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

Deddy Hartanto[1], Jusak A. Nugraha[2], Theresia Indah Budhy[3]
[1]Departement of Clinical Pathology, Medical Faculty of Wijaya Kusuma University Surabaya
[1,2,3]Master Program in Immunology Sekolah Pasca Sarjana, Airlangga University Surabaya
[1]e-mail: klinik_h2lc@yahoo.com

Abstrak

Kasus SARS-CoV-2 telah meningkat menjadi 463.182.124 yang dilaporkan di seluruh dunia pada 16 Maret 2022 dengan jumlah kematian 6.079.600 (Worldmeter, 2022). Jumlah SARS-CoV-2 di Indonesia pada 17 Maret 2022 bertambah 5.939.082 dengan jumlah kematian 153.212 (KPCPEN, 2022). Vaksinasi merupakan upaya pemerintah Indonesia untuk mencegah infeksi berat dan menurunkan angka kematian. Uji klinis di China dan Brazil telah membuktikan bahwa terjadi penurunan imunogenisitas antibodi setelah 6 bulan. Menurut IDI (2021) kasus kematian Covid-19 didominasi oleh laki-laki (84%) dan perempuan (16%). Untuk mengatasi potensi tersebut, pemerintah Indonesia telah memprioritaskan booster vaksin ke-3 dengan platform mRNA-1273. Tujuan penelitian ini adalah untuk menganalisis perbandingan titer antibodi total protein Spike-RBD (Receptor Binding Domain) SARS-CoV-2 setelah vaksinasi booster mRNA-1273 dosis ke-3 dan pascavaksinasi dua dosis primer. menginaktivasi seluruh virus pada petugas kesehatan. Penelitian ini dilakukan dengan observasi dengan pendekatan kohort. Didapatkan hasil uji dua sisi Mann Whitney dengan nilai signifikansi 0,000, hasil uji korelasi titer antibodi dengan jenis kelamin memiliki nilai 0,702 dan -0,366 untuk hubungan titer antibodi dengan umur. Terdapat perbedaan bermakna antara dosis Vaksinasi primer 2 dosis CoronaVac dan vaksinasi ke -3 (booster) mRNA-1273, jenis kelamin berhubungan kuat dengan titer antibodi S-RBD dan usia tidak berhubungan dengan titer antibodi S-RBD.

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

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-C0V-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-C0V-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

109

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 210 U/ml (high titer) 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

Test Statistics[a]	
	Capacity
Mann-Whitney U	000
Wilcoxon W	231000
Z	-6197
Asymp Sig (2- tailed)	000

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

Characteristics	All samples (n=27)
Age (Years),	median (IQR)
Gender, n (%)	39(26-59)
Men	12 (44,4)
Women	15 (55,6)

There was a negative relationship/correlation that was observed analytically between the total antibody titer level of S-RBD and the respondent's gender after the 3rd dose of vaccination (stage 2) because there was an increase in the total antibody titer of 100% from different genders (Table.2) so that no correlation test was carried out, but before the 3rd vaccination (stage 1) there was a significant difference in the total antibody titer of S-RBD 210 U/ml (High titer) between men and women, namely 0% versus 53% while the total antibody titer of S-RBD 0.8 to 210 U/ml (Low titer) also showed a significant difference between women and men, namely 47% versus 100% (Table 2).

Table 3. Gender Correlation Test With Antibody Titers

(Titer total antibodi) Phase 1	Gender
Phase 1 Pearson Correlation	
1	.702**
Sig. (2-tailed)	
.000	
N	
27	27
Gender Pearson Correlation	
.702 **	1
Sig. (2-tailed)	.000
N	
27	27
** Correlation is significant at the 0.01 level (2-tailed).	

In the Pearson correlation test, it was found that the relationship interval between the 1st stage of the S-RBD antibody titer and the respondent's gender was 0.702 where the Pearson coefficient classification table stated that it was in the strong category, besides that the sig (2 tailed) count had a value of 0.000 < 0.005 then states that there is a relationship between the level and the gender of the respondent (Table 3).

Table 4. Antibody Titer Correlation Test and Age

Titer total antibody S-RBD (total stage 1&2)	Age
1	-.366
Sig. (2 tailed)	.061
N	
27	27
-.366	1
Sig. (2 tailed)	.061
N	
27	27

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)

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

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

REFERENCES

A.R. Falsey et al.. (2021). Phase 3 safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine. *The New England Journal of medicine*, 2348-2360.

Adityo Susilo, C.M. (2020). Corona disease 2019 : Tinjauan literatur terkini. *Jurnal penyakit dalam Indonesia*, Vol 7,No.1.

AJ. Romero-Olmedo et al. (2022). Induction of robust cellular and humoral immunity against SAR-CoV-2 after a third dose of BNT162b2 vaccine in previously unresponsive older adults. *Nature Microbiology*, 195-199.

Astra Zeneca. (2021, maret 22). *AZD1222 US Phase III trial met primary efficacy endpoint in preventing COVID-19 at interim analysis*. Retrieved from Astra zeneca: www.astrazeneca.com

Augustine,R.et al.. (2020). Rapid Antibody Based COVID-19 Mass Surviellance Relevance, Challenges, and Prospects in a Pandemic and Post-Pandemic World. *J. Clin.Med*, 9,3372.

Carter,L.J. et al.. (2020). Assay Techniques and Test Development for COVID-19 Diagnosis. *ACS Cent.sci*, 6, 591-605.

Chen,Y. et al.. (2020). Emerging coronavirus : Genome structure, replication, and pathogenesis. *J. Med. Virology*, 92, 418-423.

Chen.Y. et al.. (2020). Structure analysis of the receptor binding of 2019-nCov. *Biochem. Biophys. Res Commun*.

Cheng,M.P. et al.. (2020). Diagnostic Testing for Severe Acute Respiratory Syndrome- Related Coronavirus 2 : a Narrative Review. *Ann. Internal Medicines*, 172,726-734.

Chih-Cheng Lai, et al.. (2020). Severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) and coronavirus disease-2019 (COVID-19) : The epidemic and the challenges. *Int. Journal of Antimicrobial Agents*, 1-2, 0924-8579.

Corbett,K.S. et al.. (2020). Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates. *N. Engl.J*.

Costa Clemens et al.. (2022). Heterologous Versus homologous Covid-19 booster vaccination in previous recipients of two doses of Coronavac COVID-19 vaccine in Brazil (RHH-001): a phase 4, non-inferiority,single blind, randomised study. *Lancet*, 521-529.

Cui,J. et al.. (2019). Origin and evolution of pathogenic coronaviruses. *Nat. Rev. Microbiology*, 181-192.

DA Collier. (2021). Age-related immune response heterogenecity to SARS-CoV-2 vaccine BNT162b2. *Nature*, Vol 596, 417-422.

Dutta,N.K. et al.. (2020). The nukleocapsid Protein of SARS-CoV-2 : A Target for Vaccine development. *J.Virology*, 94.

Enya Qing, T. (2020). SARS Coronavirus Redux. *Trends in Immunology*, Vol.41,4.

Folegatti,P.M. et al.. (2020). Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-

CoV-2 : A preliminary report of a phase 1/2, single blind,randomized controlled trial. *Lancet*, 396,467-478.

Hobman,T.C. et al.. (2020). COVID-19 Pandemic : Insight into structure, function, and hACE2 receptor recognition by SARS-CoV-2. *PLoS Pathog.*, 16.

Hoffman,M. et al.. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and Is blocked by Chilinically proven protease Inhibitot. *Cell*, 181, 271- 280.

Huang,C.et al.. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan,China. *Lancet*, 395,497-506.

Jacofsky,D. et al.. (2020). Understanding Antibody Testing for COVID-19. *J. Arthoplast*, 35,S74-S81.

Kemenkes RI. (2021, Januari 19). *Kemenkes RI*. Retrieved from 1,2 Juta Dosis Vaksin COVID-19 ditargetkan bagi tenaga kesehatan: https://sehatnegriku.kemkes.go.id

kemenkes RI. (2021, agustus 1). *Kemenkes tegaskan vaksinasi booster hanya untuk tenaga kesehatan*. Retrieved from Kementerian Kesehatan Republik Indonesia: www.kemkes.go.id

Kilic,T. et al.. (2020). Molecular and Immunological Diagnostic Test of Covid-19 : Current status and Challenges. *J. Science*, 23, 101406.

Kim, D. et al.. (2020). The Architecture of SARS-Co-V-2 Transcriptome. *Cell*, 181,914-921.

KPCPEN. (2022, maret 17). Retrieved from Komite Penanganan COVID 19 dan Pemulihan Ekonomi Nasional: www.covid19.go.id

Le, C. (2016). Introductory Biostatistics. *New jersey : John wiley & Sons, Inc*.

Li, F. (2016). Structure, Function, and Evolution of Coronavirus Spike Proteins. *Annual Review Virology*, 3,237-261.

Li, Y. et al.. (2020). Stability issues of RT-PCR testing of SARS-CoV-2 for hospitalized patients clinically diagnosed with COVID-19. *J.Med. Virology*, 92, 903-908.

Liu,Y. et al.. (2020). The Development of Coronavirus 3CL-like protease (3CL(pro)) inhibitors from 2010-2020. *Eur.J.Med.Chem*, 206,112711.

Mahmoud,I.S. et al.. (2020). SARS-CoV-2 entry in host cells-multiple targets for treatment and prevention . *Biochimie*, 175, 93-98.

Mercurio,I. et al.. (2020). Protein structure analysis of the interactions beetwen SARS-CoV-2 spike protein and human ACE2 receptor : From Conformational changes to novel neutralizing antibodies. *Cell Mol. Life Science*.

Mok CKP et al. (2021). Comparison of the immunogenicity of bnt162b2 and coronavac covid-19 vaccine in hongkong. *Respirology*.

Mollaei et al.. (2020). Comparison five primer sets from different genome region of COVID-19 for detection of virus infection by conventional RT-PCR. *Iran Journal Microbiology*, 185-193.

Mousavizadeh,L. et al.. (2020). Genotype and phenotype of COVID-19 : Their roles in pathogenesis. *J.Microbiology Immunology Infection*.

Ozma,M.A.,et al.. (2020). Clinical manifestation, diagnosis, prevention and control of SARS-CoV-2 (COVID-19) during the outbreak period. *Infez.Med*, 28, 153-165.

Prazuck,T. et al.. (2020). Evaluation of performance of two SARS-CoV-2 Rapid IgM-IgG combined antibody tests on capillary whole blood samples from fingertip . *Plos ONE*, 15,e0237694.

Perez-Then et al. (2022). Neutralizing antibodies against the SARS-CoV-2 delta and

omicron variants following heterologous coronavac plus bnt162b2 booster vaccination. *Nat Med.*

Rehman,S.U et al.. (2020). Evolutionary Trajectory for the Emergence of Novel Coronavirus SARS-CoV-2 . *Pathogen*, 9,240.

Rose R et al. (2022). Humoral immune response after different SARS-CoV-2 vaccination regimens. *BMC Medicine*, 1-13.

Salazar E. et al. (2020). Convalescent plasma anti SARS-CoV-2 spike protein ectodomain and receptor-binding domain igg corolate with virus neutralization. *J clin Invest*, 130 (12) : 6728-38.

Schoeman, D. et al.. (2019). Coronavirus envelope protein : current knowledge. *Journal Virology*, 16,69.

Shyu, D. et al.. (2020). Laboratory test for Covid-19 : A Review of Peer-Reviewed Publications and Implications for Clinical use. *Mo.Med*, 117, 184-195.

Steensels et al. (2021). Comparation of sars-cov-2 antibody respone following vaccination with bnt162b2 and mrna-1273. *JAMA*, 326 (15); 1533-5.

Survey Tim Mitigasi IDI. (2021). *Data Kematian Dokter di Indonesia akibat penyakit COVID-19* . Jakarta: instagram : Tim Mitigasi PB IDI, Update data : 7 september 2021 (23.59 WIB).

Thanh Le,T. et al.. (2020). The COVID-19 vaccine development landscape. *Nat.Rev. Drug. Disc.*, 19, 305-306.

Udagama,B. et al.. (2020). Diagnosis COVID-19 : The Disease and Tools for Detection. *ACS Nano*, 14, 3822-3835.

Wang,F. et al.. (2020). An Evidence Based Prespective on mRNA-SARS-CoV-2 vaccine development. *Med. Sci. Monit.*, 26,e924700.

Wang,W et al.. (2020). Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. *J.Med. Virology*, 92, 441-447.

Weissleder,R. et al.. (2020). COVID-19 diagnostics in context. *Sci. Transl.Med*, 12.

Worldmeter. (2022). Retrieved from www.worldmeters.info/coronavirus.

X.N. Li. et al. (2021). Effectiveness of inactivated SARS-CoV-2 vaccines against the Delta Variant infection in Guangzhou : a test negative case control real world study. *Emerging Microbes & Infection*, vol 10 ; 1751-1759.

Z. Li et al. (2022). Characterization of SARS-CoV-2 Specific Humoral and Cellular Immune Responses Induced by Inactivated COVID-19 Vaccines in a Real-World Setting. *frontiers in Immunology*, 1-12.

Xu,H. et al.. (2020). High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int. J. Oral Sci.*, 12,8.

Zhang Y. et al.. (2021). Safety , Tolerability, and immunogenicity of an inactivated SARS-CoV-2 Vaccine in healthy adults aged 18-59 th: A Randomised,double-blind,placebo-controlled,phase 1/2 clinical trial. *Lancet*, 21(2) : 181-92.