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Short Communication

# Antibody response after a third dose mRNA-1273 vaccine among vaccinated healthcare workers with two doses of inactivated SARS-CoV-2 vaccine

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ABSTRACT

*Background:* Health care workers (HCWs), a high-risk group for contracting COVID-19 disease, are being prioritized to receive COVID-19 vaccination. A third dose messenger RNA (mRNA) vaccine, mRNA-1273 (Moderna), after 2 doses of inactivated vaccine (CoronaVac), has been used to increase the level of protection against SARS-CoV-2 among Indonesian HCWs. However, data regarding antibody response after mRNA-1273 booster dose are limited.

*Objective:* To evaluate the receptor-binding domain (RBD) of the SARS-CoV-2 spike (S) protein (anti-S) titers induced by the third mRNA-1273 vaccine among fully vaccinated HCWs with CoronaVac.

*Results:* A total of 90 HCWs with no history of SARS-CoV-2 infection and who had received the third dose of vaccination were included in this study. The mRNA-1273 vaccine booster was administered 6 months after completing primary vaccination with CoronaVac. After the third dose, the anti-S antibodies level significantly increased, from a median of 41.7 U/mL (interquartile range [IQR], 22.4-92.5) to 28 394 U/mL (IQR, 20 837-41 646) ($p < 0.0001$). After the third dose, seropositivity with the anti-S antibodies level >210 U/mL was observed in all HCWs. Age was negatively associated with the anti-S antibodies level after the mRNA-1273 booster.

*Conclusion:* The heterologous prime booster with CoronaVac and mRNA-1273 vaccine booster elicit a pronounced antibody response against SARS-CoV-2 infection.



Health care workers (HCWs) are at the frontline battling against the COVID-19 pandemic and are categorized as a priority target group for COVID-19 vaccines. CoronaVac (Sinovac Life Sciences, China), an inactivated SARS-CoV-2 vaccine, was the initially available vaccine platform and primarily administered to Indonesian HCWs. Although previous clinical trial studies in China (Zhang et al., 2021) and Turkey (Tanriover et al., 2021) have evidenced the immunogenicity of 2-dose CoronaVac, the antibody levels predictive for SARS-CoV-2 protection has declined over time (Mok et al., 2021). To address the potential waning immunity, the administration of the third COVID-19 vaccine dose for Indonesian HCWs has started in August 2021. The SARS-CoV-2 messenger RNA (mRNA) (mRNA-1273, Moderna) vaccine has been used as the third (booster) dose for Indonesian HCWs. This study aims to assess the total antibodies specific to the receptor-binding domain (RBD) of the SARS-CoV-2 S protein (anti-S) titers elicited after the third mRNA-1273 dose among fully vaccinated HCWs with CoronaVac.

A total of 90 HCWs at Siloam Teaching Hospital, Indonesia, were included in this retrospective cohort study. The inclusion criteria were: (1) fully vaccinated HCWs with CoronaVac who received the mRNA-1273 vaccine as the third dose between August 10, 2021, and September 24, 2021, (2) HCWs who had not previously been infected with SARS-CoV-2, as confirmed by negative

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**Table 1**
Baseline demographic and characteristics before and after the third mRNA-1273 dose

| Characteristics | All (n=90) |
|---|---|
| Age (years), median (IQR) | 31 (26-44) |
| Gender, n (%) | |
| Female | 79 (88) |
| Male | 11 (12) |
| Analysis before third dose | |
| Days after second vaccine, median (IQR) | 144 (142-146) |
| Total antibodies titers, median (IQR), U/mL | 41.7 (22.4-92.5) |
| The positivity anti-S antibodies, n (%) | |
| ≥ 0.8 U/mL | 90 (100%) |
| > 210 U/mL | 10 (11%) |
| Analysis after third dose | |
| Days after second vaccine, median (IQR) | 236 (234-237) |
| Days after third vaccine, median (IQR) | 57 (44-60) |
| Total antibodies titers, median (IQR), U/mL | 28 394 (20 837-41 646) |
| The positivity anti-S antibodies, n (%) | |
| ≥ 0.8 U/mL | 90 (100%) |
| > 210 U/mL | 90 (100%) |
| Interval between second and third dose (days), median (IQR) | 178 (176-191) |

IQR = interquartile range

**Table 2**
Multiple linear regression on $\log_2$ transformation of anti-S antibodies level

| Variables | $\beta$ (95% CI) | p-value |
|---|---|---|
| Age (years) | -0.024 (-0.040 to -0.008) | 0.003 |
| Gender | | |
| Female | Reference | |
| Male | -0.205 (-0.677 to 0.267) | 0.391 |
| Interval between the third dose vaccination and testing (days) | -0.039 (-0.053 to -0.026) | <0.0001 |

reverse-transcriptase PCR testing that was performed regularly in the hospital.

Serological testing for total antibodies specific to the RBD of the SARS-CoV-2 S protein (anti-S) was performed using the Elecsys anti-SARS-CoV-2 S electrochemiluminescence immunoassay (ECLIA) with the Cobas e601 analyzer (Roche Diagnostics), according to the manufacturer's instruction. A test result ≥ 0.8 U/mL or more was considered positive. Samples above 250 U/mL were diluted further (1:10, 1:100, and 1:1000) within the measurement range of the assay (0.4-250 U/mL).

The median age of participants was 31 years (interquartile [IQR], 26-44), and 88% were female (**Table 1**). The third vaccine was administered a median (IQR) of 178 (176-191) days after the second vaccination. The anti-S antibodies level increased significantly after the third vaccination from a median of 41.7 U/mL (IQR, 22.4-92.5) to 28 394 U/mL (IQR, 20 837-41 646) ($p < 0.0001$). All HCWs had positive anti-S antibodies, ≥ 0.8 U/mL, before and after the third vaccination. However, the percentage of HCWs with anti-S antibodies level > 210 U/mL was significantly different before and after the third vaccination (11% vs 100%, $p < 0.0001$). A significant negative correlation was observed between the anti-S antibodies level and the age of the participant after the third dose ($r = -0.219$; $p = 0.03$), but not before the third dose of vaccination ($r = -0.053$; $p = 0.61$). Age remained independently associated with the $\log_2$-transformed anti-S antibodies level after mRNA-1273 booster dose in multiple linear regression analysis ($p = 0.003$, **Table 2**).

The antibody level, in particular antibody toward RBD of the S protein (anti-S), has been shown to correlate with virus-neutralizing titers, suggesting the quantification of this antibody can be predictive for SARS-CoV-2 protection (Salazar et al., 2020). Similar to other studies (Kwok et al., 2021; Mok et al., 2021), our study has shown that the decline of anti-S antibodies occurred quickly among the fully vaccinated HCWs with CoronaVac (Cucunawangsih et al., 2021). Therefore, considering the short-term immune response after CoronaVac vaccination and the occupational risk of HCWs for acquiring SARS-CoV-2 infection, HCWs are prioritized to receive a booster dose of the mRNA-1273 vaccine.

The heterologous boosting strategy refers to administering a vaccine that differs from the previous vaccine platform, potentially improving the immunogenicity and expanding the breadth of cellular and humoral immunity against current SARS-CoV-2 variants of concern (Barros-Martins et al., 2021; Munro et al., 2021). Heterologous boosting of CoronaVac with mRNA vaccine have shown to induce a greater antibody response compared with other booster vaccine platforms and also produce neutralizing antibodies against ancestral, Delta, and Omicron SARS-CoV-2 variants (Cheng et al., 2022; Costa Clemens et al., 2022; Perez-Then et al., 2022). The mRNA-1273 vaccine booster was administered 6 months after the second CoronaVac vaccination. Administering the vaccine booster led to a strong immune boost in all HCWs, with the anti-S antibodies significantly increasing to > 210 U/mL. This level is suggested by the United States Food and Drug Administration for the high titer of anti-SARS-CoV-2 antibodies in convalescent plasma for COVID-19 treatment as measured using the Elecsys anti-SARS-CoV-2 assay. Furthermore, agreeing with previous studies (Abu Jabal et al., 2021; Steensels et al., 2021), our result showed that age was negatively associated with the antibody response after the third dose of vaccine. The reduced vaccine response in older adults is possibly related to immune senescence (Poland et al., 2018).

Limitations of this study include a single-center study, a small sample size, lack of data on cellular immunity and neutralizing antibodies, and the short follow-up. In conclusion, our study showed that a heterologous regimen of 2 doses of prime CoronaVac followed by a single mRNA-1273 booster dose significantly enhances anti-S antibodies levels, which could improve protection against SARS-CoV-2 infection. In the current condition where Indonesia has started the COVID-19 booster vaccination program for the general population, our finding provides valuable information regard-

ing the serologic response that can be achieved with heterologous prime booster vaccination using a CoronaVac and mRNA-1273 vaccine booster.

## Declaration of Competing Interest

The authors have declared no conflicts of interest.

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## Ethics Approval

This study was approved by the research ethics committee of the Faculty Medicine of Pelita Harapan University (No: 137/K-LKJ/ETIK/IV/2021).

## Author Contributions

Designing research studies (CC, RW, NL), acquiring data (CC), analyzing data (CC, RW, NL, IS), interpreting the results (CC, RW, NL, IS), and writing the manuscript (CC, RW, NL, IS).

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