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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

DOI: 10.1111/all.14545

## Cross-sectional pilot study exploring the feasibility of a rapid SARS-CoV-2 immunization test in health and nonhealthcare workers

To the Editor,

Coronaviruses (CoV) are large, enveloped, positive-strand RNA viruses and until the first outbreak of SARS in 2002 had long been considered pathogens with low hospitalization incidence for healthy people. SARS-CoV-2 is a novel pathogenic CoV responsible for a new type of pneumonia. Initial reports placed the initial outbreak in Wuhan (China) in December 2019, and it has since spread and caused hundreds of thousands of deaths worldwide.<sup>1</sup> The virus pandemic has spread extremely fast, and it is reasonable to suggest that further outbreaks may appear along the next years before effective treatments or vaccines are available in the market.<sup>2</sup> Thus, in the meantime, only by achieving a better diagnostic monitoring and by understanding the interactions between the virus and host immune response will we be able to rationally manage future outbreaks.

The immune response to SARS-CoV-2 is currently under study and needs to be better characterized. However, it has been previously reported that viral infection involves activation of CD8 + cytotoxic cells, antibody-producing B cells, and innate immune response that in some patients triggers a so-called "cytokine storm".<sup>3</sup> Moreover, whether immune responses to SARS-CoV-2 generate long-term memory or whether immunized patients have long-term sterilizing immunity is still unknown.

Spain has been devastated by the COVID-19 pandemic with more than 280 000 confirmed cases, from which more than 67 000 were in Madrid, causing a huge personal, health system, and economic burden.<sup>4</sup> In fact, more than 20% of infected subjects were healthcare workers.<sup>4</sup>

We aimed to generate an immune response map to SARS-CoV-2 in a very specific population of a Medical School where both healthcare workers and nonhealthcare workers cohabit, and elucidate the main risk factors that can be associated with COVID-19

diagnosis in each population. With that purpose, we analyzed a population of 100 people mainly ascribed to the Medical School of San Pablo CEU University and one of its University Hospitals, HM Montepíncipe (HMM), where students perform the last 4 years of the medical degree. The population of study included 50 medical doctors from HMM that were exposed to viral loads on a daily basis (healthcare workers) and 50 researchers and teachers from the medical school that can be considered as a representative sample of the general population (nonhealthcare workers). In this study, we used the so-called "fast" IgM/IgG immunological commercial kits (REAL 2019-NCOV RAPID TEST CASSETTE) to analyze the population immunity.

Healthcare workers were recruited and classified in two subgroups depending on whether they were diagnosed or not for COVID-19 by RT-PCR (Appendix S1).

Table 1 shows that healthcare workers with a confirmed diagnosis by RT-PCR display a significant association with symptoms such as fever, cough, fatigue, dysgeusia, and anosmia. Moreover, diarrhea, even if it does not show a significant association, presents an OR of 2.65, suggesting this symptom as a novel risk factor associated with COVID-19 diagnosis. Moreover, the immunological tests demonstrate that almost 96% of the subjects diagnosed by RT-PCR were positive for IgG with an OR of 42.2. Thus, it seems there is a clear association between symptoms, RT-PCR results, and the positive results for IgG test.

Moreover, in the nonhealthcare workers population, no RT-PCR was performed for diagnosis and only 7 out of 50 subjects (14%) in the group were positive for IgG. Interestingly, these results agree with those recently published by the Spanish Ministry of Health regarding a seroprevalence study in Spanish population (n = 60 000 citizens) with different range of age, region, economic income, etc. The epidemiological study shows a seroprevalence of 11% in Madrid.

**TABLE 1** Summary table of healthcare workers according to RT-PCR diagnosis

	NO RT-PCR N = 26	RT-PCR (+) N = 24	OR	P ratio	P overall
Field: Hospital	26 (100%)	24 (100%)	Ref.	Ref.	.
Age	45.4 (8.84)	44.6 (10.1)	0.99 [0.93;1.05]	.773	.780
Gender					
Female	21 (80.8%)	14 (58.3%)	Ref.	Ref.	.155
Male	5 (19.2%)	10 (41.7%)	2.90 [0.83;11.4]	.097	
Fever					
NO	24 (92.3%)	6 (25.0%)	Ref.	Ref.	<.001
Yes	2 (7.69%)	18 (75.0%)	30.9 [6.59;255]	<.001	
Cough					
NO	20 (76.9%)	7 (29.2%)	Ref.	Ref.	.002
Yes	6 (23.1%)	17 (70.8%)	7.59 [2.22;29.7]	.001	
Fatigue					
NO	21 (80.8%)	4 (16.7%)	Ref.	Ref.	<.001
Yes	5 (19.2%)	20 (83.3%)	18.8 [4.80;94.1]	<.001	
Pneumonia					
NO	25 (96.2%)	17 (70.8%)	Ref.	Ref.	.021
Yes	1 (3.85%)	7 (29.2%)	8.91 [1.36;242]	.020	
Headache					
NO	20 (76.9%)	11 (45.8%)	Ref.	Ref.	.049
Yes	6 (23.1%)	13 (54.2%)	3.78 [1.14;13.8]	.029	
Diarrhea					
NO	22 (84.6%)	16 (66.7%)	Ref.	Ref.	.249
Yes	4 (15.4%)	8 (33.3%)	2.65 [0.69;11.9]	.158	
Dysgeusia					
NO	22 (84.6%)	9 (37.5%)	Ref.	Ref.	.002
Yes	4 (15.4%)	15 (62.5%)	8.52 [2.35;38.1]	.001	
Anosmia					
NO	21 (80.8%)	9 (37.5%)	Ref.	Ref.	.005
Yes	5 (19.2%)	15 (62.5%)	6.59 [1.91;26.4]	.002	
IgG					
Neg	18 (69.2%)	1 (4.17%)	Ref.	Ref.	<.001
Pos	8 (30.8%)	23 (95.8%)	42.2 [6.95;1126]	<.001	

Furthermore, Table 2 shows that in this group, positive IgG subjects present a significant association with fatigue, dysgeusia, and anosmia. Surprisingly, no association was found with symptoms such as fever or cough.

A possible explanation for these results might be that healthcare workers were exposed to higher viral loads and during more time along the peak of the pandemic, while nonhealthcare workers were confined at home. In fact, almost all of them presented the above-mentioned symptoms during the first 2 weeks of lockdown. IgM results were not conclusive in either group.

This pilot study is the first step in the elucidation of a "population immunological map" in our special community in the Medical School with healthcare and nonhealthcare workers. The results demonstrate that the prevalence of COVID-19 is higher in

healthcare workers, as expected. Additionally, this pilot study provides the knowledge and the positive controls (healthcare workers with positive RT-PCR) for the development of future methodological strategies aiming to set up new immunological tests for herd immunity follow-up (ELISA, neutralization assays, etc). This will be helpful if we take into account the shortage of commercial kits for SARS-CoV-2 immunological tests during the pandemic, and the limitations of these tests in terms of specificity and sensitivity.<sup>5,6</sup>

Additionally, the results obtained from this rationale together with the information related to previous pathologies and risk factors will allow the design of personalized strategies of reincorporation into academic activities in the future. This will significantly reduce the human and economic burden of future COVID-19 infection waves in our community. The proposed strategy can be easily

	Neg N = 43	Pos N = 7	OR	P ratio	P overall
Field: University	43 (100%)	7 (100%)	Ref.	Ref.	.
Age	42.1 (13.4)	43.1 (10.2)	1.01 [0.95;1.07]	.837	.811
Gender					
Female	24 (55.8%)	5 (71.4%)	Ref.	Ref.	.684
Male	19 (44.2%)	2 (28.6%)	0.53 [0.06;2.90]	.481	
Fever					
NO	41 (95.3%)	5 (71.4%)	Ref.	Ref.	.089
Yes	2 (4.65%)	2 (28.6%)	7.61 [0.67;87.4]	.096	
Cough					
NO	39 (90.7%)	5 (71.4%)	Ref.	Ref.	.192
Yes	4 (9.30%)	2 (28.6%)	3.83 [0.40;27.6]	.222	
Fatigue					
NO	39 (90.7%)	4 (57.1%)	Ref.	Ref.	.048
Yes	4 (9.30%)	3 (42.9%)	6.86 [0.98;47.2]	.052	
Pneumonia: NO	43 (100%)	7 (100%)	Ref.	Ref.	
Headache					
NO	40 (93.0%)	6 (85.7%)	Ref.	Ref.	.464
Yes	3 (6.98%)	1 (14.3%)	2.33 [0.07;24.2]	.553	
Diarrhea					
NO	39 (90.7%)	6 (85.7%)	Ref.	Ref.	.546
Yes	4 (9.30%)	1 (14.3%)	1.74 [0.06;15.6]	.684	
Dysgeusia					
NO	42 (97.7%)	5 (71.4%)	Ref.	Ref.	.048
Yes	1 (2.33%)	2 (28.6%)	14.3 [1.00;502]	.050	
Anosmia					
NO	43 (100%)	4 (57.1%)	Ref.	Ref.	.002
Yes	0 (0.00%)	3 (42.9%)	N/A	.	

**TABLE 2** Summary table of nonhealthcare workers according to IgG Test

implemented by several research laboratories and might help in better activity plans in other locations to be ready for future outbreaks.

## KEYWORDS

antibodies, COVID-19, immune response

## ACKNOWLEDGMENTS

We would like to thank Francisco Rodriguez, PhD, Ramses Reina, PhD and Luis Martinez Gil, PhD for kindly providing essential molecular tools (full length Spike protein and VLP reporters for neutralization assay and VLPs for ELISA) to perform the planned assays. We acknowledge the collaboration of all the participants in the study as well as nurses in the Oncology department at HMM. We would like to thank Tomás Clive Barker Tejeda for his help revising the manuscript. Dr Escibese has nothing to disclose. Dr Nistal Villan has nothing to disclose. Dr Fernandez Martinez has nothing to disclose. Dr Rico has nothing to disclose. Dr Martín Antoniano has nothing to disclose. Dr de la Cuerda has nothing to disclose. Dr Chivato has nothing to disclose. Dr Barber has nothing to disclose.

## CONFLICTS OF INTEREST

The authors declare that they do not have any conflict of interest in relation to this study.

## FUNDING INFORMATION

This work was supported by ISCIII (Project number, PI19/00044 and PI18/01467) and co-funded by European Regional Development Fund "Investing in your future" for the thematic network and co-operative research centers ARADyAL RD16/0006/0015.

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DOI: 10.1111/all.14551

## Atopic status protects from severe complications of COVID-19

To the Editor,

SARS-CoV-2 infection may induce a broad spectrum of consequences ranging from asymptomatic infection to fatal pneumonia.<sup>1</sup> The most severe complication is the acute respiratory distress syndrome (ARDS) which is often fatal. The so-called “IL-6 cytokine storm” and a disseminated intravascular cascade in the lung characterize most severe cases of COVID-19. The coincidence of these events with the rise of the adaptive immune response suggests that the response itself may play a role. In effect, COVID-19 patients with agammaglobulinemia recovered without lung complications.<sup>2</sup> Atopic status is the genetic predisposition to produce a Type 2 immune response to environmental antigens. Such response relies on some key cytokines, including interleukin (IL) 4, IL-5, IL-9, and IL-13.<sup>3</sup> In infection, the Th2 response counteracts the microbicidal Th1 response, which could limit the tissue damage induced by Th1-mediated inflammation<sup>4</sup> on one hand, but also cause a less efficient anti-virus response, as shown in a study on experimental Coronavirus 229E infection in healthy volunteers, where atopy appeared to be associated with a more severe rhinitis score.<sup>5</sup> Further, atopic subjects show a reduced expression of ACE2, the SARS-CoV-2 receptor, which could be associated with reduced susceptibility to the virus.<sup>6</sup> We therefore hypothesized that atopic subjects infected by

SARS-CoV-2 might have a milder clinical course than nonatopic subjects, and tested this hypothesis in a large cohort of hospitalized COVID-19 patients.

We performed a retrospective study on patients with SARS-CoV-2-induced pneumonia, as confirmed by the detection of viral nucleic acid in nasal and/or pharyngeal clinical specimens, hospitalized in several Italian hospitals. Doctors recorded clinical data (age, sex, smoking habits, diabetes, hypertension, coronary heart disease, and thrombosis) along with respiratory allergy and graded the severity of the respiratory disease at the end of the hospital stay as mild, severe, or very severe based on no need for respiratory assistance, need for noninvasive respiratory assistance or need for invasive respiratory assistance or death, respectively. Patients were considered “atopic” in the presence of an unequivocal history of respiratory allergy to airborne allergens confirmed by positive skin prick tests performed by a specialist allergy center and/or by elevated specific IgE. All allergy investigations had been performed before hospitalization. Patients' data were anonymized, and the internal review board of the promoting center approved the study. The association between severity of COVID-19 and both the atopy status and the clinical co-factors recorded was studied in both univariate and multivariate analyses (details in the Appendix S1). Type I statistic error probability values <5% were considered significant.