DIFFERENCES IN TOTAL S-RBD ANTIBODY SARS-CoV-2 POST-VACCINATION mRNA-1273 3rd DOSAGE (HETEROLOGOUS PRIME BOOSTER) WITH POST-PRIME VACCINATION INACTIVATED WHOLE VIRUS TWO DOSES (HOMOLOGOUS) IN HEALTH PERSONNEL SURABAYA H2LC CLINIC

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Abstract


Kata kunci: Vaksin, Titer antibodi dan Booster

Abstract

SARS-CoV-2 cases have increased to 463,182,124 reported worldwide as of March 16, 2022 with a death toll of 6,079,600. Indonesia on March 17, 2022 has increased by 5,939,082 with a death toll of 153,212 (KPCPEN, 2022). SARS-CoV-2 is closely related to the coronavirus. One of the efforts made to prevent the risk of severe infection and reduce the death rate from the SARS-CoV-2 virus in Indonesia is a vaccination program. According to IDI (2021) cases of Covid-19 deaths are dominated by men (84%) and women (16%). Clinical trials in China and Brazil have shown that, the immunogenicity of two doses of the vaccine decreases over time and there is a decrease in low antibody concentrations after 6 months of running time. To overcome this potential, the Indonesian government gives priority to the 3rd vaccine booster. The purpose of this study was to analyze the comparison between the total antibody titer for the Spike-RBD (Receptor Binding Domain) SARS-CoV-2 protein after the 3rd dose of mRNA-1273 booster vaccination and post-vaccination of two doses of primary inactivated whole virus in health workers. This research was conducted by observation with a cohort approach. It was concluded that the results of the Mann Whitney two-sided test with a significance value of 0.000, the antibody titer correlation test results with gender had a value of 0.702 and -0.366 for the relationship between antibody titer and age. There was a significant difference between the primary vaccination dose of 2 doses of CoronaVac and the 3rd vaccination (booster) mRNA-1273, gender was strongly associated with S-RBD antibody titer and age was not associated with S-RBD antibody titer.

Keywords: Vaccine, Antibody Titer and Booster

DOI 10.20473/jbp.v24i2.2022.111-117
INTRODUCTION

Cases of SARS-CoV-2 have increased to 463,182,124 reported worldwide as of March 16, 2022 with a death toll of 6,079,600 (Worldmeter, 2022). And by the World Health Organization (WHO) it has been declared a pandemic since March 11, 2020. SARS-CoV-2 is closely related to the acute respiratory syndrome-like coronavirus that was derived from 2 bats, namely bat -SL-CoVZC45 and bat SL-CoVZXC21, but further for its similarity from SARS-CoV (79% similarity) and MERS-CoV (50% similarity) (Lai CC, et.al., 2020).

The genomic structure of the 2019-nCoV RNA virus is closely related to severe acute respiratory syndrome (SARS)-CoV, therefore 2019-nCoV is currently given a new name 'SARS-CoV-2' with the name of the disease called Coronavirus disease 2019 (COVID-19). (Enya Qing, 2020). This virus spreads from human to human through droplets or direct contact and infection is estimated to have a mean incubation period of 6.4 days and a basic reproduction rate ranging from 2.24 to 3.58. Among patients with pneumonia caused by the SARS-CoV-2 virus, fever is the most common symptom, followed by a dry cough. GGO (Glass Ground Opacity) images in both lung fields are often found from chest CT scans. (Lai CC, et.al., 2020)

The number of SARS-CoV-2 cases reported in Indonesia on March 17, 2022 has increased by 5,939,082 with a death toll of 153,212 (KPCPEN, 2022). One of the efforts made to prevent the risk of severe infection and reduce the death rate from the SARS-CoV-2 virus in Indonesia is a vaccination program. The Indonesian government has implemented a COVID-19 vaccination program starting on January 13, 2021 for Phase I of 1.2 million doses of vaccine with an inactivated whole virus platform, namely CoronaVac (produced by the Sinovac company, China) with priority given to health workers in health care facilities both at home Hospitals, Public Health Centers, TNI and Polri health service facilities in Java and Bali. then 1.

The Indonesian government gives priority to health workers because they are at the forefront and have a high risk in efforts to overcome the COVID-19 pandemic. According to the recommendations of ITAGI and SAGE, if vaccine availability is limited in the early stages, the target group is at risk, which in this case is health workers and supporting staff working in health care facilities. The CoronaVac vaccine is given to health workers as much as 2 doses per person with an interval of 14 days (distance from the first dose to the second dose) (Kemenkes RI, 2021).

After 5 months have passed from administering the 1st and 2nd doses of vaccine to health workers since January and February 2021, the mortality rate of health workers in Indonesia began to decline significantly until May 2021 and June 2021. However, data from the IDI Mitigation Team survey The number of doctor deaths as a part of health workers in handling Covid-19, increased significantly again by 52 people while the peak in July 2021 as many as 216 doctors died which coincided with the peak of the 2nd wave in Indonesia, which was triggered by the dominance of the Delta variant. from SARS-CoV2 (IDI Mitigation Team Survey, 2021).

From the data on doctor deaths by sex in Indonesia due to Covid-19 disease, 84% were male and the remaining 16% were female (IDI Mitigation Team Survey, 2021). This is interesting to study further because in a previous study in Wuhan, China, after being given 2 doses of vaccination with the platform inactivated whole virus SARS-CoV-2, it turned out that female subjects had higher antibody concentrations IgG S-RBD SARS-CoV-2 and its neutralizing antibody levels compared to men vaccinated with the same platform. In addition, the specific S,N,M protein T helper CD4+ and T cytotoxic CD8+ also increased higher in women than men who were given 2 doses of the vaccine (Z. Li et al., 2022).
Recent clinical trials in China and Brazil have shown that, the immunogenicity of two doses of the CoronaVac vaccine, had a predictive level of antibody for protection against SARS-CoV-2 decreased over time and a decrease in antibody concentration was low after 6 months of running time (Zhang Y. et al., 2021) (Costa Clemens et al., 2022). In several other studies, it was shown that older people had lower antibody responses than younger people after a complete 2-dose vaccination. A 3rd booster vaccine is needed in the elderly population group at high risk, especially facing the VOC (variant of concern) currently circulating. In addition, the 3rd booster vaccine showed a stronger increase in humoral and cellular immunity against the SARS-CoV-2 virus after vaccination (AJ.Romero–Olmedo et al,2022) (DA Collier,2021).

The latest clinical trial phase 4 in Brazil the heterologous booster with different platform showed significantly higher concentrations of SARS-CoV-2 IgG antibodies and neutralizing antibody levels compared to the 3rd vaccine booster on the same platform (homologous booster) using the inactivated whole virus vaccine (coronaVac). The conditions concluded from this study indicate that the heterologous booster produces a stronger immune response than the homologous booster and may increase the protection against the SARS-CoV-2 virus (Costa Clemens et al., 2022).

To overcome the potential for decreased immunity in primary vaccinations that have been given two doses of Coronavac after 6 months have passed, the Indonesian government gives priority to the 3rd vaccine booster which will be held starting in August 2021, to health workers as an effort to reduce the risk of the number of deaths in Indonesia. health workers, supported by ITAGI recommendations and previously collected data, the increasing number of deaths of health workers due to infection with the SARS-CoV-2 virus in June and July 2021. The 3rd vaccination used as a booster uses a messenger RNA platform (mRNA-1273, moderna) in almost all medical personnel in Indonesia and a small proportion if there is a risk of allergies using the same booster vaccine platform from the previous 2 doses of primary vaccination (Kemenkes RI, 2021).

With the findings of this study, it is hoped that differences of antibody levels will be obtained when two doses of primary vaccination are given on the same vaccine platform (homologous) with a booster vaccine that uses a different vaccine platform from the primary vaccine (heterologous), in addition to knowing the immunogenicity of each vaccine. each vaccine platform was measured and how efficient it was in increasing protection against SARS-CoV-2 infection and whether there was a correlation between antibody levels as measured by gender, and age in each of the groups studied. Besides that, it can be a reference for further research on new variants of SARS-CoV-2 that may appear in the future.

**RESEARCH METHOD**

This research was conducted using the analytical observational method in August to September 2021. The data analysis process was carried out in a retrospective cohort. The research location is the H2LC Pratama Clinic, which is located on Jl. Pucang anom 83 Surabaya. The sample used is medical personnel and support personnel who work in health facilities in clinics and hospitals in Surabaya and its surroundings. The data processing in this study used the Man Whitney comparative test and the Pearson correlation test.

**RESULT AND DISCUSSION**

Serological assay for the total specific antibody (spike receptor binding domain) S-RBD of the SARS-CoV-2 protein was performed using Elecsys anti-SARS-CoV-2 S electrochemiluminescence immunoassay (ECLIA) method with a Cobas e 411 analyzer (ROCHE Diagnostics) , according to the manufacturer's instructions. The test result
0.8 U/ml or more is interpreted as positive / reactive to form antibodies. Samples having a value of 250 U/ml were further diluted 1:100 to the highest limit of 25 000 U/ml.

The median age of the participants was 39 years (IQR, 26-59) and sex was 44.4% male and 55.6% female (Table 2). The level of S-RBD total antibody titer increased significantly after the 3rd mRNA-1273 vaccine from a median of 105.92 U/ml (IQR, 3.19-267.72) to 23 534 (IQR 10 132-25 000).

All health workers at the Surabaya H2LC clinic whose blood samples were taken had a positive result / reactive total antibody titer of S-RBD 0.8 U/ml both before and after the 3rd dose of mRNA-1273 vaccination. However, the percentage of H2LC clinical health workers who were examined with a total S-RBD antibody titer ≥10 U/ml had a significant difference from those before (stage 1) and after the 3rd dose of vaccination (stage II) i.e. 29.6% versus 100%.

Table 1. Vaccine Comparative Test of doses 2 and 3

<table>
<thead>
<tr>
<th>Test Statistics</th>
<th>Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mann-Whitney U</td>
<td>000</td>
</tr>
<tr>
<td>Wilcoxon W</td>
<td>231000</td>
</tr>
<tr>
<td>Z</td>
<td>-6197</td>
</tr>
<tr>
<td>Asymp Sig (2-tailed)</td>
<td>000</td>
</tr>
</tbody>
</table>

In the Mann-Whitney test, it can be seen that in the Asymp Sig/ Asymptotic significance column on both sides is 0000 so that the probability is less than 005, the HO is rejected, which means that before (1st stage post-vaccine 2 doses of CoronaVac) and after (2nd stage with after the 3rd dose of mRNA-1273 vaccination) there was also a significant difference.

Table 2. Antibody Titer Correlation Test With Gender Before the 3rd Vaccine

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All samples (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years), median (IQR)</td>
<td>39(26-59)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Gender Correlation Test With Antibody Titers

<table>
<thead>
<tr>
<th>(Titer total antibody) Phase 1</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 Pearson Correlation</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td></td>
</tr>
<tr>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>Gender Pearson Correlation</td>
<td></td>
</tr>
<tr>
<td>.702 **</td>
<td>1</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td></td>
</tr>
<tr>
<td>.000</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>27</td>
</tr>
</tbody>
</table>

** Correlation is significant at the 0.01 level (2-tailed).
The researchers found that all health workers at the H2LC clinic who had their total S-RBD antibody titer checked for SARS-CoV-2 1 month after being vaccinated with the mRNA-1273 booster (moderna) and 6 months earlier had been vaccinated with 2 doses of coronaVac, the results were able to increase strongly the total titer of S-RBD antibody was 100-1000x from the previously obtained titer and all the results showed high titers. These results show conformity with the high antibody titer standard (High titer), which is > 210 U/ml set by the Food and Drugs Administration United State of America (FDA USA), for the treatment of COVID-19 using antibody plasma convalescence as measured by tools and methods. the same using the Elecsys anti SAR-CoV-2 S assay (XN Li. et al., 2021)(Z. Li et al., 2022)

Furthermore, in line with previous research (Steensels et al., 2021) from the results of our study, it was shown that there was no negative correlation between age and antibody titer response before being given two doses of the same platform vaccine or after the 3rd dose of vaccine with a different platform. Decreased response to vaccination in old age is more likely to be related to immune senescence (LL Cunha et al., 2020) (DA Collier, 2021) (AJ. Romero-Olmedo et al., 2022).

**CONCLUSION AND SUGGESTION**

Our research shows that the respondents of health workers and support staff at the Surabaya H2LC clinic after the 3rd mRNA-1273 (Heterologous prime booster) vaccination who had previously received 2 doses of primary vaccination (Homologous) inactivated whole CoronaVac virus experienced a significant difference to stimulate titers. total antibody S-RBD SARS-CoV-2 and is expected to increase protection against infection with the SARS-CoV-2 Virus.

From this study interestingly, it was also found from statistical tests that there was

### Table 4. Antibody Titer Correlation Test and Age

<table>
<thead>
<tr>
<th>Titer total antibody S-RBD (total stage 1&amp;2)</th>
<th>Age</th>
<th>Sig. (2 tailed)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>-.366</td>
<td>27</td>
</tr>
<tr>
<td>Sig. (2 tailed)</td>
<td></td>
<td>.061</td>
<td>27</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td>-.366</td>
<td>1</td>
</tr>
<tr>
<td>Sig. (2 tailed)</td>
<td></td>
<td>.061</td>
<td>27</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

At the level of the total S-RBD antibody titer and the age of the respondent in the Pearson correlation test, the relationship interval was -0.366 where the Pearson coefficient classification table stated that it was in the unrelated category, besides that the sig (2 tailed) count had a value of 0.061 > 0.005 then stated that there was no correlation between the total S-RBD titer and the age of the respondent (Table 4).

The total titer level of S-RBD antibody has shown an association with the virus neutralization titer, which is suspected to be the quantity of the antibody that can predict the protection of the SARS-CoV-2 Virus.(Mok CKP et al., 2021)(Salazar E. et al., 2020)

Booster vaccination with different platforms (heterologous prime booster) has the potential to improve immunogenicity and expand cellular and humoral immunity against variant of concern (VOCs) from SARS-CoV-2.(Munro APS et al., 2021) (Rose R et al., 2022)

Post-vaccination Heterologous prime mRNA booster 3rd dose previously given 2 doses of inactivated Whole virus (coronaVac) showed stronger antibody response stimulation compared to boosters from other different platforms and also stimulated neutralizing antibody titers against SARS-CoV-2 variant virus Wuhan arrives with new variants such as Delta and Variant Omicron(Costa Clemens et al., 2022) (Perez-Then et al., 2022)
a relationship between the total antibody titer of S-RBD with gender and the percentage of high titer of total S-RBD antibody there was a significant difference in women, which was higher than men in stage 1, which 6 months earlier they had received 2 doses of primary inactivated whole virus (coronaVaC) vaccination. This can be continued in future research to prove what variables affect the increase in the SARS-CoV-2 S-RBD antibody titer against gender in the group of individuals studied.

Acknowledgement
All authors are thankful to Master's Program in Immunology Graduate School, Airlangga University Surabaya for academic support.

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