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SARS-CoV-2 IgG response in symptomatic and asymptomatic COVID-19-infected healthcare workers

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Background	Healthcare workers (HCWs) accounted for a significant proportion of COVID-19 infections worldwide. Retrospective seroprevalence surveys are often used to screen for unidentified previous infection with SARS-CoV-2. However, the rate of humoral response in HCWs affected by COVID-19 is not well-defined.
Aims	To assess the specific IgG humoral response in symptomatic and asymptomatic SARS-CoV-2-infected HCWs and identify potential factors associated with humoral response.
Methods	We prospectively recruited 204 HCWs with RT-PCR-confirmed COVID-19 infection to evaluate SARS-CoV-2 humoral response. Serum-IgG antibodies against SARS-CoV-2 were analysed using two commercially available serological assays. A logistic regression was performed to identify independent factors associated with positive IgG serology test.
Results	Overall, the SARS-CoV-2 IgG seropositivity rate was 77%. This seropositivity rate was higher in symptomatic than in asymptomatic COVID-19 infection (83% versus 57%; $P < 0.001$) and in older HCWs.. The seropositivity rate did not diminish with time. In logistic regression, only a history of COVID-19 symptoms and age were identified as independent factors associated with the detection of anti-SARS-CoV-2 IgG antibodies.
Conclusions	SARS-CoV-2 IgG antibodies are found significantly more frequently in symptomatic and in older HCWs. The fact that not all COVID-19 HCWs develop detectable IgG is vital for the interpretation of COVID-19 seroprevalence surveys.
Key words	COVID-19; healthcare workers; infection; occupational medicine; SARS-CoV-2; serology.

Introduction

Healthcare workers (HCWs) have an increased risk of acquiring SARS-CoV-2 infection in comparison with other individuals in the community. HCWs represent a significant proportion of COVID-19 infections worldwide, with >570 000 infections and 2500 deaths reported up to September 2020 [1].

Retrospective seroprevalence surveys are usually used to screen for unidentified previous SARS-CoV-2 infection [2]. However, the rate of humoral response in HCWs affected by COVID-19 is not well-defined, especially in those who are asymptomatic or have mild symptoms. For that reason, these seroprevalence surveys are difficult to interpret and probably underestimate the real rate of SARS-CoV-2 infection in this high-exposure population.

This study aimed to assess the specific IgG humoral response in SARS-CoV-2-infected HCWs and identify potential factors associated with humoral response.

Methods

We prospectively recruited volunteer HCWs with previous RT-PCR-confirmed COVID-19 infection to evaluate SARS-CoV-2 IgG humoral response between 13 August and 26 November 2020, at the Hospital Cosme Argerich, Buenos Aires, Argentina.

Key learning points

What is already known about this subject:

- Healthcare workers have an increased risk of acquiring SARS-CoV-2 infection.
- Seroprevalence surveys are usually used to screen for unidentified previous SARS-CoV-2 infection in healthcare workers.
- The detection of anti-SARS-CoV-2 antibodies is associated with a lower risk of reinfection among healthcare workers.

What this study adds:

- Not all healthcare workers have a positive serology after COVID-19 infection.
- Detectable SARS-CoV-2 IgG antibodies are more frequently observed in symptomatic and in older healthcare workers.
- The seropositivity rate in samples obtained after 8 weeks did not differ significantly from those with a shorter time interval.

What impact this may have on practice or policy:

- The fact that not all COVID-19 healthcare workers have a positive serology is vital for the interpretation of seroprevalence surveys.
- The detection of anti-SARS-CoV-2 antibodies in healthcare workers could be useful in settings where there is a limited vaccine availability.

A self-administered questionnaire was used to capture epidemiological, and clinical information. Two commercial qualitative immunoassays were used: the COVIDAR Argentina Consortium enzyme-linked immunosorbent assay (ELISA) test (Laboratorio Lemos, Argentina), which measures IgG against spike (S)-protein and the Architect chemiluminescent microparticle immunoassay (CMIA) (Abbott Laboratories, USA), which measures IgG against nucleocapsid (N)-protein. Serologic response was defined as at least one of the assays being positive.

Statistical analyses were performed using Epi Info software version 7.2. Categorical variables were described using absolute and relative frequencies and compared by the Fisher exact test. Continuous variables were described using medians with interquartile ranges (IQRs) and compared by the Anova test for differences between groups. All tests were considered significant if *P*-value was <0.05. A logistic regression was undertaken to identify independent factors associated with positive IgG serology test.

The protocol was approved by the Hospital Cosme Argerich Bioethics Committee. HCWs were included after a written informed consent.

Results

A total of 204 HCWs after COVID-19 infection were included. Clinical and epidemiological characteristics are shown in Table 1. The median time between SARS-CoV-2 diagnosis and serological test sample was 57 days (IQR 41–75); up to 8 weeks 56% and >8 weeks, 44% of the cases.

Overall SARS-CoV-2 IgG seropositivity rate was 77%. Anti-S and anti-N IgG seropositivity rate was 73% and 69%, respectively. Seropositivity rate was higher in symptomatic than in asymptomatic COVID-19 infection (83% versus 57%; $P < 0.001$). Similarly, seropositivity rate was higher in HCWs with severe COVID-19 than those with mild/moderate COVID, but this difference was not significant (96% versus 81%; P = NS). Differences in signal-to-cut-off (S/CO)

Table 1. Clinical and epidemiological characteristics of 204 COVID-19 convalescent HCWs

Characteristics	*n* (%)
Age: median (IQR)	41.5 (34–52)
Gender: male/female	61 (30)/143 (70)
Hospital activity	
Nurses	77 (38)
Physicians	42 (21)
Others	85 (42)
Most probable source of infection for SARS-CoV-2	
Unknown	128 (63)
Nosocomial close contact with COVID-19 patient	51 (25)
Household transmission	25 (12)
Staff with direct contact to COVID-19 patients	140 (69)
Any co-morbidity	41 (20)
Asymptomatic COVID-19	44 (22)
Mild/moderate COVID-19	137 (67)
Severe COVID-19	23 (11)

Data are numbers (percentages) unless stated otherwise.

ratio were observed according to the severity of the disease. Median S/CO in asymptomatic, mild, moderate and severe cases were 4.7, 6.0 and 9.9 ($P < 0.05$) for anti-S IgG; and 4.4, 4.8 and 6.3 ($P < 0.05$) for anti-N IgG, respectively.

Age was associated with increased seropositivity rate. The median age of HCWs with positive IgG serology was 43 versus 37 years for those with negative serology ($P < 0.01$).

No significant differences were observed in the overall seropositivity rate according to the time elapsed from the infection to the collection of serum samples (80% ≤ 8 weeks versus 74% > 8 weeks; P = NS). The same was observed in asymptomatic (54% versus 61%; P = NS) and symptomatic (87% versus 78%; P = NS) HCWs. In logistic regression, only a history of COVID-19 symptoms and age were identified as independent factors associated with detectable SARS-CoV-2 IgG antibodies (Table 2).

Discussion

In this group of HCWs with previous confirmed COVID-19 infection, not all had a positive SARS-CoV-2 IgG serology assay. Increased likelihood of a positive serology was observed in those HCWs with COVID-19 symptoms at the time of the infection and with increased aged. Interestingly, only about half of the asymptomatic HCWs had a positive serology. This observation is similar to previous studies [3,4]. In those studies, IgG humoral response as well as antibodies titres were lower in asymptomatic patients in comparison with those who had COVID-19-associated symptoms.

The duration of IgG humoral response is not yet well-established. Initially, some studies reported a rapid decay within weeks of antibody titres after SARS-CoV-2 infection [4,5]. In our study, seropositivity rate was independent of the time elapsed from infection to serum sampling, even in those with or without history of COVID-19 symptoms. Furthermore, the seropositivity rate in samples obtained after 8 weeks did not differ significantly from those with a shorter time interval. In addition, a prolonged persistence of IgG humoral response was recently described with a median time of antibody detection of >150 days [6,7].

Age was also associated as an independent risk factor for a positive IgG serology test. A possible explanation for this observation would be an increased mucosal antibody response and a more effective local control in younger SARS-CoV-2-exposed individuals [8]. Similarly, increasing age was recently associated with higher antibody levels and a longer duration of seropositivity [7].

Commercial SARS-CoV-2 immunoassays do not differentiate protective neutralizing antibodies from non-neutralizing or binding antibodies. Thus, the detection of antibodies is not useful to stop taking measures to protect against SARS-CoV-2 infection [9]. However, a recent published study reported that the detection of anti-S or anti-N IgG antibodies was associated with a significant lower risk of SARS-CoV-2 reinfection among HCWs up to 6 months of follow-up [10].

This study has some limitations. Subjects were enrolled in a voluntary and flexible schedule. Therefore, the time point of serum sampling was variable. Moreover, since serology was not performed prospectively, we could not study individual response kinetics.

In summary, we found that detectable SARS-CoV-2 IgG antibodies are significantly more frequent in symptomatic and in older HCWs. The fact that not all COVID-19 HCWs have a positive serology is vital for the interpretation of seroprevalence surveys. These results now highlight the importance of screening for the detection of anti-SARS-CoV-2 antibodies in HCWs, especially in settings where there is a limited vaccine availability.

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Competing interests

None declared.

Table 2. Univariate and multivariable analysis of characteristics associated with a positive serology in HCWs after confirmed COVID-19 infection

Variables	Unadjusted OR (95% CI), n = 204	P-value	Adjusted OR (95% CI), n = 204	P-value
Male sex	1.71 (0.79–3.72)	0.17		
Age	1.04 (1.01–1.08)	0.008	1.03 (1.01–1.07)	0.03
Any co-morbidity	1.25 (0.53–2.94)	0.60		
COVID-19 symptoms	3.74 (1.81–7.74)	0.004	3.10 (1.47–6.54)	0.002
Severe COVID-19	7.38 (0.97–56.36)	0.05	4.17 (0.53–32.94)	0.17

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