Received: 9 July 2021 | Revised: 1 September 2021 | Accepted: 2 September 2021

DOI: 10.1002/jmv.27318

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Should a third booster dose be scheduled after two doses of CoronaVac? A single-center experience

Metin Yigit[1] | Aslinur Ozkaya-Parlakay[2] | Yasemin Cosgun[3] | Yunus E. Ince[1] | Yunus E. Bulut[4] | Emrah Senel[5]

[1]Department of Pediatrics, Ankara City Hospital, Ankara, Turkey

[2]Division of Pediatric Infectious Disease, Department of Pediatrics, Ankara City Hospital, Yildirim Beyazit University, Ankara, Turkey

[3]Microbiology Reference Laboratories Department, National Arboviruses and Viral Zoonotic Diseases Laboratory, Public Health General Directorate of Turkey, Ankara, Turkey

[4]Public Health Directorate of Ankara, Ankara, Turkey

[5]Department of Pediatric Surgery, Ankara City Hospital, Yildirim Beyazit University, Ankara, Turkey

Correspondence

Metin Yigit, Department of Pediatrics, Ankara City Hospital, 06800 Bilkent, Ankara.
Email: metinyigit.md@gmail.com

Abstract

In the 10th month of the pandemic, coronavirus disease 2019 (COVID-19) vaccination was given first to healthcare workers in Turkey after receiving emergency use approval from the Ministry of Health. This study, which was performed at the COVID-19 reference center in Ankara (the capital of Turkey) aimed to evaluate the seroconversion rate of the CoronaVac vaccine. The anti-spike immunoglobulin G response to the two-dose vaccination was retrospectively examined in healthcare workers who had no previous history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The postvaccine seroconversion rate was investigated by measuring the antibody levels of healthcare workers who had received CoronaVac. Vaccination was administered as 600 SU in 28-day intervals. The healthcare workers' anti-SARS-CoV-2 immunoglobulin G levels were used to determine the seroconversion rate 2 months after the second dose of the vaccine. Of the healthcare workers, 22.9% (n = 155) were seronegative. The younger the age of the participant, the higher the level of anti-SARS-CoV-2 immunoglobulin G. Furthermore, anti-SARS-CoV-2 immunoglobulin G levels were much higher in women than men.

KEYWORDS

booster dose, COVID-19, inactivated vaccine

1 | INTRODUCTION

Healthcare workers (HCWs) have been on the frontline of the fight against the coronavirus disease 2019 (COVID-19) pandemic since its outbreak in December 2019. The pandemic has posed substantial challenges for HCWs and healthcare systems in many countries. Not only are HCWs under the burden of excess working hours, but they are also at huge risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection to due to direct contact with infected patients. Thus, shortly after the CoronaVac vaccine was given emergency use approval by the Republic of Turkey Ministry of Health, vaccination was given first to HCWs, beginning on January 14, 2021. The HCWs received two doses of the inactive CoronaVac vaccine with the recommended dosing interval of 28 days between the first and second doses.

CoronaVac is an inactivated and aluminum-adjuvant vaccine that was developed by Sinovac Life Science Company.[1] This vaccine, which is produced in Vero cells, induces humoral responses against SARS-CoV-2 and has an acceptable safety profile in vaccinated individuals, with limited adverse reactions.[2–4] This study aimed to evaluate the seroconversion rate of the CoronaVac vaccine retrospectively by examining the antibody response to the two-dose vaccination in HCWs with no previous history of SARS-CoV-2 infection.

2 | MATERIALS AND METHODS

Two 0.5-ml doses of the CoronaVac vaccine containing 600 SU of SARS-CoV-2 virus antigen were administered intramuscularly with a 28-day dosing interval. To determine the anti-SARS-CoV-2 immunoglobulin G (IgG) antibody levels, blood samples from 678 HCWs were collected by hospital management 2 months after the second dose of the vaccine. The HCWs, who were volunteers, included pediatricians, pediatric nurses, and auxiliary healthcare staff who worked at the Children's Hospital of Ankara City Hospital. Since individuals who have had prior SARS-CoV-2 infection may generate a higher antibody response to vaccination than those who have not, any participants with a previous history of SARS-CoV-2 infection were excluded from the study. The hospital management organized the sampling, transportation, and timing of the samples before our study. In our study, we analyzed the results of these samples retrospectively with the permission of the Children's Hospital of Ankara City Hospital management.

After receiving approval from the Ministry of Health, the authors' institution, and the ethics committee, the results of the samples which were analyzed at the Ankara Microbiology Reference Laboratories of the Public Health General Directorate of Turkey, were evaluated retrospectively. Analyses were performed in a macro-ELISA device (Roche Cobas 8000-e801analyzer) with an electrochemiluminescent (ECLIA) technique using a commercial kit (Elecsys Anti-SARS-CoV-2; Roche). This technique uses a recombinant protein to represent the nucleocapsid (N) antigen of the virus. The tests were run and evaluated according to the manufacturer's instructions. A cut-off index (COI) < 1.0 was considered negative for anti-SARS-CoV-2 antibodies, while a COI ≥ 1.0 was considered positive. The results were determined as COI, and semi-quantitative results were obtained. Although the results are reported qualitatively, semi-quantitative values are used in statistical calculations.

The Statistical Package for the Social Sciences version 23.0 (IBM Corp.) was used to analyze the data. Descriptive statistics (including frequencies and means) for all variables were calculated. The results were expressed as mean ± standard deviation, median, range (minimum–maximum), and number (%). The Kolmogorov–Smirnov test was used to examine whether the numerical variables showed normal distribution. The Mann–Whitney *U* test investigated differences between the two independent groups in terms of binary variables. Kruskal–Wallis test was used for comparison of more than one independent group. Spearman's correlation coefficient was used to determine whether there was a significant relationship between binary variables. The level of statistical significance was established as $p < 0.05$.

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.

This study was conducted in conformity with the principles of the Declaration of Helsinki and approved by the Republic of Turkey Ministry of Health, the Ethics Committee of Ankara City Hospital Ethics Committee, and the Institutional Review Board of the Children's Hospital of Ankara City Hospital.

TABLE 1 Descriptive features of the participants

Variables	*n* (%)
Age (year) (mean ± SD)	37.5 ± 9.8
Median	37
Age groups (years)	
20–35	305 (45%)
36–50	284 (41.9%)
51–65	89 (13.1%)
Gender	
Female	511 (75.4%)
Male	167 (24.6%)
Anti-SARS-CoV-2 IgG	
<1 (Negative)	155 (22.9%)
1–1.99	45 (6.6%)
2–9.99	138 (20.4%)
10–99.99	232 (34.2%)
>100	108 (15.9%)

Abbreviations: IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

3 | RESULTS

Of the 678 participants, 511 (75.4%) were women, and 167 (24.6%) were men. The mean age was 37.5 ± 9.8 years old, and the median age was 37 years old. The mean age of men was 39.4 ± 9.7 years old, while the mean age of women was 36.8 ± 9.8 years old (Table 1).

When the antibody levels of the HCWs were examined retrospectively, 22.9% ($n = 155$) of the samples were seronegative (<1), and 77.1% were seropositive. The distribution of the antibody titers was as follows: 22.9% ($n = 155$) were less than 1; 6.6% ($n = 45$) were between 1 and 1.99; 20.4% ($n = 138$) were between 2 and 9.99; 34.2% ($n = 232$) were between 10 and 99.99; and 15.9% ($n = 108$) were over 100 (Table 1).

Anti-SARS-CoV-2 IgG levels were much higher in women than in men ($p < 0.001$; Table 2). Additionally, a significant relationship was found between age and anti-SARS-CoV-2 IgG levels ($p < 0.001$). According to the correlation analyses, the younger the age of the HCW, the higher that individual's levels of anti-SARS-CoV-2 IgG ($r = -0.312$, $p < 0.001$; Table 2). No relationship was found between age or gender and antibody levels in the seronegative participants ($p > 0.05$).

4 | DISCUSSION

This study retrospectively evaluated the seroconversion rate of the CoronaVac vaccine using anti-SARS-CoV-2 IgG antibody levels after two-dose vaccination in HCWs with no prior SARS-CoV-2 infection. About one-fifth of the participants were seronegative. To the best of

TABLE 2 Anti-SARS-CoV-2 IgG levels based on age and gender

Variables	Anti-SARS-CoV-2 IgG levels Mean ± SD	Minimum	Maximum	*p*
Gender				
Female (*n* = 511)	42.5 ± 57.7	0.074	262.5	*p* < 0.001
Male (*n* = 167)	31.3 ± 55.6	0.072	244.9	
Age groups				
20–35 years (*n* = 305)	56 ± 64.7	0.074	262.5	
36–50 years (*n* = 284)	28 ± 47.7	0.072	244.9	*p* < 0.001
51–65 years (*n* = 89)	21,8 ± 43.2	0.081	213.4	
Correlation analyses between age and anti-SARS-CoV-2 IgG levels				
Correlation coefficient				−0.312
p				0.000
Number				678

Abbreviations: IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

the authors' knowledge, this was one of the first studies to show a significant decrease in anti-SARS-CoV-2 IgG antibody levels with increasing age.

In a study conducted in Chile to evaluate the efficacy of the CoronaVac vaccine, participants were administered 600 SU vaccines on Days 0 and 14, and the vaccine response was assessed on Days 14, 28, and 42. Seroconversion rates on Day 42 were 95.6% for participants 18–59 years and 87.5% for participants 60 years and older. However, the statistical significance of the difference between age groups was not emphasized, and attention was drawn to the high rate of seropositivity in both age groups.[5]

A study by Bayram et al.[6] found that seropositivity rates of HCWs after the first and second doses of vaccination with CoronaVac were 77.8% and 99.6%, respectively. When the results of HCWs with a prior polymerase chain reaction confirmed SARS-CoV-2 infection and those who were unsure of prior SARS-CoV-2 infection were excluded, seropositivity after the first dose was found to be 70.5%. In HCWs who may have had prior SARS-CoV-2 infection, seropositivity the rate after the first dose was 71.4%. After the second dose of CoronaVac, anti-SARS-CoV-2 IgG antibodies were detected in 99.6% of the HCWs; only 0.4% remained seronegative after receiving the second dose of the vaccine.[6] Although the seropositivity rate was found to be high in this study conducted in Turkey, the seropositivity rate after the second dose in our study was 77.1%.

A randomized, double-blind, and placebo-controlled Phase 1–2 study conducted in February 2021 in the People's Republic of China reported that the vaccine response for CoronaVac after two doses of vaccination did not decrease with age.[3] The effectiveness of the vaccine was reported to be 97%. In Phase 3 studies by Sinovac, this rate was reported to be 51% for all patients, 84% for those with conditions requiring medical treatment, and 100% for those with conditions requiring hospitalization.[7] The present study found that vaccine response was better in younger participants than in older participants and that seropositivity rates after two vaccination doses were nearly 78%.

The BNT162b2mRNA vaccine produced by Pfizer and BioNTech was the first vaccine approved for emergency use by the United States Food and Drug Administration.[8] The efficiency of BNT162b2mRNA was found to be 95% in a Phase 3 study with more than 43 000 participants, and no significant difference was found between age groups in terms of effectiveness.[9] In the Phase 3 study of another messenger RNA (mRNA) vaccine—mRNA-1273 (Moderna)—which included 30 000 patients, the effectiveness of the vaccine was found to be 94.1%.[10,11] For participants aged 18–65 years, vaccine efficacy was 95.6%, while efficacy for those over 65 was 86.4%.[11] Similar to the results of studies conducted with inactivated vaccines, the efficiency of the mRNA vaccines was found to be high in studies with mRNA vaccines, and no decrease was observed in vaccine effectiveness with age.

Goel et al.[12] found that antibody titers declined 6 months after immunization with mRNA vaccines but remained detectable in all subjects. In a study conducted by Lopez Bernal et al.[13] with participants over the age of 16, the efficacy of the BNT162b2mRNA vaccine against the alpha variant was 93.7% and the efficacy against the delta variant was 88%. It is noteworthy that the efficacy of the vaccine varies according to the variants and the efficacy against the delta variant decreases. Thus, it is possible that new mutations that emerge in individuals with suboptimal or waning immunity will erode the effectiveness of natural and vaccine-elicited immunity.[14]

The present study had some limitations. It was conducted in a single center, and the prevaccination levels of SARS-CoV-2 antibodies in the participants were unknown. And also, the participants with asymptomatic infection could not be detected in the time between vaccination and sampling. It may have a minor impact on the results of discrimination between antibodies elicited from vaccines and those by natural infection. Additionally, whether antibody response can predict clinical response in case of exposure to the infectious agent cannot be determined.

5 | CONCLUSION

In light of the studies in the literature and the present analysis, extensive clinical response studies are needed for both inactivated vaccines and mRNA vaccines to illuminate the long-term medical effects of the COVID-19 pandemic and the unknowns of the immunization process. Planning and applying a booster dose after two doses of CoronaVac is appropriate for people in risk groups, such as healthcare professionals, people with chronic diseases, and elderly

individuals. Doing so will preserve the continuity of herd immunity until further studies have been conducted.

ACKNOWLEDGMENTS

This manuscript is not under simultaneous consideration by any other publication. An honorarium, grant, or other forms of payment was not given to any author to produce the manuscript. All authors significantly contributed to the work, have approved the final manuscript, and takes full responsibility for the manuscript.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Metin Yigit: *Study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content*. Aslinur Ozkaya-Parlakay: *Analysis and interpretation of data, critical revision of the manuscript for important intellectual content, conducted behavioral assessments*. Yasemin Cosgun: *Study concept and design, analysis and interpretation of data*. Yunus Emre Ince and Emrah Senel: *Study concept and design, critical revision of the manuscript for important intellectual content*. Yunus Emre Bulut: *Analysis and interpretation of data*.

DATA AVAILABILITY STATEMENT

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

ORCID

Metin Yigit https://orcid.org/0000-0003-3536-4456
Yasemin Cosgun https://orcid.org/0000-0002-3815-8036

REFERENCES

1. Sharma O, Sultan AA, Ding H, Triggle CR. A review of the progress and challenges of developing a vaccine for COVID-19. *Front Immunol*. 2020;11(585354):1–17. https://doi.org/10.3389/fimmu.2020.585354
2. Zhang M-X, Zhang T-T, Shi G-F, et al. Safety of an inactivated SARS-CoV-2 vaccine among healthcare workers in China. *Expert Rev Vaccines*. 2021;13:1-8. https://doi.org/10.1080/14760584.2021.1925112
3. 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. https://doi.org/10.1016/S1473-3099(20)30843-4
4. Gao Q, Bao L, Mao H, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. *Science*. 2020;80-(6499):77-81. https://doi.org/10.1126/science.abc1932.369
5. Bueno SM, Abarca K & González PA et al. Interım report: safety and immunogenicity of an inactivated vaccine agaınst SARS-CoV-2 in healthy Chilean adults in a phase 3 clinical trial. medRxiv. 2021. https://doi.org/10.1101/2021.03.31.21254494
6. Bayram A, Demirbakan H, Günel Karadeniz P, Erdoğan M, Koçer I. Quantitation of antibodies against SARS-CoV-2 spike protein after two doses of CoronaVac in healthcare workers. *J Med Virol*. 2021;93:5560-5567. https://doi.org/10.1002/jmv.27098
7. SINOVAC科兴. 2021. 为人类消除疾病提供疫苗. Accessed July 5, 2021. http://www.sinovac.com/?optionid=754%26;auto_id=9
8. Ledford H. US authorization of first COVID vaccine marks new phase in safety monitoring. *Nature*. 2020;588(7838):377-378. https://doi.org/10.1038/d41586-020-03542-4
9. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603-2615. https://doi.org/10.1056/nejmoa2034577
10. Corbett KS, Flynn B, Foulds KE, et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates. *N Engl J Med*. 2020;383(16):1544-1555. https://doi.org/10.1056/nejmoa2024671
11. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384(5):403-416. https://doi.org/10.1056/nejmoa2035389
12. Goel RR, Painter MM & Apostolidis SA et al. mRNA vaccination induces durable immune memory to SARS-CoV-2 with continued evolution to variants of concern. bioRxiv. 2021. https://doi.org/10.1101/2021.08.23.457229
13. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 vaccines against the B.1.617.2 (delta) variant. *N Engl J Med*. 2021;385(7):585-594. https://doi.org/10.1056/NEJMOA2108891
14. Wang Z, Schmidt F, Weisblum Y, et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. *Nature*. 2021;592(7855):616-622. https://doi.org/10.1038/s41586-021-03324-6

How to cite this article: Yigit M, Ozkaya-Parlakay A, Cosgun Y, Ince YE, Bulut YE, Senel E. Should a third booster dose be scheduled after two doses of CoronaVac? A single-center experience. *J Med Virol*. 2022;94:287-290. https://doi.org/10.1002/jmv.27318