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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Letter to the Editor

Anti-SARS-CoV-2 antibody detection in healthcare workers of two tertiary hospitals in Athens, Greece

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To the editor

COVID-19 is caused by the severe acute respiratory syndrome coronavirus −2 (SARS-CoV-2 virus) and has afflicted more than 40 million people worldwide causing over a million deaths. Very early it was recognized that COVID-19 is multi-system. Fever, headache, myalgias arthralgias and lymph node enlargement are early clinical manifestations [1,2]. In severely-ill patients, the disease may progress to septic shock, acute respiratory distress syndrome (ARDS), acute kidney injury, disseminated intravascular coagulation [3] and rhabdomyolysis [4]. COVID-19 poses a heavy burden for health systems and society, therefore reliable methods to evaluate viral loads in biological fluids and anti-SARS-CoV-2 antibody positivity in the serum were rapidly developed. This is important for two reasons. First, it needs to be determined whether infected populations bear antibodies that can neutralize and clear the virus and whether these antibodies can protect these populations from re-infection. This is critical information given the ongoing second wave of the pandemic in Europe.

Secondly, public health protection necessitates the monitoring of infected and recovering populations. This is particularly important for health workers. The main route of transmission is person-to-person spread and health workers are a critical population. First, they can, if being asymptomatic carriers, spread the disease in vulnerable populations and also, they are indispensable for the health system sustainability. Our study employs a validated assay to reliably detect anti-SARS-CoV-2 IgG antibodies in health workers and addresses the impact of positivity in this sensitive population on public health policy.

321 health workers, from two tertiary hospitals in Athens, Greece were recruited following ethical approval from the Boards of both hospitals. All participants, including doctors, nurses and assistive personnel, signed informed consents and filled health-related questioners. Participants which had been tested positive for SARS-CoV-2 by PCR were excluded. Serum samples were anonymised, and ELISA testing was performed blindly. The period of sampling was from April 25th until May 10th, 2020.

We used an FDA-approved and independently validated ELISA method (Euroimmun, Lübeck, Germany) according to the manufacturer's instructions [5]. The cut-off for positivity is determined as the OD value of the sample measured at 450 nm divided by the OD value of the provided calibrator >1.1. This method has been used in two independent serological surveys showing 93% sensitivity and 100% specificity.

Participants were stratified according to their relative risk of exposure to symptomatic SARS-CoV-2 carriers. Group A comprised of 57 participants (see Table 1) who were all anaesthesiologists in a COVID-19 reference hospital. These were considered as high risk as they have all potentially being in close contact with a symptomatic carrier, nevertheless bearing all appropriate protective measures. Group B comprised of 140 participants (Table 1) who were doctors, nurses or assistive personnel of a tertiary hospital. These were considered as medium risk as they may have been on close contact with a symptomatic carrier. This group during the pandemic was serving either in the Emergency department of the hospital or the Internal medicine and Pulmonology Departments. Finally, group C comprised of 124 participants (Table 1) considered as low risk. These were also doctors, nurses and assistive personnel serving in Departments where it was less likely that they have been in contact with symptomatic carriers.

Anti-SARS-CoV-2 antibodies were positive in 2/57 participants of group A (3.5%), 3/140 participants of group B (2.14%) and 2/124 participants of group C (1.61%). The observed differences were not statistically significant (Fisher's exact test, $p > 0.05$). In total 7/321 samples were positive (2.18%) with an average positivity index of 1.42. None of our positive subjects were PCR-positive. A sample was considered IgG positive only when confirmed in two separate assay runs. Interestingly, all positive samples were from doctors. 3 of 7 participants (42.85%) with detectable antibodies reported common cold-associated symptoms in the past two months before sampling. In the whole study population, 106/321 subjects (33.02%) reported common cold-associated symptoms. General malaise, anosmia, cough, sore throat, dyspnoea or fever were not reported. 4 of 7 IgG-positive subjects (57.15%) reported no symptoms at all while none of our subjects, either IgG-positive or IgG-negative were hospitalized. The transmission route in the positive subjects could not be elucidated in any of the cases, i.e. whether their positivity reflects an intra- or extra-hospital exposure.

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Table 1
Participant clinical and serological characteristics.

	Group A (High Risk)	Group B (Med Risk)	Group C (Low Risk)	Total
	N = 57	N = 140	N = 124	N = 321
Sex	44 F, 13 M	78 F, 62 M	96 F, 28 M	218 F, 103 M
Age (Years)	45.08 (AVG)	41.27 (AVG)	43.08 (AVG)	42.71 (AVG)
Profession				
Doctor	35 (61.40%)	98 (70%)	45 (36.29%)	178 (55.45%)
Nurse	18 (31.58%)	33 (23.58%)	53 (42.75%)	104 (32.40%)
Other	4 (7.02%)	9 (6.42%)	26 (20.96%)	39 (12.15%)
SARS-CoV-2 IgG status	2 positives (3.5%)	3 positives (2.14%)	2 positives (1.61%)	7 positives (2.18%)
Clinical signs	1 (common cold symptoms reported)	2 (common cold symptoms reported)	NO	3 (common cold symptoms reported)

Our study reveals a relatively low percentage of exposure (even though there is no direct comparator) suggesting that efficient protective measures were applied in both hospitals. In order to protect the hospital stuff and eliminate the possibility of intra-hospital viral transmission, in both hospitals every patient that arrived at the Emergency Department, was obliged to wear a surgical face mask and underwent temperature measurement while a brief medical and travel history was taken. If the patient was a suspected positive COVID-19 case, was transferred in an isolated space, where medical and nursing stuff was wearing protective clothing and masks. If hospitalization was needed, the patient was treated in a special Unit by trained stuff until the SARS-CoV-2 PCR was negative. In case of a positive PCR, the patient was transferred to a reference hospital.

Our results are comparable to other major health workers population serological surveys. A German study has shown a 1.6% positivity in a similar sample size (n = 316) to ours [6] while another study from a Belgian hospital revealed a 6.4% seropositivity [7]. Whether these differences reflect the epidemiological condition of the general population in the given moment or methodological issues regarding antibody assays is unclear.

Regarding titers, our positive population had an average titer of 1.42. Unpublished data from our lab using the same assay, show that symptomatic COVID-19 patients with severe disease have an average titer >5, while mild-symptomatic patients have an average titer >3. This might be clinically useful to stratify patients, pending the second wave of the pandemic in Greece. Serial dilutions of control PCR positive patients were also tested in up to 1:128 dilutions, to confirm the assay sensitivity and that it truly is able to measure low-titer antibodies.

Our results cannot be extrapolated with any statistical certainty to the general population to determine the percentage of asymptomatic or sub-clinical infections. The number of recorded deaths (approx. 200 up to September 2020) as a proxy for population exposure shows that Greece was not heavily affected during the first wave of the pandemic. Our results, albeit for a very specific population, probably show roughly the same as only 1.6% of the low-risk group was sub-clinically infected.

It is crucial that Greek hospitals do nor become incubators for the disease in the next pandemic waves. Combined molecular and serological surveys are crucial to ensure public health protection.

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Declaration of Competing Interest

None.

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