Diagnostic Microbiology and Infectious Disease 104 (2022) 115758

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Original Article

Heterologous booster COVID-19 vaccination elicited potent immune responses in HCWs

Neşe Saltoğlu[a], Harika Öykü Dinç[b], İlker İnanç Balkan[a], Günay Can[c], Doğukan Özbey[d], Ayşe Nur Beytur[a], Elif Keskin[d], Beyhan Budak[a], Okan Aydoğan[e], Bilgül Mete[a], Rıdvan Karaali[a], Sevgi Ergin[d], Bekir Kocazeybek[d,*]

[a] Department of Infectious Diseases and Clinical Microbiology, Cerrahpaşa Medical Faculty, Istanbul University-Cerrahpaşa, Istanbul, Turkey
[b] Department of Pharmaceutical Microbiology, Faculty of Pharmacy, Bezmialem Vakıf University Istanbul, Istanbul, Turkey
[c] Department of Public Health, Cerrahpaşa Medical Faculty, Istanbul University-Cerrahpaşa, Istanbul, Turkey
[d] Department of Medical Microbiology, Cerrahpaşa Medical Faculty, Istanbul University-Cerrahpaşa, Istanbul, Turkey
[e] Department of Medical Microbiology, Faculty of Medicine, Istanbul Medipol University, Istanbul, Turkey

ARTICLE INFO

Article history:
Received 15 April 2022
Revised in revised form 14 June 2022
Accepted 23 June 2022
Available online 1 July 2022

Keywords:
COVID-19
Vaccine
BNT162b2
CoronaVac
Antibody

ABSTRACT

The objective of our study was to evaluate the antibody responses of health care workers (HCWs) who were vaccinated with booster dose BNT162b2 6 months after 2 doses of the CoronoVac vaccine. The study included 318 HCWs vaccinated with inactive CoronaVac SARS-CoV-2 vaccine in 2 doses. Anti-spike/RBD IgG levels were measured immediately before and 1 month after the booster dose. In the sixth month after CoronaVac vaccination, the median of antibody levels of 1212.02 AU/ML, while it was 9283 AU/mL after BNT162b2 vaccination. IgG antibody titers of over 1050 AU/mL (which is equivalent to 1:80 dilution in the plaque reduction neutralization test) were detected in HCWs 15.09% and 97.8%, respectively. Our results showed that antibody titers increased 8-fold after the booster dose. We believe that the administration of the mRNA vaccine as a booster dose can provide more effective protection against COVID-19 infection, especially in individuals with risk factors.

1. Introduction

The COVID-19 pandemic has adversely affected health care systems around the globe [Dong et al., 2020,Guan et al., 2020]. Although the effectiveness of vaccines decreases due to diminishing antibody titers over time and escape mechanisms of variants from the immune system, the role of vaccines in the fight against the pandemic cannot be denied [(Planas et al., 2021)]. However, reduced antibody responses are observed over time in individuals who have been vaccinated against COVID-19 [(Widge et al., 2020)]. Due to emerging variants of concern, especially Delta and Omicron, vaccination strategies have changed worldwide. There is significant international interest in heterologous prime-boost COVID-19 vaccination to more robust immune response and longer-term protection despite its immunogenicity and reactogenicity being controversial. In light of changing recommendations regarding the use of the vaccines, several countries are advising that individuals should now receive an alternative prime-boost vaccine as their booster dose, most commonly mRNA vaccines such as the BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine [(Shaw et al., 2021)]. As of November 4, 2021, the Ministry of Health recommended homologous or heterologous prime-boost at least 3 months after the last dose to people who vaccinated 2 doses of inactivated COVID-19 vaccine [(n.d.)]. Despite the real-life data on the immunogenicity of mRNA vaccines as a booster after inactive vaccines being limited, there is an urgent need to determine the humoral responses following heterologous vaccination. This study aimed to evaluate SARS-CoV-2 IgG response before and after heterologous vaccination (CoronaVac/BNT162b2) in health care workers (HCWs).

2. Materials and methods

The study is a prospective, single-center, and observational cohort study. The study cohort comprised 620 HCWs who were vaccinated with 2 doses of inactivated CoronaVac (Sinovac Life Sciences, Beijing, China) and who preferred the BNT162b2 mRNA vaccine as a prime-boost. Peripheral blood samples were obtained shortly before and 28 days after the BNT162b2 vaccination upon their informed consent. Those who's not available for blood sampling on the 28th day of prime-boost vaccination were excluded from the study. The samples were stored in microtubes at −20°C until assayed. On the assay day, serum samples were first brought to +4°C and then to room temperature (+18°C, +25°C) and made ready for use.

* Corresponding author. Tel.: +90 (212) 632 00 31.
E-mail address: bzeybek@iuc.edu.tr (B. Kocazeybek).

https://doi.org/10.1016/j.diagmicrobio.2022.115758
0732-8893/

2.1. Immuno-serological tests

Chemiluminescent microparticle immunoassay (CMIA) method was used to detect SARS-CoV-2 IgG titers (SARS-CoV-2 IgG II Quant antibody test kit; Abbott Laboratories, Chicago, USA), demonstrating the quantity of neutralizing antibodies against the receptor-binding region (RBD) of the spike protein S1 subunit of SARS-CoV-2. The antibody results of the studied sera were evaluated as Arbitrary Unit/mL (AU/mL). The antibody concentrations obtained in AU/mL were multiplied by the correlation coefficient of 0.142 and converted to the "Binding Antibody Unit (BAU/mL)" in the WHO's International Standard for Anti-SARS-CoV- 2 immunoglobulins [(n.d.)]. Accordingly, 50 AU/mL or 7.1 BAU/mL and above concentrations were considered positive. This test has been reported to be 100% compatible with the plaque reduction neutralization test (PRNT), and a concentration of 1050 AU/mL was associated with a 1:80 dilution of PRNT [(n.d.)].

2.2. Statistical analysis

The Statistical Package for Social Sciences (SPSS) software version 21 (IBM Corp.; Armonk, NY) was used to evaluate the data. Qualitative data are presented as numbers and percentages, and quantitative data are presented as median and IQR25-75. χ^2 test and Fisher's exact test were used in the evaluation of qualitative data, Student's *t*-test, Mann Whitney U test, and Kruskal Wallis test were used in the comparison of quantitative data. Spearman analysis was used for the correlation analysis, and the $P < 0.05$ value was considered significant in all analyses.

3. Results

HCWs ($n = 318$) in the study had a mean age of 40.31 ± 11.92 years (range between 21−66) of whom 186 were female (58.5%), and 132 (41.5%) were male. Of the 60 participants with prior history of COVID-19 at least 4 months ago, 23 (45.9%) were male, and 37 (54.1%) were female, with a mean age of 38.1 ± 11.9 years. Of the infection-naïve group, 110 (42.63%) were male, 148 (57.36%) were female, and the mean age was 40.87 ± 11.89. No significant difference was detected between SARS-CoV-2 seropositivity in individuals according to gender, comorbidities, and blood groups ($P > 0.05$). SARS-CoV-2 IgG seropositivity was found to be significantly higher in the group under 40 years of age compared to the group aged 40 years and over ($P = 0.035$). SARS-CoV-2 IgG seropositivity was also significantly higher in participants with a prior history of COVID-19 ($P = 0.035$) (Table 1).

In the 6th month after CoronaVac vaccination, the median antibody level of 1212.02 AU/ML, while it was 9283 AU/mL after BNT162b2 vaccination. When the median antibody titers were compared before and after the third dose, a significantly higher antibody titer was found after the booster dose ($P < 0.0001$) (Table 2). The rate of IgG antibody titers above 1050 AU/mL (equivalent to 1:80 dilution in the plaque reduction neutralization test) before the third dose was 15.09%, while it was 97.8% after the third dose.

The evaluated median antibody titers in terms of gender, age, and BMI, did not differ significantly in before and after the booster dose ($P > 0.05$) (Table 3). A significant difference was detected between median antibody titers in HCWs who have hypothyroidism when evaluated for comorbidities ($P < 0.05$) (Table 3). The median antibody titer was found to be significantly higher in individuals without cardiovascular disease than in patients with cardiovascular disease ($P < 0.05$). Median antibody titers were significantly higher in patients with a history of COVID-19 prior to the booster dose ($P < 0.001$). After the booster dose, there was no significant difference between the median antibody titers in the participants according to the comorbidities ($P > 0.05$) (Table 3).

4. Discussion

In this study, antibody responses were evaluated in HCWs vaccinated with 2 doses of CoronaVac (Sinovac) who were vaccinated with mRNA vaccine (BNT162b2) as a booster dose. We demonstrated booster dose of BNT162b2 mRNA vaccines leads to enhanced humoral immune responses in participants after 2 doses of inactivated vaccine. Due to the stimulation of both humoral and cell-mediated immunity, it is expected that higher antibody titers will be detected in individuals with inactivated vaccines and a history of COVID-19 [(Dinc et al., 2022)]. Heterologous prime-boost has been recommended for may offer immunologic advantages to extend the breadth and longevity of protection provided by the currently available vaccines [(Atmar et al., 2022)].

In Turkey, an optional third dose of the mRNA vaccine was administered to health personnel. In our study, an approximately 8-fold increase in median antibody titers was observed after heterologous booster vaccination with BNT162b2. However, unlike in health care workers who were vaccinated with 2 doses of CoronaVac, similar results were obtained between titers between subjects with and without a history of COVID-19 in this study. We believe that the differences between antibody titers in these studies result from the different vaccines, such as inactivated and mRNA vaccines, and their stimulation mechanism of the immunity [(Dinc et al., 2022)].

As the debate over booster vaccines heats up, concerns are mounting about the duration of vaccine-based immunity. Some studies showed that the emergence of new variants of concern has resulted in the reduced effectiveness of available vaccines against COVID-19 [(Hitchings et al., 2021; Liao et al., 2021; Lim et al., 2021; Souza et al., 2021)]. Similarly, studies from Israel reported that after 2 doses of BNT162b2, vaccine efficacy and antibody titers reduced within 6 months [(Bar-On et al., 2021; Kertes et al., 2021)]. Hence, many countries administered new strategies named mix-and-match. The mix-and-match strategy, using heterologous vaccines in the first, second, third doses, might successfully solve the efficacy struggles. Moreover, this strategy has been associated with higher cellular and humoral immune responses without significantly increasing the adverse reactions.

A study reported from China showed that heterologous boosting with recombinant viral vector vaccine Convidecia (Ad5-nCov) elicited significantly increased mean titers of neutralizing antibody against SARS-CoV-2 than homologous boosting with CoronaVac in participants who had previously vaccinated 1 or 2 doses of CoronaVac. The study was suggested that heterologous boosting with Convidecia following initial vaccination with CoronaVac is safe and more immunogenic than homologous boosting [(Li et al., 2022)]. Pérez-Then et al. [(Pérez-Then et al., 2022)] reported that a CoronaVac prime vaccination of 2 doses followed by a BNT162b2 booster induces elevated virus-specific antibody levels and potent neutralization activity against the ancestral virus (wild-type) and the Delta variant, resembling the titers obtained after 2 doses of mRNA vaccines. In a study reported from Turkey, a decrease in antibody titers was found third month of vaccination with CoronaVac and an increase in antibody titers with both homologous and heterologous booster doses administered 4.5 months later [(Çağlayan et al., 2022)]. In addition, the administration of the BNT162b2 as a heterologous booster had a significant increase in antibody response compared to the administration of a homologous booster with CoronaVac. According to the method we used in the study IgG antibody titers of over 1050 AU/mL which is equivalent to 1:80 dilution in the plaque reduction neutralization test were detected in is quite high (97.8%) after the booster dose. While according to our study showed a significant increase in antibody titers after the heterologous vaccination, data are based on a short follow-up period. EMA and ECDC stated that 6 months after heterologous vaccination might be a decrease in protection against

Table 1
Demographic and clinical data according to SARS-COV-2 IgG seropositivity.

	<50 AU/mL *n* (%)	≥50 AU/mL *n* (%)	*P*
Gender			
Male	10 (7,6)	122 (92,4)	0,207
Female	8 (4,3)	178 (95,7)	
Age			
<40	4 (2,7)	143 (97,3)	0,035*
≥40	14 (8,2)	157 (91,8)	
Body-Mass Index (BMI)			
Normal	9 (6,0)	141 (94,0)	0,939
Overweight	6 (5,2)	109 (94,8)	
Obese	3 (6,5)	43 (93,5)	
Department			
Basic Medical Sciences	0 (0,0)	9 (100,0)	0,844
Internal Medical Sciences	7 (8,3)	77 (91,7)	
Surgical Medical Sciences	3 (7,5)	37 (92,5)	
Administrative Staff	2 (7,1)	26 (92,9)	
Allergy			
Absent	17 (5,6)	285 (94,4)	0,568
Present	1 (7,1)	13 (92,9)	
Autoimmune Disorder			
Absent	17 (5,5)	292 (94,5)	0,398
Present	1 (12,5)	7 (87,5)	
Neurological Disorder			
Absent	18 (5,7)	298 (94,3)	-
Present	0 (0)	0 (0)	
Malignity			
Absent	17 (5,4)	298 (94,6)	0,111
Present	1 (50)	1 (50)	
Diabetes Mellitus (DM)			
Absent	17 (5,6)	286 (94,4)	0,567
Present	1 (7,1)	13 (92,9)	
Hypertension (HT)			
Absent	17 (5,7)	279 (94,3)	1,000
Present	1 (4,8)	20 (95,2)	
Hypothyroidism			
Absent	18 (5,9)	286 (94,1)	1,000 f
Present	0 (0,0)	13 (100,0)	
Chronic Cardiovascular Disease			
Absent	18 (5,8)	293 (94,2)	1,000 f
Present	0 (0,0)	5 (100,0)	
Chronic Lung Disease			
Absent	18 (5,7)	299 (94,3)	-
Present	0 (0,0)	0 (0,0)	
Prior History of COVID-19			
Absent	18 (7,0)	240 (93,0)	0,035*
Present	0 (0,0)	60 (100,0)	
Blood Type			
O (Neg or Pos)	5 (5,6)	85 (94,4)	0,949
A (Neg or Pos)	9 (6,5)	129 (93,5)	
B (Neg or Pos)	2 (3,9)	49 (96,1)	
AB (Neg or Pos)	2 (6,7)	28 (93,3)	

symptomatic infection [(n.d.)]. Concordantly, an extended follow-up period may offer a new perspective on booster dose intervals.

Real-life data regarding SARS-CoV-2 IgG antibodies following inactivated COVID-19 vaccine are limited. IgG positivity after 2 doses of inactivated vaccination is reported to be between 77.3% and 99.4% [Dinc et al., 2022, Keskin et al., 2022; Seyahi et al., 2021; Tanriover et al., 2021]. Especially, the long-term protection of the inactivated vaccine is uncertain. In this study, antibody titers were assessed sixth month of 1 dose of mRNA booster in those vaccinated with 2 doses of CoronaVac. This study presents real-life data regarding antibody levels changes with heterologous mRNA booster 6 months after 2 doses of the inactivated CoronaVac vaccine. We believe that the study will make a significant contribution to the literature.

In previous studies reported from our hospital, antibody titers were decreased third month after administering 2 doses of CoronaVac compared to the first month [(Balkan et al., 2022)]. We only included HCWs who preferred the mRNA-BNT162b2 vaccine over CoronaVac as a booster dose, and this may have caused bias. In

Table 2
SARS-CoV-2 IgG median levels in blood samples taken before and after the booster dose from HCWs who participated in the study.

	Before booster dose of BNT162b2 Median (%25−75 IQR)	After booster dose of BNT162b2 Median (%25−75 IQR)	*P*
SARS-CoV-2 IgG, AU/mL	1212.02 (123.5−556.5)	9283.4 (6196.9−14264.9)	0,000*

Table 3
Evaluation of antibody titers in HCWs according to demographic and clinical data before and after the booster dose.

	Before booster dose of BNT162b2 *Median (IQR 25%–IQR 75%)*	*P*	After booster dose of BNT162b2 *Median (IQR 25%–IQR 75%)*	*P*
Gender				
Male	210,20 (117,30–530,90)	0,473	9419,70 (5681,90–14264,90)	0,727
Female	219,05 (127,95–615,575)		9275,05 (6488,45–14134,60)	
Age				
<40	228,00 (129,90–481,30)	0,610	9165,60 (6491,40–14067,00)	0,883
≥40	207,50 (121,90–695,00)		9551,00 (5502,20–14385,00)	
Body Mass Index (BMI)				
Normal	207,00 (122,50–485,20)	0,242	9129,65 (6007,75–14324,55)	0,606
Overweight	247,00 (134,30–643,10)		9235,70 (6504,50–14078,00)	
Obese	171,40 (114,95–348,375)		11055,55 (6505,30–16010,58)	
Autoimmune Disorder				
Absent	216,90 (123,35–542,45)	0,645	9333,70 (6262,45–14284,65)	0,815
Present	435,60 (124,73–1583,53		8445,00 (6064,55–12433,40)	
Malignity				
Absent	221,20 (123,80–556,50)	-	9333,70 (6298,90–14264,90)	-
Present	-		-	
Allergy				
Absent	213,55 (123,08–532,83)	0,568	9376,70 (6325,25–14274,78)	0,267
Present	304,85 (138,05–800,68)		7095,30 (4271,60–13310,50)	
Diabetes Mellitus				
Absent	221,20 (123,20–546,30)	0,658	9329,10 (6298,90–14236,80)	0,860
Present	165,50 (121,95–642,93)		9311,25 (5732,18–15500,80)	
Hypertension				
Absent	227,50 (123,35–571,43)	0,152	9331,40 (6302,98–14295,53)	0,612
Present	146,10 (118,90–325,15)		8828,70 (4507,90–13397,00)	
Hypothyroidism				
Absent	208,65 (122,63–552,30)	0,035*	9376,70 (6206,05–14257,88)	0,938
Present	442,40 (191,95–1585,20)		8739,20 (6595,55–15228,20)	
Chronic Cardiovascular Disease				
Absent	224,70 (124,10–556,50)	0,018*	9329,10 (6298,90–14264,90)	0,389
Present	110,80 (77,25–130,75)		9093,70 (4582,20–11087,75)	
Other Conditions				
Absent	226,15 (125,75–554,85)	0,282	9251,20 (6325,25–14274,78)	0,894
Present	189,30 (94,25–603,75)		11254,30 (5447,80–14646,35)	
Prior History of COVID-19				
Absent	184,60 (115,45–354,45)	<0,001	9860,90 (6343,90–14975,80)	0,138
Present	1162,80 (325,10–2713,95)*		8783,95 (5683,50–11703,80)	

addition, although the humoral immune responses were assessed with the SARS-CoV-II IgG test, which is 100% compatible with PRNT, the specific T-cell responses could not be assessed.

This study is crucial in that showed a parallel increase in antibody titers when an mRNA booster is administered 6 months after the administration of 2 doses of CoronaVac in HCWs with or without a prior history of COVID-19. Our results showed that the heterologous prime-boost regimen was safe and significantly immunogenic. We believe that the administration of the mRNA vaccine as a booster dose can provide more effective protection against COVID-19 infection, especially in individuals with risk factors.

Ethics Approval

This study was approved by the Republic of Turkey Ministry of Health General Directorate of Health Services Scientific Research Studies Commission (Date: September 18, 2021), Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Scientific Research and Evaluation Commission (Date: February 17, 2022, and Number: 314719), and Bezmialem Vakıf University Clinical Research Ethics Committee approval (Date: April 5, 2022).

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding

The authors declare that this study has been supported by IU-Cerrahpaşa Scientific Research Projects Unit (Project ID: 35900).

Author Contributions

All authors contributed to the study conception and design. Material and method preparation were performed by N.S, İ.İ.B., G.C., S.E., B. K. Data collection and analysis were performed by H.Ö.D., D.Ö., B.M., R.K., A.N.B, E.K., O.A. B.B. Statistical analysis and interpretation were performed by G.C. The first draft of the manuscript was written by N. S. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors report no conflicts of interest relevant to this article.

References

[1] Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real-time. Lancet Infect Dis 2020;20:533–4.
[2] Guan W, Ni ZY, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. New Engl J Med 2020;382:1708–20. doi: 10.1056/NEJMoa2002032.
[3] Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. Nature 2021;596:276–80. doi: 10.1038/s41586-021-03777-9.

[4] Widge AT, Rouphael NG, Jackson LA, Anderson EJ, Roberts PC, Makhene M, et al. Durability of responses after SARS-CoV-2 mRNA-1273 vaccination. N Engl J Med 2020;384:80–2. doi: 10.1056/NEJMc2032195.
[5] Shaw RH, Stuart A, Greenland M, Liu X, Van-Tam JSN, Snape MD. Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data. Lancet 2021;397:2043–6.
[6] Republic of Turkey Ministry of Health: COVID-19 Vaccinatıon Information Platform. Available at: https://covid19asi.saglik.gov.tr/EN-80435/34when-should-i-get-my-third-dose-of-covid-19-vaccine.html (Accessed April 6, 2022).
[7] World Health Organization. Establishment of the WHO international standard and reference panel for anti-SARS-CoV-2 antibody. WHO/BS/2020.2403. 2020. Available at: https://www.who.int/publications/m/item/WHO-BS-2020.2403 (Accessed April 6, 2022).
[8] Abbott SARS-CoV-2 Immunoassays. Available at: https://www.corelaboratory.abbott/int/en/offerings/segments/infectious-disease/sars-cov-2 (Accessed April 6, 2022).
[9] Dinc HO, Saltoglu N, Can G, Balkan II, Budak B, Ozbey D, et al. Inactive SARS-CoV-2 vaccine generates high antibody responses in health care workers with and without prior infection. Vaccine 2022;40:52–8. doi: 10.1016/j.vaccine.2021.11.051.
[10] Atmar RL, Lyke KE, Deming ME, Jackson LA, Branche AR, El Sahly HM, et al. Homologous and heterologous Covid-19 booster vaccinations. New Engl J Med 2022. doi: 10.1056/NEJMoa2116414.
[11] Liao Y, Zhang Y, Zhao H, Pu J, Zhao Z, Li D, et al. Intensified antibody response elicited by boost suggests immune memory in individuals administered two doses of SARS-CoV-2 inactivated vaccine. Emerg Microbes Infect 2021;10:1112–5. doi: 10.1080/22221751.2021.1937328.
[12] Lim WW, Mak L, Leung GM, Cowling BJ, Peiris M. Comparative immunogenicity of mRNA and inactivated vaccines against COVID-19. Lancet Microbe 2021;2:e423. doi: 10.1016/S2666-5247(21)00177-4.
[13] Souza WM, Amorim MR, Sesti-Costa R, Coimbra LD, Brunetti NS, Toledo-Teixeira DA, et al. Neutralisation of SARS-CoV-2 lineage P.1 by antibodies elicited through natural SARS-CoV-2 infection or vaccination with an inactivated SARS-CoV-2 vaccine: an immunological study. Lancet Microbe 2021;2:e527–35. doi: 10.1016/S2666-5247(21)00129-4.
[14] Hitchings MDT, Ranzani OT, Torres MSS, Barbosa de Oliveira S, Almiron M, Said R, et al. Effectiveness of CoronaVac among health care workers in the setting of high SARS-CoV-2 Gamma variant transmission in Manaus, Brazil: A test-negative case-control study. Lancet Reg Health Am 2021;1:100025. doi: 10.1016/j.lana.2021.100025.
[15] Kertes J, Baruch Gez S, Saciuk Y, Supino-Rosin L, Stein NS, Mizrahi-Reuveni M, et al. Effectiveness of the mRNA BNT162b2 vaccine six months after vaccination: findings from a large Israeli HMO. Emerg Infect Dis 2021;28:338–46. doi: 10.1101/2021.09.01.21262957.
[16] Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Alroy-Preis S, et al. Protection of BNT162b2 vaccine booster against Covid-19 in Israel. N Engl J Med 2021;385:1393–400. doi: 10.1056/NEJMoa2115926.
[17] Li J, Hou L, Guo X, Jin P, Wu S, Zhu J, et al. Heterologous AD5-nCOV plus CoronaVac versus homologous CoronaVac vaccination: a randomized phase 4 trial. Nat Med 2022. doi: 10.1038/s41591-021-01677-z.
[18] Pérez-Then E, Lucas C, Monteiro VS, Miric M, Brache V, Cochon L, et al. Neutralizing antibodies against the SARS-CoV-2 Delta and Omicron variants following heterologous CoronaVac plus BNT162b2 booster vaccination. Nat Med 2022. doi: 10.1038/s41591-022-01705-6.
[19] Çağlayan D, Süner AF, Şiyve N, Güzel I, Irmak Ç, Işik E, et al. An analysis of antibody response following the second dose of CoronaVac and humoral response after booster dose with BNT162b2 or CoronaVac among health care workers in Turkey. J Med Virol 2022 Epub ahead of print. doi: 10.1002/jmv.27620.
[20] EMA. EMA and ECDC recommendations on heterologous vaccination courses against COVID-19: 'mix-and-match' approach can be used for both initial courses and boosters. Available at: https://www.ema.europa.eu/en/news/ema-ecdc-recommendations-heterologous-vaccination-courses-against-covid-19-mix-match-approach-can-be (Accessed April 6, 2022).
[21] 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, randomized, placebo-controlled, phase 3 trial in Turkey. Lancet 2021;398:213–22.
[22] Keskin AU, Bolukcu S, Ciragil P, Eren Topkaya A. SARS-CoV-2 specific antibody responses after the third CoronaVac or BNT162b2 vaccine following a two-dose CoronaVac vaccine regimen. J Med Virol 2022;94:39–41.
[23] Seyahi E, Bakhdiyarli G, Oztas M, Kuskucu MA, Tok Y, Sut N, et al. Antibody response to inactivated COVID-19 vaccine (CoronaVac) in immune-mediated diseases: a controlled study among hospital workers and elderly. Rheumatol Int 2021;41:1429–40.
[24] Balkan II, Dinc HO, Can G, Karaali R, Ozbey D, Caglar B, et al. Waning immunity to inactive SARS-CoV-2 vaccine in health care workers: booster required. Ir J Med Sci 2022;28:1–7. doi: 10.1007/s11845-022-02984-1.