Original article

Adverse reactions and production of neutralizing anti-SARS-CoV-2 antibodies after ChAdOx1 COVID-19 vaccination: A cross-sectional study in a single center

Yeon Jeong Jeong [a,b], Youn Jeong Kim [a,b,*,1], Si Hyun Kim [a,b], Jaeeun Yoo [a,c], Jaewoong Lee [a,c], Seungok Lee [a,c,**,2], Sang Il Kim [a,d]

[a] Division of Infectious Diseases, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea
[b] Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, South Korea
[c] Department of Laboraotry Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea
[d] Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea

A B S T R A C T

Adverse events following vaccination with the ChAdOx1 COVID-19 vaccine may be associated with the titer of neutralizing antibodies (NAbs) against SARS-CoV-2. In this cross-sectional study, a total of 82 HCWs who received the ChAdOx1 COVID-19 vaccine and did not have previous COVID-19 history were enrolled during March 2021. Blood samples were collected from HCWs 3 weeks after the first and second doses of vaccine, and NAbs were estimated using two types of commercially available kits, the cPass™ SARS-CoV-2 NAbs Kit (Genscript Biotech, Piscataway, NJ, USA) and R-FIND SARS-CoV-2 NAbs ELISA (SG Medical, Seoul, Korea). Median percent signal inhibition of NAbs was significantly higher after the second than after the first dose of vaccine, as determined using both the Genscript (median 43.1[IQR 71.2] vs. 93.6[83.1], p = 0.004) and R-FIND (53.2[82.6] vs. 76.8 [90.6], p = 0.03) kits. The percent signal inhibition of NAbs after the second dose of vaccine was higher in HCWs with than without systemic adverse events after the second dose, as determined using both the Genscript (p = 0.03) and R-FIND (p = 0.07) kits. The two doses of the ChAdOx1 vaccine induced high value of NAbs 3 weeks after vaccination. Immune responses were stronger in HCWs with than without adverse reactions after the second dose of ChAdOx1 vaccine.

© 2022 The Author(s). Published by Elsevier Ltd on behalf of King Saud Bin Abdulaziz University for Health Sciences.
CC_BY_NC_ND_4.0

Introduction

Since the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in China at the end of 2019, the virus has spread worldwide. As of July 21, 2021, there have been over 190 million confirmed cases of COVID-19, including over 4 million deaths[1]. Several potential vaccines against COVID-19 for hope to decrease mortality and prevent infection risk have been developed. In Korea, the COVID-19 vaccination campaign using BNT162b2 COVID-19 vaccine (Pfizer–BioNTech, New York, USA) and ChAdOx1 COVID-19 vaccine (Astrazeneca, Cambridge, U), has been administrated for high risk groups including health care workers (HCWs) and older patients in nursing hospitals since February 26, 2021.

Various serologic assays have been developed to test for anti-SARS-CoV-2 antibodies in infected patients and in individuals administered with COVID-19 vaccines. However, the interpretation of serologic results and their clinical significance remain uncertain. Neutralizing antibodies (NAbs) are those that block the virus, making them crucial for recovery from infection and protection against viral disease. Measuring the concentration of NAbs is a standard method of evaluating immune responses to a vaccine [2]. Antibody production can be affected by various factors, including immune disorders, treatment with immunosuppressants, and age [3]. Although adverse reactions following vaccination have been

* Correspondence to: Division of Infectious Diseases, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 56, Donsu-Ro, Bupyung-Gu, Incheon 21431, South Korea.
** Correspondence to: Department of Laboratory Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 56 Dongsu-ro, Bupyeong-gu, Incheon 21431, South Korea.
E-mail addresses: muze1004@catholic.ac.kr (Y.J. Kim), lsok@catholic.ac.kr (S. Lee).
[1] https://orcid.org/0000-0001-5870-1801
[2] https://orcid.org/0000-0003-4538-8427

reported to potentially indicate stronger immune responses [4], it is unclear whether common adverse reactions after COVID-19 vaccination correlate with neutralizing antibody production.

Surrogate virus neutralization tests (sVNTs) have become commercially available. Several studies have shown that the results of sVNTs correlate with those of both conventional virus neutralization tests (cVNTs) and pseudovirus-based neutralization tests (pVNTs), indicating that sVNTs are particularly useful for evaluating antibody production in response to vaccines [5,6].

To determine the difference of levels between two types of commercially available sVNT that measure NAbs against SARS-CoV-2, the present study assessed the levels of NAbs, as determined by both methods, in HCWs administrated ChAdOx1 COVID-19 vaccine. This study also analyzed whether levels of NAbs were associated with adverse events following vaccination.

Materials and methods

Study population

A cross-sectional study in a single center was conducted during the first months of the vaccination roll-out (March 2021). We enrolled HCWs at Incheon St. Mary's Hospital who received the ChAdOx1 SARS-CoV-2 vaccine and did not have a previous history of COVID-19 infection. Participants were excluded if they (1) did not provide informed consents; (2) had history for positive SARS-CoV2 PCR result before vaccination or for COVID-19 infection or (3) had COVID-19 like symptoms at enrollment. Blood samples were collected twice from each participant, the first 21 ± 2 days after the first dose of vaccine and the second 21 ± 2 days after the second dose of vaccine. Baseline characteristics, adverse events, and use of antipyretics were determined through questionnaires. The survey form was distributed to eligible participants at the day of the vaccination. A designated researcher explained to them about the survey form. All participants were asked about solicited adverse events including eight systemic adverse events and five local adverse events, occurred for 7 days after each injection. The data from survey was collected by spontaneous report from the participants and collected by the researcher on the day 8 after each infection.

Serologic assays

All plasma samples were stored at − 80 °C before the assays. Antibody concentrations were determined using two commercially available sVNTs: commercial cPass™ SARS-CoV-2 Neutralization Antibody Detection Kits (Genscript Biotech, Piscataway, NJ, USA) and a newly developed R-FIND SARS-CoV-2 Neutralizing Antibody ELISA (SG Medical, Seoul, Korea). The manufacturer-reported sensitivity and specificity of cPass™ and R-FIND were 93.80% and 99.40%, and 98.2% and 99.4%, respectively. Each test was performed according to the manufacturer's instructions. Each assay is a competitive ELISA that detects circulating NAbs against SARS-CoV-2 by blocking the interaction between the receptor binding domain (RBD) of the viral spike glycoprotein and the host cell surface receptor ACE2. Percent inhibition was calculated as (1 – optical density (OD) of the sample / OD of the negative control) x 100%. Signal inhibition ≥ 30% on both tests was considered positive for the presence of SARS-CoV-2 NAbs.

The percent inhibition on sVNTs was reported to correlate with cVNT titers as previous reports[5,6].

Ethics

The study was approved by the ethics committee of Incheon St. Mary's Hospital (study number: OC20TIS10104) and conformed to the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all study participants who voluntarily agreed to participate.

Statistical analysis

Continuous data were expressed as the median (interquartile range [IQR]) and compared using independent t-test or one-way analysis of variance (ANOVA). Categorical data were expressed as percentages and compared using Chi-squared tests. All statistical analyses were performed using SPSS (version 14.0; SPSS Inc., Chicago, IL, USA), with p-values < 0.05 considered statistically significant.

Results

This study enrolled 82 HCWs, of median age 41.5 years (range, 23–64 years). The 82 participants included 66 (80.5%) women and 16 (19.5%) men, and included 11 (13.4%) physicians, 41 (50.0%) nurses, 22 (26.8%) administrative assistants, seven nurse's aides (8.5%), and one (1.2%) radiology technician.

Using R-FIND kits, positive NAbs were found after the first and second vaccine doses in 65 (79.3%) and 78 (96.3%) HCWs (p = 0.58). Using Genscript kits, however, positive NAbs were found in 62 (75.6%) participants after the first dose and in 80 (97.6%) after the second dose (p = 0.01). Median percent signal inhibition of NAbs was significantly higher after the second than after the first dose using both Genscript (43.1 [71.2] vs. 93.6 [83.1], p = 0.004) and R-FIND (53.2 [82.6] vs. 76.8 [90.6], p = 0.03) kits. The percent signal inhibitions of NAbs measured by the Genscript and R-FIND kits showed strong positive correlations after both the first (r 0.89, p < 0.0001) and second (r 0.90, p < 0.0001) doses of vaccine.

Table 1 showed the percent signal inhibition of NAbs measured by Genscript and R-FIND kits according to baseline characteristics of the study participants. Gender and job category did not differ significantly in both tests. After the first dose of vaccine, the median percent signal inhibition, as measured by the Genscript and R-FIND kits in participants aged 20–30 years, was 55.5% (IQR, 58.9) and 62.3% (IQR, 50.1), respectively. In participants aged > 60 years, the median percent signal inhibition, as measured by the Genscript and R-FIND kits after the first dose of vaccine, was 37.9% (IQR, 0.81) and 51.3% (IQR, 3.6), respectively. These findings indicated that NAbs tended to be higher in younger than in older HCWs, although these differences were not statistically significant (Genscript, p = 0.4; R-FIND, p = 0.8).

Systemic adverse events were reported more frequently after the first (n = 57, 69.5%) than after the second (n = 41, 50%) dose of vaccine (Table 2). The most commonly reported systemic adverse reaction after the first dose was myalgia (n = 48, 58.5%), followed by fatigue (n = 45, 54.8%), headache (n = 35, 42.7%), fever (n = 32, 39.0%) and chills (n = 32, 39.0%). After the second dose, fatigue (n = 29, 35.4%)

Table 1
Percent signal inhibition of NAbs in HCWs measured by two sVNT methods as a function of baseline characteristics.

Variables		After first dose				After second dose			
		GeneScript, median (IQR)	P value	SG, Median (IQR)	P value	GeneScript, median (IQR)	P value	SG, Median (IQR)	P value
Total		43.1 (71.2)	–	53.2 (82.6)	–	93.6(83.1)	–	76.8(90.6)	–
Gender	Male, n = 16	41.4 (47.8)	0.45	53.4 (67.6)	0.82	93.6(51.6)	0.80	79.4(62.3)	0.87
	Female, n = 66	45.5 (71.2)		52.1(82.6)		93.4(83.1)		75.7(88.4)	
Ages yrs	20–30, n = 12	55.5 (58.9)	0.4	62.3(50.1)	0.8	92.7(27.4)	0.3	71.2(42.1)	0.5
	31–40, n = 25	35.4(61.4)		44.4(73.2)		94.1(51.5)		78.6(51.6)	
	41–50,n = 26	41.8 (53.8)		54.6(78.9)		93.6(52.8)		78.9(67.2)	
	51–60,n = 17	43.0(42.6)		53.6(60.3)		93.5(82.7)		69.8(87.2)	
	> 60, n = 2	37.9(0.81)		51.3(3.6)		94.8(4.0)		83.1(2.7)	
Job	Physicians, n = 11	35.3(37.8)	0.3	44.3(42.1)	0.21	92.8(50.9)	0.70	73.7(60.1)	0.92
	Nurses,n = 41	48.5(66.8)		62.9(73.2)		94.1(70.7)		77.1(88.2)	
	Nurses' aides, n = 7	60.9(62.9)		54.6(82.6)		94.6(83.4)		70.4(74.1)	
	Administrators, n = 22	40.3(48.1)		52.4(66.5)		92.7(44.7)		76.9(67.2)	
	Radiologist, n = 1	58.5(-)		75.3(-)		90.4(-)		78.6(-)	

NAbs; neutralizing antibodies, sVNT; surrogate virus neutralization tests

Table 2
Percentage of adverse effects.

	After the first dose (n = 82), n (%)	After the second dose (n = 82), n (%)	P value
Systemic AE*	57 (69.5%)	41 (50%)	0.009
Fever	31 (37.8%)	19 (23.2%)	0.03
Chills	32 (39.0%)	8 (9.8%)	0.0001
Myalgia	48 (58.5%)	26 (31.7%)	0.001
Headache	35 (42.7%)	19 (23.2%)	0.007
Fatigue	45 (54.8%)	29 (35.4%)	0.014
Nausea	11 (13.4%)	2 (2.5%)	0.01
Diarrhea	3 (3.7%)	0 (0%)	-
Dyspnea	3 (3.7%)	0 (0%)	-
Local AE*	50 (60.9%)	54 (65.8%)	0.56
Pain	47 (57.3%)	51 (62.2%)	0.54
Tenderness	44 (53.7%)	44 (53.7%)	-
Erythema	11 (13.4%)	6 (7.3%)	0.27
Induration	7 (8.5%)	2 (2.4%)	0.18
Itching	7 (8.5%)	9 (11.0%)	0.75
Use of antipyretics Acetaminophen	48 (58.5%)	18 (21.9%)	0.0001

* Participants were able to choose multiple symptoms.

was the most frequently reported systemic adverse event, followed by myalgia (n = 26, 31.7%). Local adverse events were reported more frequently after the second (n = 50, 57.3%) than after the first (n = 54, 65.8%) dose of vaccine, with pain at the injection site being the most frequent local adverse event, reported by 57.3% and 65.8% participants after the first and second doses, respectively. Use of acetaminophen was reported by 58.5% of participants after the first dose and by 21.9% after the second dose of vaccine. No severe adverse reactions were reported.

Fig. 1 showed the percent signal inhibition of NAbs measured by the Genscript and R-FIND kits as a function of adverse events. When measured with the Genscript kits, NAbs after the second dose of vaccine were significantly higher in HCWs with than without systemic adverse events (94.9 [70.5] vs. 90.5 [83.1], p = 0.03), and were higher in HCWs with than without local adverse events, although the latter difference was not statistically significant (93.9 [70.8] vs. 91.3 [82.6], p = 0.29). When measured with the R-FIND kits, the

levels of NAbs after the second dose of vaccine were higher in HCWs with than without systemic adverse events (79.4 [88.4] vs. 71.7 [77.3], p = 0.06) and with than without local adverse events (78.5 [90.6] vs. 74.7 [73.8], p = 0.07), although these differences were not statistically significant. After the first dose, the use of acetaminophen was not associated with the percent signal inhibition of NAbs using both the Genscript (47.1 [71.2] vs. 39.7 [48.2], p = 0.13) and R-FIND (57.6 [74.0] vs. 49.0 [77.1], p = 0.34). NAb titers were higher in HCWs who did than in those who did not take acetaminophen after the second dose of vaccine, as determined using the Genscript (94.8 [29.1] vs. 92.4 [83.1], p = 0.01) and R-FIND (80.5 [42.9], vs. 75.7 [88.3], p = 0.08) kits.

Discussion

The present study showed that the levels of NAbs, as measured using Genscript and R-FIND kits, were markedly higher after the second than after the first dose of ChAdOx1 COVID-19 vaccine. In addition, HCWs with systemic adverse reactions after the second dose had a stronger immune response than participants without adverse reactions. Generally, stronger immune responses after vaccination have been associated with higher rates of side effects, such as aches and fever. The present study showed similar results, in that levels of NAbs after ChAdOx1 COVID-19 vaccination were positively associated with adverse reactions. Adverse reactions after vaccination are likely to relate the activation of immune and inflammatory pathways, and they may be associated with the antibody levels after vaccination if adverse reactions are considered to process of vaccination.

The national government of Korea introduced an immunization program against COVID-19 in April 2021, using both the BNT162b2 and ChAdOx1 COVID-19 vaccines. Vaccination was prioritized, although many people tended to avoid vaccination with ChAdOx1 because of its association with frequent adverse reactions and rare severe adverse events such as vaccine induced thrombocytopenic thrombosis [7]. The present study showed that 76.8% and 74.4% of HCWs experienced ≥ 1 local or systemic adverse event after the first and second doses of vaccine, respectively, but none experienced a life-threatening adverse event. ChAdOx1 vaccine has an acceptable
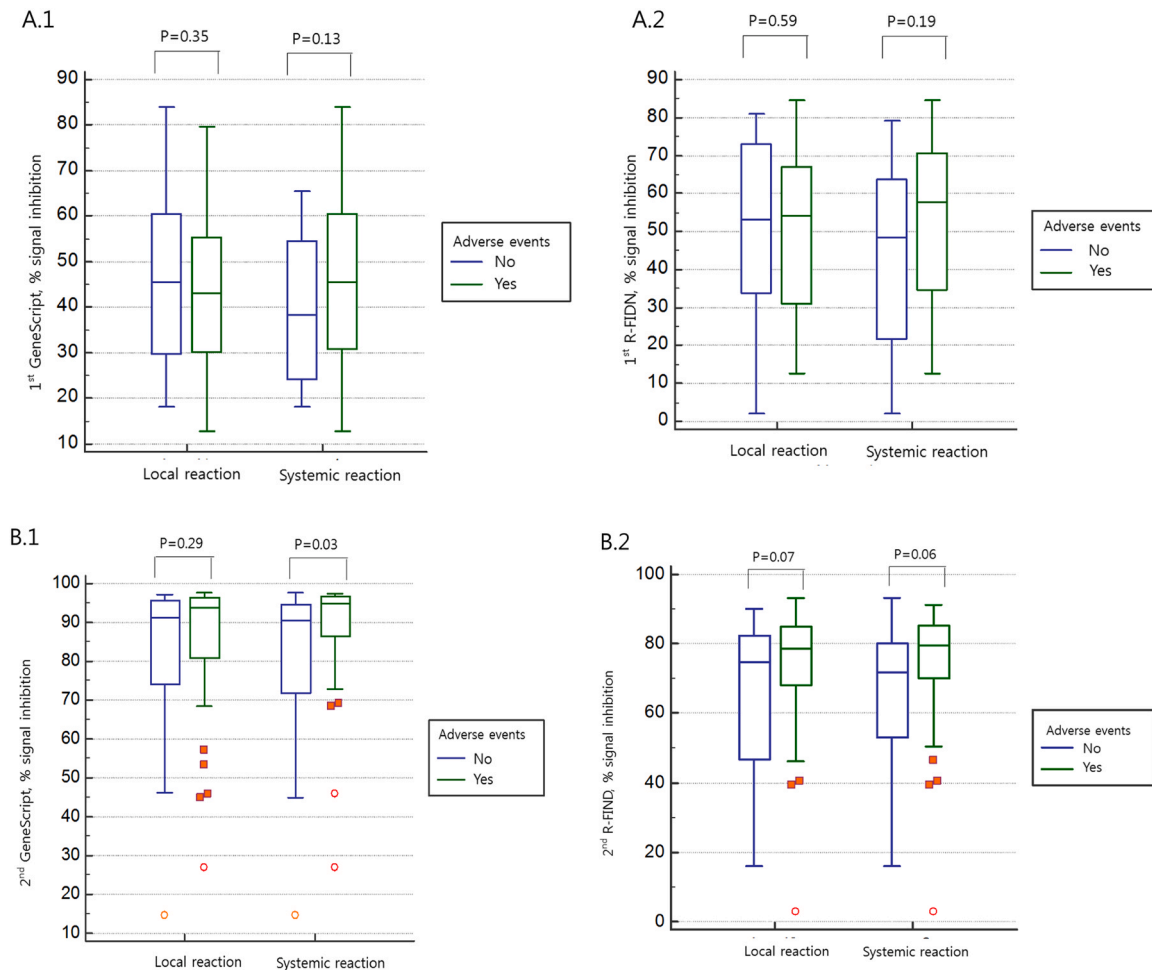
Fig. 1. Relationship between percent signal inhibition of NAbs and the occurrence of adverse events. A. NAbs and adverse reaction after the first dose of vaccine. (1) NAbs and adverse reaction after the first dose of vaccine using Genscript. (2) NAbs and adverse reaction after the first dose of vaccine using R-FIND kits. B. NAbs and adverse reaction after the second dose of vaccine. (1) NAbs and adverse reaction after the second dose of vaccine using Genscript. (2) NAbs and adverse reaction after the second dose of vaccine using R-FIND kits.

safety in our study despite the small number of HCWs. Similar to other studies of the efficacy of the ChAdOx1 vaccine, NAbs were higher after two doses than after one dose [8]. Three weeks after the second dose, 98.8% (80/81) of participants, as tested using commercial Genscript kits, and 97.5% (79/81) as tested with SG kits, had protective levels of NAbs, consistent with previous findings [8,9]. Our study revealed that two doses of ChAdOx1 produced enough level of neutralizing antibody response, although the persistence of NAbs after vaccination and their ability to protect against COVID-19 variants have not been determined.

Some vaccines are less effective in elderly individuals because of age-related immunosenescence, which involve functional changes in the immune system and advances in natural age [10–13]. Few studies have assessed the efficacy of COVID-19 vaccines in elderly people. A comparison of participants aged 16–55 and > 55 years administered the BNT162b2 vaccine found that antibody levels were lower in the older age group [14]. Another study found that factors associated with lower antibody in vaccinated persons included male, advanced age, current use of steroids, and longer length of time from vaccination [15]. Our data showed that NAbs tended to be lower in older HCWs after ChAdOx1 vaccination, but that the difference was not statistically significant. Our study did not include a sufficient number of older people, indicating a need for additional studies assessing the efficacy or duration of protection after COVID-19 vaccination among elderly participants.

The present study has several limitations. First, sample sizes were small. Second, although HCWs without a history of COVID-19 were enrolled, we did not perform SARS-CoV2 PCR or antibody tests before vaccination. Nevertheless, this study focused on HCWs in a hospital setting. In general, most HCWs are tested for COVID-19 more frequently than the general population and are closely monitored for COVID-19-like symptoms throughout the pandemic. In addition, there has been no outbreak of COVID-19 in our hospital to date.

Declaration of Competing Interest

The authors declare no conflict of interest.

References

[1] World Health Organization WHO Coronavirus (COVID-19) Dashboard, [(accessed on 13 January 2021)]; Available online: https://covid19.who.int/.

[2] Zinkernagel RM. On natural and artificial vaccinations. Annu Rev Immunol 2003;21:515–46.

[3] Goel RR, Apostolidis SA, Painter MM, Mathew D, Pattekar A, Kuthuru O, et al. Longitudinal analysis reveals distinct antibody and memory B cell responses in SARS-CoV2 naive and recovered individuals following mRNA vaccination. medRxiv 2021. https://doi.org/10.1101/2021.03.03.21252872. Preprint.

[4] Zhuang CL, Lin ZJ, Bi ZF, Qiu LX, Hu FF, Liu XH, et al. Inflammation-related adverse reactions following vaccination potentially indicate a stronger immune response. Emerg Microbes Infect 2021;10(1):365–75.

[5] Tan CW, Chia WN, Qin X, Liu P, Chen MI, Tiu C, 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):1073–8.

[6] Marien J, Michiels J, Heyndrickx L, Nkuba-Ndaye A, Ceulemans A, Bartholomeeusen K, et al. Evaluation of a surrogate virus neutralization test for high-throughput serosurveillance of SARS-CoV-2. J Virol Methods 2021;297:114228.

[7] Tobaiqy M, Elkout H, MacLure K. Analysis of thrombotic adverse reactions of COVID-19 astrazeneca vaccine reported to eudravigilance database. Vaccines 2021;9(4).

[8] Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397(10269):99–111.

[9] Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet 2020;396(10249):467–78.

[10] van Dijk-Hard I, Soderstrom I, Feld S, Holmberg D, Lundkvist I. Age-related impaired affinity maturation and differential D-JH gene usage in human VH6-expressing B lymphocytes from healthy individuals. Eur J Immunol 1997;27(6):1381–6.

[11] Allen JC, Toapanta FR, Chen W, Tennant SM. Understanding immunosenescence and its impact on vaccination of older adults. Vaccine 2020;38(52):8264–72.

[12] Goronzy JJ, Weyand CM. Understanding immunosenescence to improve responses to vaccines. Nat Immunol 2013;14(5):428–36.

[13] McElhaney JE, Xie D, Hager WD, Barry MB, Wang Y, Kleppinger A, et al. T cell responses are better correlates of vaccine protection in the elderly. J Immunol 2006;176(10):6333–9.

[14] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020;383(27):2603–15.

[15] Nace DA, Kip KE, Mellors JW, Peck Palmer OM, Shurin MR, Mulvey K, et al. Antibody responses after mRNA-Based COVID-19 vaccination in residential older adults: implications for reopening. J Am Med Dir Assoc 2021;22(8):1593–8.