%, 11.3%, and 14.5%, respectively. The weighted estimates based on past PCR positivity were 13.9%, 19.4%, and 24.9%, respectively, for the entire healthcare system population after accounting for participation bias.

KEYWORDS

SARS-CoV-2; seroprevalence; immunity; health-care workers; surveillance; serology

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has had major negative health, economic and societal impacts. Health-care workers (HCW) are essential employees who maintain health-care systems for the public, while facing risks of being exposed to infected patients and environments [1,2]. Therefore, understanding of transmission dynamics and infection burdens among HCW is important.

Seroprevalence can vary across geographic areas and sampling times [3]. Thus, it is worthwhile to evaluate anti-SARS-CoV-2 seroprevalence in different settings and populations. We investigated the seroprevalence among HCW at Cambridge Health Alliance (CHA), a public, community-based health-care organization in the Greater Boston-area of Massachusetts, USA, in late June 2020, three months after the initial SARS-CoV-2 outbreak. At that time in Massachusetts, the first wave had ended, and the state recorded the fourth highest COVID-19 per-capita mortality rate of all US states, roughly double the rates of the UK, Italy, and Spain [4].

Methods

All HCW were invited to participate in the cross-sectional study via the organization's e-mail. An electronic survey was used to obtain informed consent, and if affirmative, capture demographic information, including age, sex, race, ethnicity, home address, zip code, occupation, and unit. Information from a preexisting occupational health COVID-19 database, which contained previous SARS-CoV-2 RT-PCR results independent from the current study, was merged with the study database and anonymized. A unique study ID-code was generated through the surveys and a pre-labeled Whatman card was mailed to each participants'

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residence with supplies and instructions for self-collection by finger-prick. On-site sampling was also available. All consented HCW who provided a sample were included in the study. Participants' samples were checked before analyses by making sure that the blood-spot area of the card had been fully filled with a blood stain and the stain saturated both sides of the card across an area of at least 3 mm in diameter.

Specimens were collected in June 2020. Dried blood samples were analyzed at the Broad Institute, Cambridge, MA. The enzyme-linked immunosorbent assay (ELISA) determined anti-SARS-CoV -2 IgM and IgG to the receptor binding domain (RBD) of the spike protein [5], with a specificity of greater than 99.5% and sensitivity greater than 80%. Estimated antibody abundance in test samples were compared to the mean and standard deviations (SD) of cross-reacting background signals from 200 pre-pandemic dried blood spots collected in the US in late 2019 by Molecular Testing Labs in WA. Cutoffs of 3 and 6 SD above pre-pandemic levels for indeterminate and positive results were established by the New York Department of Health to distinguish a specific signal from anti-SARS-CoV-2 antibodies from cross-reactivity to other coronaviruses. Positive results were based on either a positive IgM and/or IgG. We further refined cutoffs using a sensitivity analysis approach, where z-scores exceeding 6 standard deviations (SD) as 'low' or the most conservative estimate, greater than 4.5 SD as the 'medium' estimate, and greater than 3 SD as the 'high' estimate to accurately reflect all of our participants with a known previous positive SARS-CoV-2 PCR. Samples with values less than or equal to 3 SD were considered negative in all models. Aggregate results were shared with the HCW. The Institutional Review Board of Cambridge Health Alliance approved the study (IRB-1136/04/20), and the merged existing COVID-19 testing database had previously received an IRB exemption [6].

Characteristics of participant and non-participant HCW were compared using t-test for variables following normal distribution, or Wilcoxon rank-sum test for those with skewed distributions, for continuous variables, and Pearson's chi-squared tests (for variables with counts ≥5 in both groups) or Fisher's exact tests (for variables with any cell count <5) for categorical variables. We calculated weighting scores based on participants' previous cumulative PCR positivity to account for potential participation bias, which was derived from 'the cumulative PCR positivity rate for the overall CHA employee population in June at time of the antibody study divided by PCR positivity rate of those participating in the serology study'. Statistical analyses were conducted using the R software (version 3.6.3). All tests performed were two-sided and a p-value <0.05 was considered statistically significant.

Results

Among an estimated eligible workforce of 5,204 personnel, 433 (8.3%) HCW participated. Most samples were self-collected at home (approximately 75%). Compared with non-participants, participants were older, more likely to be female, of non-Hispanic white race and less likely to reside in a community with a higher COVID-19 attack rate and had a lower rate (1.85%) of RT-PCR confirmed COVID-19 infection compared to non-participants (3.29%) (Table 1). More non-frontline staff participated (81.4% vs. 75.4%, p = 0.007; Pearson's chi-squared test).

Using low, medium, and high testing thresholds, 8.1%, 11.3% and 14.5% of participants had detectable antibodies, respectively. Using the SARS-CoV-2 RT-PCR positivity from both cohorts and applying a weighting score for the higher cumulative PCR positivity rate to the participants' estimated seroprevalence, we derived weighted low, medium, and high seroprevalence estimates of 13.9% (95% CI: 10.6–17.1%), 19.4% (95% CI:

Table 1. Demographic characteristics of the health system's workforce: overall and according to Participation in the COVID-19 serology study.

	Overall (*N* = 5204)	Participants in the serology study (*N* = 433)	Non-participants (*N* = 4771)	*P*-value
Age (*n* = 5204)	44.3 ± 13.5	46.5 ± 13.0	44.1 ± 13.5	<0.001
Sex (*n* = 4908)				
Female	3676 (70.6%)	341 (78.8%)	3335 (69.9%)	0.025
Race (*n* = 4566)				
Non–Hispanic white	2565 (56.2%)	335 (77.4%)	2230 (46.7%)	<0.001
African American	887 (19.4%)	12 (2.8%)	875 (18.3%)	
Hispanic	594 (13.0%)	28 (6.5%)	566 (11.9%)	
Others	520 (11.4%)	33 (7.6%)	487 (10.2%)	
Residential area COVID-19 cumulative attack rate (per 100,000) [a]	1510.2 (897.4–2014.8) (*n* = 4627)	1152.4 (840.5–1717.5) (*n* = 426)	1627.5 (928.2–2285.7) (*n* = 4201)	<0.001[b]
Cumulative COVID-19 infection rate by PCR result	165/5204 (3.17%)	8/433 (1.85%)	157/4771 (3.29%)	0.134

Mean±SD for age. Count (%) for sex and race. Median (Q1–Q3) for residential area COVID-19 cumulative attack rate.
[a]Limited to those residing in New England area.
[b]Wilcoxon rank sum test with continuity correction.

Table 2. SARS-CoV-2 RT-PCR positivity weighted COVID-19 seroprevalence using three different positivity thresholds.

Seroprevalence estimate	Crude seroprevalence among study participants	CHA [b] employee population RT-PCR positivity weighted seroprevalence [a]
Low	35/433 (8.1%)	13.9% (95% CI: 10.6–17.1%)
Medium	49/433 (11.3%)	19.4% (95% CI: 15.7–23.1%)
High	63/433 (14.5%)	24.9% (95% CI: 20.9–29.0%)

Low: at least one of the IgG or IgM antibody abundance z-scores is >6 SD from pre-pandemic. Medium: at least one of the IgG or IgM antibody abundance z-scores is >4.5 SD from pre-pandemic. High: at least one of the IgG or IgM antibody abundance z-scores is >3 SD from pre-pandemic.

95% confidence interval (95% CI) derived from normal approximation to the binomial calculation.

[a]Crude seroprevalence multiplied by 1.72 (i.e. cumulative PCR positivity rate for the overall CHA employee population in June (3.17%) at time of the antibody/seroprevalence study divided by PCR positivity rate of those participating in the serology study (1.85%)).

[b]Cambridge Health Alliance, a community-based health-care organization.

15.7–23.1%), and 24.9% (95% CI: 20.9–29.0%), respectively, for the healthcare system's entire HCW population at the time of serology testing (Table 2).

Discussion

The estimated seroprevalence of SARS-CoV-2 ranged between 14% and 25% in our HCW population, consistent with reports of 0.8% to 31.2% positivity rate among 3,248 geographically diverse HCW at 13 academic institutions during April 3 to 19 June 2020 [7]. It is evident that HCW seroprevalence differs across areas over time [3]. An early study (March 25 to April 21) of German HCW found a low IgG seroprevalence of 1.6% [8], another of Indiana HCW during April 29 to May 8 found seroprevalence of 1.6% [9], while multi-site surveillance of New York City HCW conducted from April 20 to June 2 demonstrated an average seroprevalence of 13.7% [10].

Consistent with previous findings, we demonstrated that seroprevalence to SARS-CoV-2 exceeded RT-PCR positivity by 4–8 fold, and that infected HCW are often unrecognized, possibly related to asymptomatic or subclinical COVID-19 infections, underreporting of symptoms, or a nonsystematic HCW testing strategy [11].

The study's strengths include a sensitivity analysis (Table 2) with upper and lower-bound seroprevalence estimates, immunity cutoffs based on pre-pandemic data, and using an ELISA assay measuring RBD-targeted antibodies, which are specific markers of previous and recent infection and highly correlated with neutralizing antibodies [12]. Moreover, dried blood samples correlate very well with venous blood samples in serology surveys [13]. Limitations included negative participation bias (less frequent participation from HCW who were minorities, lived in communities with higher infection rates, and had prior positive SARS-CoV-2 RT-PCR assays). This forced us to extrapolate the seroprevalence of the larger CHA population using a RT-PCR weighted estimate. Second, due to participation bias, we were unable to directly examine sociodemographic risk factors; however, we previously published that both HCW race and community attack rates were significant independent predictors of a previous positive SARS-CoV-2 RT-PCR result [14]. In conclusion, the present study shows the estimated seroprevalence among HCW in the Greater Boston area at the end of the first wave ranged from 13.9% (low estimate; 95% CI: 10.6–-17.1%) to 19.4% (medium estimate; 95% CI: 15.7–-23.1%), and 24.9% (high estimate; 95% CI: 20.9–29.0%) for the healthcare system's entire HCW population.

Key learning points

What is already known about this subject

- Health-care personnel (HCW) are at high risk of being affected by the SARS-CoV-2 pandemic.
- Investigating seroprevalence among HCW can assess past infection and possible immunity.
- Seroprevalence varies across sites and times.

What this study adds

- Additional snapshot of seroprevalence among HCW at the end of first wave of the SARS-CoV-2 outbreak in Massachusetts, USA.

What impact this may have on practice or policy

- Seroprevalence investigations in different time and site settings are needed to comprehend transmission dynamics and possible immunity of the population.

Disclosure statement

S.N.K. has received COVID-19-related consulting fees from Open Health and owns shares of Regeneron, Moderna and Astra-Zeneca. All other authors declare no competing interests.

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