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RESEARCH ARTICLE

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Evaluation of antibody response after COVID-19 vaccination of healthcare workers

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Abstract

The common goal of all vaccines developed against COVID-19, although they have been designed with different methods, is to develop an effective immunity and antibody response against SARS-CoV-2. However, the postvaccination immune response and antibody levels differ between individuals. This study examined the relationship between postvaccine seropositivity rates, age, gender, smoking, and body mass index (BMI), and antibody titers. A total of 314 healthcare workers (HCW) who were not previously infected with COVID-19 and who had received two doses of CoronaVac inactivated vaccine participated in the study. Seropositivity against the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein was measured from the participants 4 weeks after the second dose of vaccine using the electrochemiluminescence (ECLIA) method. In addition, the antibody developed against the nucleocapsid protein (NCP) was evaluated and compared using Elecsys Anti-SARS-CoV-2 kit. One hundred and eighty-one of the participants were female (57.6%) with a median age of 39 (interquartile range [IQR], 10) and 133 (42.4%) were male with a median age of 41 (IQR, 11). 99.6% of the volunteers developed seropositivity 4 weeks after the second dose of vaccine. It was also observed that the rate of RBD protein antibody titer was >250 U/ml in smokers, which is quite low compared to nonsmokers ($p = 0.032$), and that high RBD antibody titers were proportionally lower in obese participants, according to BMI values, compared to those with normal BMI (49.5% and 9.9%). It was observed that seropositivity developed in almost all participants after the CoronaVac vaccine. However, it was determined that the antibody titer measured varied depending on factors such as smoking, BMI, and duration.

KEYWORDS
CoronaVac, healthcare workers, receptor binding domain, seropositivity, spike protein

The authors declare that there is no conflict of interest.

1 | INTRODUCTION

To control the COVID-19 pandemic caused by SARS-CoV-2, which has led to serious mortality and morbidity, and social and economic in many countries since its emergence in January 2020, it is important to identify infected people and people with a positive immune response to the virus.[1–3] The response of an individual's immune system is the most important marker for the determination of mortality and morbidity.[4] Effective and reliable COVID-19 vaccines are needed to identify specific antibodies and reduce the worldwide spread of COVID-19.[5] Although the vaccines presently approved by the WHO have been designed using different technologies, the goal of all of them is to stimulate a person's immune system. The postvaccine immune response has several aspects: innate response, humoral response, cellular response, and cytokine response. Although the humoral immune response constitutes only a part of the immune response, the humoral response is far easier to detect than the others due to its widespread use and standardization.[6,7]

Various tests have been developed capable of detecting immunoglobulin M (IgM), IgA, and IgG antibodies from blood samples of patients who were previously or are currently infected with SARS-CoV-2. These serological tests are performed using various viral antigens and recombinant proteins to capture SARS-CoV-2-specific antibodies.[8] The spike protein (S) expressed by SARS-CoV-2, and its other structural protein, the nucleocapsid protein (NCP), are known as the major targets of antibodies.[9,10] The NCP is associated with the viral genome and is produced in large quantities in the early stages of the infection. Moreover, due to the high specificity of the NCP, no cross-reactivity is observed even with closely related viruses; therefore, antibody tests for the NCP are quite specific.[11] The S-protein binds to the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of the host cell. The entry of the virus into the cell is mediated by the receptor-binding protein (RBD) in the structure of the S-protein. As the S-protein has an important role in the entry of the virus into the cell, it is an important target in the inactivation of the virus and the postvaccine immune response.[12] Both proteins are highly immunogenic and used as essential proteins in COVID-19 testing.[13]

Preventing the entry into, fusion with, and exit of the virus from the cell, neutralizing antibodies play an important role in the antibody-mediated killing of the virus in SARS-CoV-2 infections.[14] The fact that the target of neutralizing antibodies is the RBD part of the S-protein[13] has caused the existing vaccines to be produced using the whole virus or to be designed specifically for this protein.[15] As the antibody response to the S-protein is correlated with neutralizing antibodies,[13,16] the major goal is to obtain an Anti-S antibody response in the immune response that develops after vaccination. Moreover, accurate measurement of the antibody response that occurs as a consequence of vaccinations plays an important role in determining the success rate of the vaccine and whether people are protected against the infection.[12] However, the antibody response stimulated by the vaccine is affected by many factors depending on both the individual and the vaccine,[17] which can positively or negatively affect the protection against the virus.

COVID-19 vaccination began in our country, Turkey, in January 2021 with an inactive vaccine, CoronaVac (Sinovac Life Sciences). The group most likely to encounter infection, HCW, were vaccinated first. The vaccination was administered in two doses at a 4-week interval. In the present study, we aimed to examine the antibody response of HCW 4 weeks after the second dose of vaccine; investigate the relationship of this antibody response with the person's age, gender, body mass index (BMI), smoking, vaccine side effects, and various diseases, if any; reevaluate the RBD antibody level 3 months after the second dose of vaccine, and compare the antibody response developed against the NCP with the RBD antibody response.

2 | MATERIALS AND METHODS

2.1 | Participants

A total of 314 HCW aged 21–64 participated in the study. Those who had had two doses of inactivated whole-virion CoronaVac (Sinovac Life Sciences) virus vaccine administered in Turkey, and who had had the second dose of vaccine 4 weeks prior were included in the study. Those who were previously infected with COVID-19 infection, had not completed vaccination, or who had had the second dose of vaccine too recently were excluded from the study. This study was approved by the Ethics Committee of the Faculty of Medicine, Alanya Alaaddin Keykubat University (February 24, 2021; 04-05) and by the Scientific Research Committee of the Ministry of Health of the Republic of Turkey (Permit no: 10354421-2021/04-05). All participants participated in the study after signing an informed consent form.

2.2 | Laboratory study

Five to ten milliliters of venous blood was taken with the standard method from the forearms of the volunteers participating in the study. The blood collected was centrifuged and the sera were separated. Serum samples were stored in a −20°C freezer until the antibody studies were performed. Before the study, the serum samples were brought to room temperature and kept until thawed. Just before the study, each serum sample was rendered ready for study by being vortexed for 20 s.

All antibodies, including IgG, formed against the RBD of the spike protein were quantitatively studied by the sandwich enzyme-linked immunosorbent assay (ELISA) method using Elecsys Anti-SARS-CoV-2 S kit (Roche Diagnostics), and the total antibodies formed against the NCP protein were qualitatively studied by electrochemiluminescence (ECLIA) using Elecsys Anti-SARS-CoV-2 kit (Roche Diagnostics). Following the company's recommendations, both tests were run on the Cobas e601 analyzer. Antibodies developed against NCP were measured according to the Cut-Off Index (COI) value. A COI ≥ 1.0 was considered positive and a COI < 1.0 was considered negative. Samples determined as greater than equal to

0.8 U/ml in the Elecsys Anti-SARS-CoV-2 S assay considered positive and the highest antibody value was measured as 250 U/ml by the device. Values measured above 250 U/ml were considered as >250 U/ml. The sera that were measured with antibody titers above 250 were not diluted or studied again. In interpreting the results, antibody titers were grouped as 1–125, 126–250, and >250 U/ml and evaluated in percentages.

2.3 | Statistical analysis

Statistical analysis was performed using SPSS version 23.0 (IBM Corporation). Conformity of data to normal distribution was determined by histogram and Kolmogorov–Smirnov tests. The difference between the groups was calculated with χ^2, Fisher's exact, Mann–Whitney *U*, and Kruskal–Wallis tests in line with suitability. The Wilcoxon test was used to compare the change in S-RBD antibody titers at 4 weeks and 12 weeks after the second dose of vaccine. A *p* value lower than 0.05 was considered to indicate statistically significant results.

3 | RESULTS

The study was carried out between March and May 2021 in the Faculty of Medicine Training and Research Hospital at Alaaddin Keykubat University in Alanya, a district in the south of Turkey where hotels are densely located and which is one of the most visited areas in the country. Three hundred and fourteen HCW who were not previously infected with COVID-19 infection and who had received two doses of vaccine participated in the study. 181 (57.6%) of the participants were female and 133 (42.4%) were male. The minimum and maximum ages of the participants were 21 and 64; the median age was 39 (IQR, 10) for women and 41 (IQR, 11) for men.

Of the participants, the RBD antibody was measured as negative in only one person. This person was a participant who smoked 20 cigarettes a day and had a BMI > 30. The RBD antibody seropositivity of the other 313 (99.6%) participants was positive.

In terms of the evaluation of the RBD antibody titers in terms of age groups, 50.3% of those with 1–125 U/ml antibody titers were in the age range of 40–49, while this rate tended to decrease towards higher antibody titers. Although 8.3% of those with a titer of 1–125 U/ml were in the age range of 20–29, this rate appeared to increase to 9.1% and 15.4% in antibody titers of 126–250 and >250 U/ml respectively. Evaluating those with an antibody titer >250 U/ml, the highest rate, 38.5%, was found in those aged from 30 to 39.

To compare the body mass indices of the participants with the antibody response, the BMI values of all participants were calculated and grouped as normal (BMI: 19–24.9), overweight (BMI: 25–29.9), and obese (BMI: 30 and above). According to our results, 55.8% and 49.5% of those with antibody titers of 126-250 and >250 U/ml, respectively, had a normal BMI. On the other hand, 15.2% of those with antibody titer of 1-125 U/ml were in the obese group. This rate appears to decrease gradually as only 10.4% and 9.9% of those with 126-250 and 250 U/ml, respectively, were in the obese group ($p = 0.316$).

When the smoking habits of the volunteers included in the study and the developed antibody response were compared, 40% of those with an antibody titer of 1–125 U/ml had a history of smoking, while this rate was decreased down to 27.5% in participants with seropositivity of >250 U/ml. However, 72.5% of those with an antibody titer of >250 U/ml were nonsmokers ($p = 0.032$).

Of the volunteers participating in the study, 7% had hypertension (HT), 2.9% had diabetes mellitus (DM), 11.8% had other chronic diseases (asthma, allergy, migraine), and 4.1% had an autoimmune disease (Hashimoto, rheumatoid arthritis, myasthenia gravis, systemic lupus erythematosus). Of those with antibody titers of 1-125, 126-250 and >250 U/ml, 8.3%, 7.8%, and 4.4%, respectively, had hypertension. Despite not being statistically significant, the rate of having high antibody titers seems to decrease gradually in people with HT.

Various side effects are seen in vaccine types developed against SARS CoV-2. Side effects developed in 12.7% ($n = 40$) of the volunteers after the inactivated virus vaccine we used. The distribution of side effects is as follows; weakness and malaise were reported in 32.5% of the participants, whereas 32.5% suffered headaches, 17.5% felt arm pain, 15% suffered fever, and 2.5% experienced muscle pain.

Antibody titers were evaluated by retaking blood 12 weeks after the second dose of vaccine to figure out whether the seropositivity of the RBD antibodies obtained after the vaccination decreased over time. For this, venous blood was taken from 40 participants whose RBD antibody titers were between 75 and 250 U/ml. Those with a titer above 250 were not included in this analysis. Remarkably, the first measured median was 92.3 (IQR, 122.1) 4 weeks after the second dose of RBD antibody, while the median value decreased down to 54.0 (IQR, 23) after 12 weeks. The difference between both antibody values was found to be statistically significant ($p = 0.001$).

Nucleocapsid antibodies are highly specific markers for the diagnosis of those previously infected with COVID-19. In our study, RBD antibody- and NCP antibody-titers were also compared in the blood taken four weeks after the second dose of vaccine. The NCP antibodies of 126 individuals with RBD antibody titers were evaluated. Accordingly, the NCP antibody was reactive in 50.7% of those with an RBD titer of 1–125 U/ml, while this rate was found to be 62.7% in those with an RBD of 126–250 U/ml ($p = 0.180$).

4 | DISCUSSION

Although the detection of the antibody response to SARS-CoV-2 provides important data to learn whether people have previously been infected with this infection, to diagnose the infection, and to determine the effectiveness of the vaccine,[18] it is also important to

identify the factors that affect the variability of this antibody response, understand the pathogenesis of COVID-19, carry out epidemiological studies, and contribute to studies on vaccines.[3]

However, the serological response can affect the quality of the immune response and the duration of immunity due to both individual characteristics and vaccine-related differences.[7]

We conducted this study to obtain information on the variability of the postvaccine antibody level with respect to various demographic characteristics.

One of the most important parameters determining the antibody response is age. Since T-cell-derived antibody production decreases and B-lymphocyte generation decreases with age, antibody response against infectious agents and after vaccination may not be sufficient.[19] In various studies carried out after vaccinations against influenza, hepatitis A, hepatitis B, pneumococcus, tick-borne encephalitis (TBE), tetanus, and SARS-CoV-2, it was observed that the postvaccination antibody response was inversely proportional to age.[9,20–22] In our study, we found that there was no statistically significant relationship between age and antibodies, however, those in the age group of 30–39 (38.5%) had higher antibody titers than other age groups.

One of the factors affecting the development of postvaccine antibodies is BMI. The reason is that CD8 cytotoxic T-cell, CD4 T-helper response, and memory T-cell response has been exhibited to be insufficient and antibody level disappears quickly after vaccination in those considered obese in terms of BMI.[7,23,24] In addition, the ACE2 receptor, which is more abundantly expressed in adipose tissue in obese individuals, predisposes people to infection compared to individuals with a normal BMI.[24] Thusly, BMI is important in the prognosis of the infection and the level of the postvaccine immune response. When the relationship between BMI and the antibody levels of the participants was evaluated, it was seen that, although not statistically significant, 49.5% of those with antibody titers higher than 250 U/ml had a normal BMI, while only 9.9% of them were obese ($p = 0.316$).

The effect of smoking on postvaccine antibody response has shown variable results with different viral vaccines. For example, the very low antibody response was measured in smokers after the hepatitis B vaccine, and it was observed that the antibody response disappeared rapidly after the influenza vaccine.[22] In another study, in contrast, no correlation was found between smoking and antibody level after influenza vaccination.[23] In the present study, the postvaccine antibody response was observed to be statistically significantly lower in smokers than in nonsmokers. The rate of nonsmokers in those with antibody titer >250 U/ml is 72.5% while the rate of smokers in the same group is 27.5% only.

Antibodies that arise as a response to humoral immunity in individuals previously infected with or vaccinated against COVID-19 are present in the blood for a certain period of time. Although antibodies produced by short-lived plasma cells in secondary lymphoid organs increase rapidly in the blood and then decrease rapidly in the first 3 months, the antibodies produced by long-lived plasma cells in the bone marrow tend to decrease more slowly in the following period.[25] Although the tendency of the antibody response to decreasing over time is a natural process of humoral immunity, the course of the postvaccine antibody response is crucial in the current pandemic period. The postvaccine humoral immune responseshowed seropositivity of 89.7% after the 2nd week, in the study of Tanrıöver et al.[26] While in our study and in the study of Bayram et al.,[27] a seropositivity of 99.6 was observed 4 weeks after the vaccine. In parallel with the natural course of the antibody response in terms of postvaccine antibody responses, it was observed to decline in the current study. A decrease in antibody titer was observed at the 12th week of the inactive whole virion vaccine in the participants who had 75–250 U/ml antibodies after excluding those with >250 U/ml antibodies. Although there was a statistically significant decrease in antibody titers, it was observed that the seropositivity of the participants still continued. Evaluating the mRNA postvaccine antibody titer, Naaber et al. also observed that the RBD antibody response obtained six weeks following the vaccine was decreased compared to the antibody response observed one week after the vaccine.[20]

Although there is not enough postvaccine data on NCP antibodies,[10] which can be detected in the blood even eight months after infection by COVID-19[27] and are quite specific in the diagnosis of COVID-19 infection, the NCP antibody response was measured as negative in three separate studies in which the NCP antibody levels were measured after an mRNA vaccine targeting only spike protein's RBD.[28–30] In a study carried out after an mRNA vaccine, the fact that NCP antibodies were negative and antibody response to spike proteins was positive has been evaluated as evidence of the vaccine.[30] In the study, carried out after the CoronaVac vaccine using inactivated virus, most of the participants were found to have a positive antibody response to NCP. In particular, we found that those with antibody titers of 126–250 U/ml had higher NCP reactivity than those with 1–125 U/ml antibodies. NCP reactivity was not checked in those with a titer of >250 U/ml, but we saw that a high rate of NCP reactivity was observed in those with a high RBD antibody titer.

The limitation of the study is that the participants did not reflect the general population, as the study was conducted in a small group of healthy volunteers. Therefore, we could not adequately examine the differences in antibody levels in the presence of various diseases that are more likely to be present in the population with the demographic data we examined. In addition, the RBD antibody level, which we reassessed 12 weeks after the vaccination, was measured in a small group and those with a titer below 250 U/ml. In the study, we examined postvaccine antibody titers. However, the neutralization test, which is an important aspect of the immune system and an indicator of cellular immunity and cellular response, could not be evaluated.

Almost all of the participants developed seropositivity after the inactivated whole-virion vaccine. Despite not being statistically significant, we found that the antibody titers were lower in the participants with a high BMI and that the antibody titer in smokers was significantly lower than in nonsmokers. Furthermore, we

TABLE 1 Comparison of demographic data, BMI, smoking habits, various diseases, and levels of NCP antibodies of HCWs with the level of total antibodies against RBD antibodies after 4 weeks of the second dose of vaccine

RBD antibody titers (n = 313)					
	n	1–125 U/ml n (%)	126–250 U/ml	>250 U/ml	
Gender					
Female	180	77 (53.1)	52 (67.5)	51 (56.0)	p= 0.111
Male	133	68 (46.9)	25 (32.5)	40 (44.0)	
Age group					
20–29	33	12 (8.3)	7 (9.1)	14 (15.4)	p = 0.156
30–39	109	43 (29.7)	31 (40.3)	35 (38.5)	
40–49	139	73 (50.3)	34 (44.2)	32 (35.2)	
50–65	32	17 (11.7)	5 (6.5)	10 (11.0)	
BMI					
Normal (19–24.9)	149	61 (42.1)	43 (55.8)	45 (49.5)	p = 0.316
Overweight (25–29.9)	125	62 (42.8)	26 (33.8)	37 (40.7)	
Obese (30 and above)	39	22 (15.2)	8 (10.4)	9 (9.9)	
Smoking habit					
Yes	102	58 (40.0)	19 (24.7)	25 (27.5)	p = 0.032
No	211	87 (60.0)	58 (75.3)	66 (72.5)	
HT					
Yes	22	12 (8.3)	6 (7.8)	4 (4.4)	p = 0.502
No	291	133 (91.7)	71 (92.2)	87 (95.6)	
DM					
Yes	9	4 (2.8)	1 (1.3)	4 (4.4)	p = 0.485
No	304	141 (97.2)	76 (98.7)	87 (95.6)	
Other chronic diseases					
Yes	37	18 (12.4)	6 (7.8)	13 (14.3)	p = 0.411
No	276	127 (87.6)	71 (92.2)	78 (85.7)	
Autoimmune diseases					
Yes	13	7 (4.8)	5 (6.5)	1 (7.7)	p = 0.187
No	313	138 (95.2)	72 (93.5)	90 (98.9)	
NCP					
Reactive	70	38 (50.7)	32 (62.7)	p = 0.180	
Nonreactive	56	37 (49.3)	19 (37.3)		

Note: Chronic diseases (asthma, allergies, migraine), autoimmune disease (Hashimoto, rheumatoid arthritis, myasthenia gravis, SLE).

Abbreviations: BMI, body mass index; DM, diabetes mellitus; HT, hypertension; NCP, nucleocapsid protein; RBD, receptor-binding domain.

observed that the RBD antibody level decreased significantly 12 weeks

after the second dose of vaccine with continued seropositivity and that the NCP antibody was proportionally more reactive in those with high RBD antibodies. More studies are needed to investigate the duration and effect of the postvaccine antibody response, as further research is carried out with different types of vaccinations against the COVID-19 pandemic (Table 1).

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AUTHOR CONTRIBUTIONS

Elif B. Uysal: Project administration, preparation of research goals and aims, writing manuscript. **Ayşegül Gözalan**: Oversight and leadership responsibility for the research activity planning and execution. **Sibel Gümüş, Bayhan Bektöre, and Hale Bozkurt**: Contributed to sample collection and data acquisition. **Elif B. Uysal and Bayhan Bektöre**: Studying ELISA testing. **Ayşegül Gözalan and Sibel Gümüş**: Contributed to the statistical analysis. All authors revised the manuscript, contributed to its final version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis*. 2021;21(2):181-192. doi:10.1016/S1473-3099(20)30843-4
2. Lee WS, Wheatley AK, Kent SJ, DeKosky BJ. Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies. *Nat Microbiol*. 2020;5(10):1185-1191. doi:10.1038/s41564-020-00789-5
3. Smits VAJ, Hernández-Carralero E, Paz-Cabrera MC, et al. The Nucleocapsid protein triggers the main humoral immune response in COVID-19 patients. *Biochem Biophys Res Commun*. 2021;5(543):45-49. doi:10.1016/j.bbrc.2021.01.073
4. Parkash A, Singla P, Bhatia M. Antibody response to Covıd-19 infectıon clinical variables at play. *medRxiv*, doi:10.1101/2020.11.20.20234500
5. Wu Z, Hu Y, Xu M, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis*. 2021;21(6):803-812. doi:10.1016/S1473-3099(20)30987-7
6. Gundlapalli AV, Salerno RM, Brooks JT, et al. SARS-CoV-2 Serologic Assay Needs for the Next Phase of the US COVID-19 Pandemic Response. *Open Forum Infect Dis*. 2020;17 8(1):ofaa555. doi:10.1093/ofid/ofaa555
7. Zimmermann P, Curtis N. Factors That Influence the Immune Response to Vaccination. *Clin Microbiol Rev*. 2019;13 32(2):e00084-18. doi:10.1128/CMR.00084-18
8. Chilamakuri R, Agarwal S. COVID-19: Characteristics and Therapeutics. *Cells*. 2021;Jan 21 10(2):206. doi:10.3390/cells10020206
9. Wang P, Liu L, Nair MS, et al. SARS-CoV-2 neutralizing antibody responses are more robust in patients with severe disease. *Emerg Microbes Infect*. 2020;9(1):2091-2093. doi:10.1080/22221751.2020.1823890
10. Dobaño C, Santano R, Jiménez A, et al. Immunogenicity and cross-reactivity of antibodies to the nucleocapsid protein of SARS-CoV-2: utility and limitations in seroprevalence and immunity studies. *Transl Res*. 2021;232:60-74. doi:10.1016/j.trsl.2021.02.006
11. Perkmann T, Perkmann-Nagele N, Koller T, et al. Anti-Spike protein assays to determine SARS-CoV-2 antibody levels: a head-to-head comparison of five quantitative assays. *Microbiol Spect*, 2021;9(1):e00247. doi:10.1128/Spectrum.00247-21
12. Salazar E, Kuchipudi SV, Christensen PA, et al. Convalescent plasma anti-SARS-CoV-2 spike protein ectodomain and receptor-binding domain IgG correlate with virus neutralization. *J Clin Invest*. 2020.130(12):6728–6738. doi:10.1172/JCI141206
13. Franco-Muñoz C, Álvarez-Díaz DA, Laiton-Donato K, et al. Substitutions in Spike and Nucleocapsid proteins of SARS-CoV-2 circulating in South America. *Infect Genet Evol*. 2020;85:104557. doi:10.1016/j.meegid.2020.104557
14. Iwasaki A, Yang Y. The potential danger of suboptimal antibody responses in COVID-19. *Nat Rev Immunol*. 2020;20(6):339-341. doi:10.1038/s41577-020-0321-6
15. Jeyanathan M, Afkhami S, Smaill F, Miller MS, Lichty BD, Xing Z. Immunological considerations for COVID-19 vaccine strategies. *Nat Rev Immunol*. 2020;20(10):615-632. doi:10.1038/s41577-020-00434-6
16. Tan CW, Chia WN, Qin X, et al. A SARS-CoV-2 surrogate virus neutralization test based on antibody-mediated blockage of ACE2-spike protein-protein interaction. *Nat Biotechnol*. 2020;38(9):1073-1078. doi:10.1038/s41587-020-0631-z
17. Formica N, Mallory R, Albert G, et al. Evaluation of a SARS-CoV-2 vaccine NVX-CoV2373 in younger and older adults. *medRxiv*. doi:10.1101/2021.02.26.21252482
18. Padoan A, Dall'olmo L, Rocca FD, et al. Antibody response to first and second dose of BNT162b2 in a cohort of characterized healthcare workers. *Clin Chim Acta*. 2021;20 519:60-63. doi:10.1016/j.cca.2021.04.006
19. Weinberger B, Grubeck-Loebenstein B. Vaccines for the elderly. *Clin Microbiol Infect*. 2012;18(Suppl 5):100-108. doi:10.1111/j.1469-0691.2012.03944.x
20. Naaber P, Tserel L, Kangro K, et al. Antibody response after COVID-19 mRNA vaccination in relation to age, sex, and side effects. *medRxiv*, doi:10.1101/2021.04.19.21255714
21. Huang YP, Gauthey L, Michel M, et al. The relationship between influenza vaccine-induced specific antibody responses and vaccine-induced nonspecific autoantibody responses in healthy older women. *J Gerontol*. 1992;47(2):M50-M55. doi:10.1093/geronj/47.2.m50
22. Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. *Vaccine*. 2006;20 24(8):1159-1169. doi:10.1016/j.vaccine.2005.08.105
23. Sheridan PA, Paich HA, Handy J, et al. Obesity is associated with impaired immune response to influenza vaccination in humans. *Int J Obes (Lond)*. 2012;36(8):1072-1077. doi:10.1038/ijo.2011.208
24. Dicker D, Bettini S, Farpour-Lambert N, et al. Obesity and COVID-19: The Two Sides of the Coin. *Obes Facts*. 2020;13(4):430-438. doi:10.1159/000510005
25. Pelleau S, Woudenberg T, Rosado J, et al. Serological reconstruction of COVID-19 epidemics through analysis of antibody kinetics to SARS-CoV-2 proteins. *medRxiv*, doi:10.1101/2021.03.04.21252532
26. Tanrıover MD, Doğanay HL, Akova M, Güner HR, Azap A. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (Coronavac): interim results of a double blind, randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet*. 2021;398(10296):213–222. 10.1016/S0140-6736(21)01429-X
27. Bayram A, Demirbakan H, Karadeniz PG, Erdoğan M, Koçer I. Quantitation of antibodies against SARS-CoV-2 spike proteinafter two doses of CoronaVac in healthcare workers. *J Med Virol*. 2021;93:5560-5567. doi:10.1002/jmv.27098
28. Van Elslande J, Oyaert M, Ailliet S, et al. Longitudinal follow-up of IgG anti-nucleocapsid antibodies in SARS-CoV-2 infected patients up to eight months after infection. *J Clin Virol*. 2021;202(136):104765. doi:10.1016/j.jcv.2021.104765
29. Mueller T. Antibodies against severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) in individuals with and without COVID-19 vaccination: A method comparison of two different commercially available serological assays from the same manufacturer. *Clin Chim Acta*. 2021;202(518):9-16. doi:10.1016/j.cca.2021.03.007
30. Ota K, Murakami S, Mukae H, Kohno S, Yanagihara K. Measurement of multiple SARS-CoV-2 antibody titer after vaccination represents

individual vaccine response and contributes to individually appropriate vaccination schedules. *medRxiv*. doi:10.1101/2021.05.21.21257575

31. Subbarao S, Warrener LA, Hoschler K, et al. Robust antibody responses in 70-80-year-olds 3 weeks after the first or second doses of Pfizer/BioNTech COVID-19 vaccine, United Kingdom, January to February 2021. *Euro Surveill*. 2021;26(12):2100329. doi:10.2807/1560-7917.ES.2021.26.12.2100329

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