THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2023.48264
Med Bull Sisli Etfal Hosp 2023;57(2):216–223

Original Research

Antibody Response to COVID-19 Vaccines in Healthcare Workers: Which One is More Successful? Homologous or Heterologous?

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ABSTRACT

Objectives: We aimed to determine the antibody levels created by COVID-19 vaccination in healthcare workers and the factors affecting the antibody response.

Methods: Our research is a single-center, observational study that was prospectively designed and retrospectively analyzed at the beginning of the COVID-19 pandemic, and included 103 healthcare workers who received the three-dose regimen of COVID-19 vaccine. In accordance with the recommendations of the Ministry of Health of Turkey, the first two doses of CoronaVac vaccine were administered routinely, while the booster dose was given as BioNTech or CoronaVac (heterologous or homologous vaccination) depending on the preference of the volunteers. Antibody titers against the SARS-CoV-2 were measured in all individuals at different time points (1 month after the second dose of CoronaVac, before the booster dose [BioNTech or CoronaVac] at the fifth month and one month after the booster dose) with AESKULISA® SARS-CoV-2 S1 IgG (AESKU DIAGNOSTICS, Wendelsheim, Germany).

Results: The mean age was 39.98±11.31 years, 62.1% of whom were women and 54.4% of them were accompanied by comorbid disease. After two doses of CoronaVac, the antibody titer averaged 49.50±33.15 U/mL in the 1st month (antibody seropositivity 86%) and the antibody titer decreased 24.01±33.48 U/mL (antibody seropositivity 49.5%) at 5th month. The mean antibody titer was found 59.73±60.20 U/ml in those who received the booster dose of homologous and 185.07±46.28 U/mL in those who were heterologous ($p<0.001$). Antibody levels were detected significantly lower after the booster dose of vaccination in patients with comorbidities ($p<0.05$).

Conclusion: Our study, which reflects the data within the scope of the Turkey Ministry of Health's COVID-19 vaccination program determined that the antibody response after heterologous vaccination is better than in homologous vaccination. Antibody titer level in the 5th month was 50% waned after two doses of inactivated vaccination. It was also shown that factors such as gender, age, body mass index, and smoking did not create a statistically significant difference in homologous and heterologous vaccination, but after the booster dose antibody levels decreased significantly in those with comorbidity.

Keywords: Antibody, COVID-19, health-care workers, SARS-CoV-2, vaccine

Please cite this article as "Karakoc ZC, Tascioglu D, Ediz B, Caglan M, Hancer VS, Tugrul TS, et al. Antibody Response to COVID-19 Vaccines in Healthcare Workers: Which One is More Successful? Homologous or Heterologous? Med Bull Sisli Etfal Hosp 2023;57(2):216–223".

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Submitted Date: January 16, 2023 **Revised Date:** March 08, 2023 **Accepted Date:** March 08, 2023 **Available Online Date:** June 20, 2023

Knowing that vaccination is the most effective method that can slow the pace of the COVID-19 pandemic and reduce mortality has led to the acceleration of vaccination efforts all over the world. As a result, CoronaVac (Sinovac Life Sciences, Beijing, China) was the first vaccine whose efficacy and safety were accepted, started to be administered to individuals in the risk group, especially healthcare workers, on January 14, 2021, with the decision of the Ministry of Health of the Republic of Turkey. CoronaVac is an inactivated vaccine and the most widely used COVID-19 vaccine in the world. Its efficacy ranges from 50.7% to 83.5% and produces an immune response against all viral proteins of SARS-CoV-2. It is difficult to measure the immune response against the vaccines, but studies have shown that measuring the level of SARS-CoV-2 antibodies in vaccinated individuals can be used to evaluate the effectiveness of the vaccine.[1-4]

With the waning antibody response over time especially in inactivated vaccines and the emergence of variant strains, booster dose vaccination has been brought to the agenda all over the world and in our country.[5,6] For these reasons, The Ministry of Health of Turkey has also accelerated its efforts for the supply of mRNA vaccines and provided access to both vaccines primarily to individuals in the risk group and then to all citizens with vaccination indications. As a result, BioNTech (Pfizer, Inc., and BioNTech) vaccine has been put into use in our country as of July 2021.

Our research is a prospective study which reflects the experience of a single center that will be evaluated retrospectively. Volunteer healthcare workers who were involved in the vaccination program during the pandemic were included in our study. Vaccinations were carried out within the program recommended by the Ministry of Health of our country. In our study, it was aimed to determine the antibody levels created by COVID-19 vaccination in healthcare workers and the factors affecting the antibody response.

Methods

Our study is a single-center, observational study that was designed prospectively at the beginning of the COVID-19 pandemic and analyzed retrospectively. One hundred and twelve healthcare workers (doctor, nurse, allied health personnel, medical secretary, laboratory technician, and pharmacist) aged 20–65 years who received three doses of COVID-19 vaccination (first dose between January 14 and January 31, 2021, second dose between 14 February and February 28, 2021, and booster dose between July 11 and August 15, 2021) at Istinye University Hospital were included in the study. With the decision of the Ministry of Health of the Republic of Turkey, CoronaVac (Sinovac Life Sciences, Beijing, China) as the whole virus SARS-CoV-2 vaccine was administered to healthcare workers at a dose of 3 mcg with an interval of 28 days as primary doses. During the pandemic period, the COVID-19 mRNA vaccine, which was approved to be applied in our country as well as all over the world, was left to the preference of health workers in the third dose vaccine administration. One group of healthcare workers continued with CoronaVac (homologous), while the other group continued with BioNTech (heterologous) as the booster dose. A total of 103 healthcare workers were included in the study, excluding those who had COVID-19 in the 3 months before the first vaccination, who did not provide at least two blood samples, and those who left the study voluntarily.

Informed consent was obtained from the volunteers. Participants' age, gender, profession, habits, chronic diseases, medicine use, body mass index (BMI), influenza vaccination history, BCG scarring, history of COVID-19 before the primer dose of vaccination and up to 6 months after the booster dose, vaccine-related local (pain and redness) and systemic (fever and anaphylaxis) side effects were recorded. The diagnosis was confirmed by studying SARS-CoV-2 RNA PCR in the nasopharyngeal swab of the individuals included in the study with suspected COVID-19. Blood samples were taken from the healthcare workers participating in the study between 28 and 35 days after the second dose of vaccination, before the third dose of vaccination (same day or 24 h before) at 5th month, and on the 28–35 days after the booster dose of vaccination for antibody level measurement, and centrifuged at 1500 g.plasma part was separated and stored at −20°C.

The enzyme-linked immunosorbent test AESKULISA® SARS-CoV-2 S1 IgG (AESKU DIAGNOSTICS, Wendelsheim, Germany) was used for the quantitative detection of IgG antibodies in serum and plasma samples targeting the recombinant S1 domain of the SARS-CoV-2 spike protein in all serum samples taken at different times. According to the manufacturer's instructions, quantitative analysis was performed using a four-parameter logistic standard curve obtained by plotting the measured optical density values for the four calibrators against their antibody activities (U/ml) using logarithmic/linear coordinates, Antibody activities of the samples were evaluated by optical density using the generated curve and were considered positive if >12 U/mL. Values measured above 199 U/mL were considered >199; not diluted or reworked.

Our study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from the Ministry of Health Scientific Research Platform (Approval Number. 2020-07-08T15_14_ form) and Istinye University Ethics Committee (2/2021.G-132). Our work was supported by the

Istinye University Scientific Research Projects fund (Project number: 2021/B19).

Statistical Analysis

The analysis of the data was performed by recording in the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA), version 11.0) program. Significant differences between groups were investigated using Student's *t*-test in comparisons of two subgroups and analysis of variance (ANOVA test) in comparisons of more than two subgroups. The test statistic probability value p <0.05 was considered statistically significant.

Results

The mean age of healthcare personnel was 39.98±11.31 years and 62.1% (n=64) were female. Participants over the age of 40 constituted 44.7% (n=46) and comorbid disease accompanied 54.4% (n=56) of the cases. Comorbidities were under follow-up and there were no individuals with uncontrolled diabetes, severe chronic obstructive pulmonary disease, end-organ damage, or severe immunosuppressive drug use. The distribution of healthcare workers by occupational groups were doctors 34% (n=35), nurses 33% (n=34) and other (healthcare personnel, laboratory technician, secretary, and pharmacist) 33% (n=34). Those who used alcohol 3 days a week or more were 5.8% (n=6) of those included in the study, while 39.8% (n=41) were regular smokers, but none of them were heavy smokers (>3 packs/day). BCG scar was present in 93.2% (n=96) of the participants. It was 11.7% (n=11) of the volunteers who received influenza vaccination regularly, which was slightly higher than the general population and healthcare workers.[7,8] Overweight cases were 43.7% (n=45). The proportion of individuals who had COVID-19 after 15 days of two doses of CoronaVac and before booster dose (approximately 5 months) 13.6% (n=14). Homologous vaccination was 16.5% (n=17), heterologous vaccination was 77.7% (n=80). Six participants were not vaccinated due to COVID-19 diagnosis. Those diagnosed with COVID-19 for 6 months follow-up after the booster shot (homologous or heterologous) were 27.7% (n=28) (Table 1). Among those

Table 1. Demographic data of healthcare workers

Parameters	n (%)
Age (years)±SD (min-max)	39.98±11.31 (22–66)
>40 years	46 (44.7)
Female gender	64 (62.1)
BMI±SD (min-max)	25.07±4.68 (18.36–49.55)
Comorbidity	56 (54.4)
Hypertension	7
Diabetes	2
Cardiovascular disease	4
Chronic lung disease	6
Autoimmune disease	10
Multiple comorbidities	15
Other	12
Profession group	
Doctor	35 (34)
Nurse	34 (33)
Other	34 (33)
Alcohol/Smoking	6 (5.8)/41 (39.8)
BCG scarring/Regular influenza vaccination	96 (93.2)/12 (11.7)
Homologous booster/Heterologous booster	17 (16.5)/80 (77.7)
Those with COVID-19 after two doses of CoronaVac	14 (13.6)
Those with COVID-19 after booster dose (6 months follow up)	28 (27.7)
Vaccine side effects (2nd dose CoronaVac)	38 (36.9)
Local/Systemic	13 (12.6)/24 (24.3)
Vaccine side effects (3rddose)	71 (69)
Local/Systemic	34 (33)/37 (36)

SD: Standart deviation; BMI: Body mass index; BCG: Bacille calmette-guerin.

with COVID-19 positivity for the homologous booster shot was 41.2%, and 21.8% for the heterologous.

The mean antibody titer in the 1st month after two doses of CoronaVac was 49.50±33.15 U/ml. In correlation with this 86% (n=88) had seropositivity. In the 5th month, the antibody titer was found to be decreased by approximately fifty percent, with an average of 24.01±33.48 U/mL, and the rate of seropositivity was 49.5% (n=48). Among those who did not have comorbid diseases the antibody positivity at the 5th month was 45.3% (n=39) and the mean antibody titer was 22.02±32.23 U/mL (Table 2). The antibody titer levels before the third vaccination of those who had COVID-19 (n=14) and those who did not have COVID-19 (n=89) were evaluated and no statistically significant difference was found (160.99±75.62 vs. 162.61±68.40) (p=0.095).

Regardless of homologous or heterologous vaccination, the mean antibody level postbooster was 162.44±68.71 U/mL. Two individuals (2.3%) were found to have no seropositivity after the booster shot. These individuals were middle-aged female volunteers who were homologous booster and had no comorbidities. The mean antibody titer after the booster dose was 59.73±60.20 U/mL in 17 individuals with homologous vaccination, and 185.07±46.28 U/mL in 71 cases with heterologous vaccination (p<0.001) (Table 2). While the antibody level was 186.80+45.64 U/mL in those who developed systemic side effects after booster dose vaccination, the antibody level was slightly lower (149.63+75.44 U/mL) in those who did not develop side effects.

When the antibody response is evaluated according to age; the mean antibody level was 52.04±33 U/mL among participants under the age of ≤40 who received two doses of CoronaVac, and waned 24.23±35.07 U/mL in the 5th month. In this group, the mean antibody level after the booster shot was 167.14±65.26 U/mL, while the antibody titer was 84.04±74.76 U/mL in homologous (n=9) and 184.72±48.07 U/mL in heterologous vaccinated individuals (n=42). Among the participants over 40 years of age, the mean antibody level was 46.28±33.43 U/mL after two doses of CoronaVac, and waned 23.72±31.78 U/ml at the 5th month. In general, the antibody response in this group was 157.52±72.59 U/mL on average after the booster dose of vaccination, while the mean was 35.42±28.76 U/mL in homologous (n=8) and 185.43±45.05 U/ml in heterologous (n=38) vaccinated volunteers. There was no difference in antibody response after heterologous vaccination in individuals ≤40 or >40 years of age (184.72 U/mL vs. 185.43 U/mL). These data suggest that the antibody levels decreased (24.01±33.48 U/mL) similarly regardless of age groups, after two doses of CoronaVac vaccination at the 5th month (Table 2).

In patients with comorbidities (n=56), the mean antibody titer was 51.70±33.82 U/mL at the 1st month and decreased 25.79±34.79 U/mL at the 5th month after two doses of CoronaVac. After the booster dose, the mean antibody titer was 145.63±76.35 U/mL, and 57.02±49.54U/mL in homologous (n=14), 179.51±54.38 U/mL in heterologous vaccinated subjects (n=39). Among those without comorbidity (n=47) the mean antibody titer was 46.92±32.51 U/mL after two doses of CoronaVac and decreased 22.02±32.23 U/mL in the 5th month. After the booster dose, the mean antibody

Table 2. Antibody titers after COVID-19 vaccinations

Parameters	Antibody titer at 1 month after two doses of CoronaVac±SD (U/mL)	Antibody titer before the booster dose (at 5th month)±SD (U/mL)	Antibody titer at 1 month after booster dose±SD (U/mL)	Antibody titer after homologous booster±SD (U/mL)	Antibody titer after heterologous booster±SD (U/mL)
Participants (n=103)	49.50±33.15	24.01±33.48	162.44±68.71	59.73±60.20*	185.07±46.28*
Female	51.33±33.63	22.64±31.06	156.84±73.70	60.59±68.91	183.69±48.53
Male	46.42±32.52	26.43±37.75	171.78±59.37	57.15±26.45	187.18±43.36
>40 years	46.28±33.43	23.72±31.78	157.52±72.59	35.42±28.76	185.43±45.05
≤40 years	52.04±33	24.23±35.07	167.14±65.26	84.04±74.76	184.72±48.07
Smoker	48.71±33.44	12.11±13.56	172.31±60.29	53.99±24.27	187.20±44.90
Non-smoker	50.03±33.22	32±40.05	155.92±73.57	61.64±69.03	183.51±47.75
BMI ≥25	50.05±34.91	23.15±32.97	143.82±78.88	40.48±31.16	170.42±63.92
Normal BMI	49.07±31.99	24.66±34.16	176.59±56.67	78.98±77.13	195.09±24.98
Comorbidity	51.70±33.82	25.79±34.79	145.63±76.35**	59.02±49.54	179.51±54.38
Without comorbidity	46.92±35.51	22.02±32.23	181.71±53.41**	71.46±110.46	190.18±37.37

SD: Standart deviation; BMI: Body mass index; *p<0.001; **p<0.05.

titer was 181.71±53.41 U/mL, while it was 71.46±110.46 U/mL in homologous (n=3), and 190.18±37.37 U/mL in heterologous vaccine (n=41) participants. Among those with multiple comorbidities (n=14); the mean antibody titer was 45.02±32.27 U/mL in the 1st month and 28.81±42.96 U/mL in the 5th month after two doses of CoronaVac. After the booster dose, the mean antibody titer was 127.31±86.95 U/mL, while it was 31.22±24.39 U/mL in homologous (n=5), and 180.70±54.88 U/mL in heterologous vaccined (n=9). Among those without multiple comorbidities (n=88) after two doses of CoronaVac the mean antibody titer was 50.21±33.41 U/mL in 1st month, and waned 23.13±31.70 U/mL in the 5th month. After the booster dose, the mean antibody titer was 169.08±63.24 U/mL, while it was 72.69±67.88 U/mL in homologous (n=12), and 185.70±45.38 U/mL in heterologous vaccined (n=71) participants (Table 2).

Among volunteers with normal BMI (n=58), the mean antibody titer was 49.07±31.99 U/mL after two doses of CoronaVac, and 24.66±34.16 U/mL in the 5th month. After the third dose of vaccination, the mean antibody titer was 176.59±56.67 U/mL, while it was 78.98±77.13 U/mL in homologous (n=9) and 195.09±24.98 U/mL heterologous vaccined (n=46) volunteers (Table 2). In those who are overweight (BMI:25–30) (n=33), the mean antibody titer was 48.43±35.69 U/mL after two doses of CoronaVac and 20±37 in the 5th month. After the third dose of vaccination, the mean antibody titer was 144.81±79.40 U/mL, while it was found 43.31±34.18 U/mL in homologous (n=5), and 167.88±67.62 U/mL in heterologous vaccined (n=22). Among obese individuals (BMI≥30), (n=12), the mean antibody titer was 54.48±33.78 U/mL after two doses of CoronaVac and 32.02±45.08 U/mL in the 5th month. After the booster dose, the mean antibody titer was 141.37±81.36 U/mL, while the it was found 35.76±31.73 U/mL in homologous (n=3) and 180.97±50.96 U/mL in heterologous vaccined (n=8). There was no statistically significant difference between the groups (antibody levels 1 month and 5th month after CoronaVac and 1 month after the booster dose) (Table 2).

Discussion

Health-care workers, who are at the forefront of the pandemic and are at high risk for SARS-CoV-2 infection, have started to be vaccinated as a priority in the COVID-19 vaccination program. The only vaccine administered in our country until April 2021 was the inactivated whole cell COVID-19 virus vaccine, CoronaVac (Sinovac Life Sciences, Beijing, China),and in July 2021, again with the decision of the Ministry of Health, the third dose of vaccination was started as CoronaVac or BioNTech (Pfizer, Inc., and BioNTech).[1]

Inactivated vaccines are the most experienced vaccines from past to present; the advantages are that they are safe, have few side effects, and suitable conditions for storage and transfer. However, since the antigenic immunity of virus vaccines caused by the inactivation process is low, antibody responses decrease over time, and therefore booster vaccinations are required. On the other hand, the production of mRNA vaccines is fast and easy. They create a long-term and more effective immune response, but the most important disadvantage of these vaccines is that they require cold chain conditions during storage and transfer.[9,10]

Against SARS-CoV-2 vaccination, our body produces antibodies against different structural proteins of the virus. Neutralizing antibodies that provide virus inhibition are mainly formed against spike protein of SARS-CoV-2 virus and can be detected by plaque reduction neutralization test. However, this test cannot be routinely studied due to the need for a special laboratory infrastructure and high cost. Therefore, spike antibodies are used in clinical practice. Although it is known that these antibodies correlate with neutralizing antibody levels, there is no standard threshold value for significant antibody titer.[11,12]

Vaccination is a cost-effective method in COVID-19, as in all infectious diseases, and billions of doses of vaccines with proven effectiveness against SARS-CoV-2 have been administered today, preventing hospitalization and death due to this disease. However, vaccine-induced immunity has been shown to decrease after mRNA vaccines, especially inactivated vaccines. At this point, immune response data on inactive and mRNA vaccinations are being published in increasing numbers.[13]

Inactivated vaccines were the first vaccine to be implemented at the beginning of the COVID-19 outbreak. Data on the efficacy of these vaccines came from China, Chile, Brazil, and our country, which approved this vaccine for emergency use in January 2021.[1,14-15] Therefore, experience with inactivated vaccines and heterologous vaccination (inactivated vaccine and mRNA vaccine) was limited to the data of these countries, and data on mRNA vaccines were supported by more widespread studies worldwide.

In this study, we aimed to investigate the antibody response of inactivated and mRNA vaccines, the antibody levels developed after heterologous and homologous vaccination, the stability over time and the factors that may affect the antibody response in health-care workers.

It was shown that the female gender had no effect on the antibody level in our participant's group consisting of 103 healthcare workers. Female and male antibody levels were similar (Tables 1 and 2). Although some studies in the literature have found that female gender may be an indepen-

dent risk factor on antibody response, some studies have also shown that gender does not have a significant effect on antibody response.[16-19]

In our study, the heterologous booster was predominant (77.7%), while those who had COVID-19 after two doses of vaccination were 13.6%, and 36.9% after booster doses in the 6-month follow-up (Table 1). It was thought that substantial increase (13.6% vs. 36.9%) was due to the change in the social behaviors of the healthcare workers, who were tired under the isolation measures for a long time due to the pandemic. And the effect of reliance created by the vaccine, together with the administration of the booster shot coinciding in the summer period may contribute to this situation. In terms of vaccine reaction, it was seen that the highest rate was shown after the booster dose (69%) (Table 1). Consistent with the literature, this situation was thought to be related to mRNA vaccines or heterologous vaccination.[15,20,21]

It has been reported that there is a decrease in the immune response induced by the vaccine against SARS-CoV-2 as a result of changes in immune system functions with advancing age.[22,23] We observed that the antibody titers were similar between age groups, and this condition may be associated with low number of advanced age cases and low homologous vaccinations in the population. Although it was found in the literature that the antibody response decreased after SARS-CoV-2 vaccinations with advancing age, in a study evaluating the antibody response after two doses of inactivated vaccines, no difference was found between age groups in terms of antibody production.[16,24,25]

Similar to advanced age, it has been reported that the antibody response observed after COVID-19 vaccination is low in morbidly obese and smokers.[26] However, there was no decrease in antibody responses after mRNA vaccines in obese and overweight patients.[27,28] In studies conducted in our country, the antibody response was found to be low in patients with high BMI, morbidly obese, and smokers after two doses of inactivated vaccine.[29,30] On the other hand, in our study, no statistically significant difference was found between BMI or smoking and antibody levels.

It has been found that the immune response to infection or vaccination is decreased in people with comorbidities, and spike antibody response is low after two doses of mRNA vaccination.[25,31,32] In our study, the antibody levels were found to be significantly lower after booster dose in patients with comorbidities (Table 2). Consistent with the literature; this study showed that the antibody levels waned over time after inactive vaccination and decreased by approximately 50% in the 5th month, and were statistically significantly higher after heterologous booster.[5,25,33] (Table 2). In similar studies conducted with healthcare professionals in our country, it was determined that the antibody response increased significantly if the booster vaccination after the first two doses of inactivated vaccine was heterologous.[30,34,35]

However, there are also limitations of our study. These are the limited number of the participants, the absence of a geriatric and pediatric population, no further dilution of antibody upper limit and the absence of antibody levels data for longer than 6 months.

Conclusion

Our article is noteworthy because the data on heterologous vaccination (inactive and mRNA vaccines) in the world are limited to only certain countries (China, Brazil, Chile..). And also, it provides information about the antibody response and stability developed after inactivated vaccine which was used widely (45% of COVID-19 vaccinations) in the world.[5] In conclusion, our study which reflects the data within the scope of the Turkey Ministry of Health's first vaccine administration program at the beginning of the COVID-19 pandemic, showed that the post-vaccination antibody response was better in heterologous vaccination than in homologous vaccination. In addition, a decrease of approximately 50% in the antibody levels in the 5th month in the follow-up of inactive vaccination is compatible with the literature. While it was shown that factors such as gender, age, BMI, and smoking did not create a statistically significant difference in homologous and heterologous vaccination, antibody response decreased significantly in those with comorbidity after the booster dose. Our data should be supported by extensive studies involving a large number of cases.

Disclosures

Acknowledgement: We would like to thank all the healthcare heroes who worked in during the pandemic and participated in our study, and the whole laboratory team, especially clinical microbiology laboratory technicians Özkan Kaşıkçı, Özer Ergül and biochemistry laboratory technician Fatih Gül.

Ethics Committee Approval: The study was approved by Ministry of Health Scientific Research Platform (Approval Number. 2020-07-08T15_14_ form); İstinye University Ethics Committee (No: 2/2021.G-132, dated 03.09.2021).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Financial support: Our work was supported by the İstinye University Scientific Research Projects fund (Project number: 2021/B19).

Authorship Contributions: Concept – Z.C.K., B.P.S., T.S.T., V.S.H.; Design – Z.C.K., B.P.S., V.S.H., D.T.; Supervision – Z.C.K., B.P.S., D.T.;

Fundings – Z.C.K., B.P.S., V.S.H., T.S.T.; Materials – Z.C.K., B.P.S., M.C.; Data collection &/or processing – Z.C.K., B.P.S., V.S.H., T.S.T., D.T., M.C.; Analysis and/ or interpretation – Z.C.K., B.P.S., B.E., M.C., D.T.; Literature search – Z.C.K., B.P.S., M.C., D.T.; Writing – Z.C.K., B.P.S., D.T.; Critical review – Z.C.K., B.P.S., D.T., V.S.H., T.S.T., B.E.

References

1. Tanriover MD, Doğanay HL, Akova M, Güner HR, Azap A, Akhan S, et al. 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;398:213-22. [CrossRef]
2. Palacios R, Batista AP, Albuquerque CSN, González Patiño E, Santos JdP, Conde MTRP, et al. Efficacy and safety of a COVID-19 inactivated vaccine in healthcare professionals in Brazil: the PROFISCOV study. SSRN 2021 Apr 14. doi: 10.2139/ssrn.3822780. [Epub ahead of print]. [CrossRef]
3. Fadlyana E, Rusmil K, Tarigan R, Rahmadi AR, Prodjosoewojo S, Sofiatin Y, et al. Phase III, observer-blind, randomized, placebo controlled study of the efficacy, safety and immunogenicity of SARS-CoV-2 inactivated vaccine in healthy adults aged 18-59 years in Indonesia. Vaccine 2021;39:6520-8. [CrossRef]
4. Jara A, Undurraga EA, González C, Paredes F, Fontecilla T, Jara G, et al. Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile. N Engl J Med 2021;385:875-84. [CrossRef]
5. Zuo F, Abolhassani H, Du L, Piralla A, Bertoglio F, de Campos-Mata L, et al. Heterologous immunization with inactivated vaccine followed by mRNA-booster elicits strong immunity against SARS-CoV-2 Omicron variant. Nat Commun 2022;13:2670. [CrossRef]
6. Zhang J, He Q, An C, Mao Q, Gao F, Bian L, et al. Boosting with heterologous vaccines effectively improves protective immune responses of the inactivated SARS-CoV-2 vaccine. Emerg Microbes Infect 2021;10:1598-608. [CrossRef]
7. Tumturk A, Tosun S, Yıldız IE, Alay H, Mistanoğlu Özatay D, Mert D, et al. Seasonal influenza vaccination coverage: a multicenter cross-sectional study among healthcare workers. Ortadogu Med J 2020;12:113-9. [CrossRef]
8. Ciblak MA; Grip Platformu. Influenza vaccination in Turkey: prevalence of risk groups, current vaccination status, factors influencing vaccine uptake and steps taken to increase vaccination rate. Vaccine 2013;31:518-23. [CrossRef]
9. Kyriakidis NC, López-Cortés A, González EV, Grimaldos AB, Prado EO. SARS-CoV-2 vaccines strategies: a comprehensive review of phase 3 candidates. NPJ Vaccines 2021;6:28. [CrossRef]
10. Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdulrazzaq N, et al. Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: a randomized clinical trial. JAMA 2021;326:35-45. [CrossRef]
11. Satarker S, Nampoothiri M. Structural proteins in severe acute respiratory syndrome coronavirus-2. Arch Med Res 2020;51:482-91. [CrossRef]
12. Lau EHY, Tsang OTY, Hui DSC, Kwan MYW, Chan W, Chiu SS, et al. Neutralizing antibody titres in SARS-CoV-2 infections. Nat Commun 2021;12:63. [CrossRef]
13. Wang J, Deng C, Liu M, Liu Y, Li L, Huang Z, et al. A fourth dose of the inactivated SARS-CoV-2 vaccine redistributes humoral immunity to the N-terminal domain. Nat Commun 2022;13:6866. [CrossRef]
14. Costa Clemens SA, Weckx L, Clemens R, Almeida Mendes AV, Ramos Souza A, Silviera MBV, et al. Heterologous versus homologous COVID-19 booster vaccination in previous recipients of two doses of CoronaVac COVID-19 vaccine in Brazil (RHH-001): a phase 4, non-inferiority, single blind, randomised study. Lancet 2022;399:521-9. [CrossRef]
15. Zhang Y, Zeng G, Pan H, Li C, Hu Y, Chu K, 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;21:181-92. [CrossRef]
16. Ward H, Whitaker M, Flower B, Tang SN, Atchison C, Darzi A, et al. Population antibody responses following COVID-19 vaccination in 212,102 individuals. Nat Commun 2022;13:907. [CrossRef]
17. Bayart JL, Morimont L, Closset M, Wieërs G, Roy T, Gerin V, et al. Confounding factors influencing the kinetics and magnitude of serological response following administration of BNT162b2. Microorganisms 2021;9:1340. [CrossRef]
18. Pellini R, Venuti A, Pimpinelli F, Abril E, Blandino G, Campo F, et al. Initial observations on age, gender, BMI and hypertension in antibody responses to SARS-CoV-2 BNT162b2vaccine. E Clinical Medicine 2021;36:100928. [CrossRef]
19. Lee SW, Moon JY, Lee SK, Lee H, Moon S, Chung SJ, et al. Anti-SARS-CoV-2 Spike protein RBD antibody levels after receiving a second dose of ChAdOx1 nCov-19 (AZD1222) vaccine in healthcare workers: lack of association with age, sex, obesity, and adverse reactions. Front Immunol 2021;12:779212. [CrossRef]
20. Riad A, Sağıroğlu D, Üstün B, Pokorná A, Klugarová J, Attia S, et al. Prevalence and risk factors of CoronaVac side effects: an independent cross-sectional study among healthcare workers in Turkey. J Clin Med 2021; 10(12):2629. [CrossRef]
21. Centers for Disease Control and Prevention (CDC). Pfizer-BioNTech COVID-19 vaccine reactions & adverse events. Available at: https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/reactogenicity.html. Accessed Dec 10, 2022.
22. Romero-Olmedo AJ, Schulz AR, Hochstätter S, Gupta Dd, Virta I, Hirseland H, et al. Induction of robust cellular and humoral immunity against SARS-CoV-2 after a third dose of BNT162b2 vaccine in previously unresponsive older adults. Nat Microbiol 2022;7:195-9. [CrossRef]
23. Palacios-Pedrero MÁ, Jansen JM, Blume C, Blume C, Stanislawski N, Jonczyk R, et al. Signs of immunosenescence correlate with poor outcome of mRNA COVID-19 vaccination in older adults. Nat Aging 2022;2:896-905. [CrossRef]

24. Collier DA, Ferreira IATM, Kotagiri P, Datir RP, Lim EY, Touizer E, et al. Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2. Nature 2021;596:417-22. [CrossRef]
25. Fonseca MHG, de Souza TFG, de Carvalho Araújo FM, de Andrade LOM. Dynamics of antibody response to CoronaVac vaccine. J Med Virol 2022;94:2139-48. [CrossRef]
26. Watanabe M, Balena A, Tuccinardi D, Tozzi R, Risi R, Masi D, et al. Central obesity, smoking habit, and hypertension are associated with lower antibody titres in response to COVID-19 mRNA vaccine. Diabetes Metab Res Rev 2022;38:e3465. [CrossRef]
27. Parthymou A, Habeos EE, Habeos GI, Deligakis A, Livieratos E, Marangos M, et al. Factors associated with anti-SARS-CoV-2 antibody titres 3 months post-vaccination with the second dose of BNT162b2 vaccine: a longitudinal observational cohort study in western Greece. BMJ Open 2022;12:e057084. [CrossRef]
28. Bates JT, Farmer AP, Bierdeman MA, Ederer DR, Carney LS, Montgomery DD, et al. IgG antibody response to the Pfizer BNT162b2 SARS-CoV-2 vaccine in healthcare workers with healthy weight, overweight, and obesity. Vaccines (Basel) 2022;10:512. [CrossRef]
29. Kara Z, Akçin R, Demir AN, Dinç HÖ, Taşkın HE, Kocazeybek B, et al. Antibody response to SARS-CoV-2 vaccines in people with severe obesity. Obes Surg 2022;32:2987-93. [CrossRef]
30. Uysal EB, Gümüş S, Bektöre B, Bozkurt H, Gözalan A. Evaluation of antibody response after COVID-19 vaccination of healthcare workers. J Med Virol 2022;94:1060-6. [CrossRef]
31. Farid E, Herrera-Uribe J, Stevenson NJ. The effect of age, gender and comorbidities upon SARS-CoV-2 spike antibody induction after two doses of Sinopharm vaccine and the effect of a Pfizer/BioNtech booster vaccine. Front Immunol 2022;13:817597. [CrossRef]
32. Amraotkar AR, Bushau-Sprinkle AM, Keith RJ, Hamorsky KT, Palmer KE, Gao H, et al. Pre-existing comorbidities diminish the likelihood of seropositivity after SARS-CoV-2 vaccination. Vaccines 2022;10:1363. [CrossRef]
33. Kwok SL, Cheng SM, Leung JN, Leung K, Lee CK, Peiris JM, et al. Waning antibody levels after COVID-19 vaccination with mRNA Comirnaty and inactivated CoronaVac vaccines in blood donors, Hong Kong, April 2020 to October 2021. Euro Surveill 2022;27:2101197. [CrossRef]
34. Keskin AU, Bolukcu S, Ciragil P, Topkaya AE. SARS-CoV-2 specific antibody responses after third CoronaVac or BNT162b2 vaccine following two-dose CoronaVac vaccine regimen. J Med Virol 2022;94:39-41. [CrossRef]
35. Saltoğlu N, Dinç HÖ, Balkan İİ, Can G, Özbey D, Beytur AN, et al. Heterologous booster COVID-19 vaccination elicited potent immune responses in HCWs. Diagn Microbiol Infect Dis 2022;104:115758. [CrossRef]