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Review Article

Different COVID-19 mRNA-based Vaccine Platforms as The Booster Dose and Their Impact on Omicron: A Literature-Based Overview

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ABSTRACT

Globally, the vaccine has been determined as one of the principal policies to tackle the COVID-19 pandemic. However, some vaccinated individuals with two complete doses of inactivated experienced SARS-CoV2 infection, including the healthcare workers (HCWs). This threat led to the emergent need for a vaccine booster with different types of platforms aiming to enhance immunity from the Omicron variant. We conducted a literature study on the concept of heterologous compared to homologous vaccines in COVID-19 vaccination. We obtained 22 studies about COVID-19 booster vaccines. Referring to seven of them, we compared and distinguished between heterologous and homologous vaccines. We then reported the literature review according to PRISMA guideline. The study demonstrated qualitatively that heterologous vaccinations boosted antibody receptor binding domain, neutralizing antibody, and spike-specific Th1 type T cell responses and had an impact on omicron infection when compared to homologous vaccines. In conclusion, heterologous, mRNA based vaccine, predominantly induces cellular and humoral responses better than the homologous vaccine. This increased immune response is expected to provide profound immunity against the Omicron.

Keywords: vaccine, COVID-19, infectious disease, heterologous, booster *vaccine, COVID-19, infectious disease, heterologous, booster*

Highlights: The combination of two different COVID-19 vaccine platforms with mRNA based vaccine platforms strengthens the immune response and is expected to be able to counteract the Omicron variant

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INTRODUCTION

In May-July 2021, various variants of SARS-COV-2 appeared, followed by its rocketing transmission in Indonesia. The Delta variant dominantly emerged.[1] Many patients were infected by this variant, including HCWs who previously received two complete doses of vaccination. Due to the surge of breakthrough infection even after completing two doses of vaccine, as recommended by the National Immunization Expert Advisory Committee or ITAGI, giving the third dose of vaccination was considered necessary.[2,3]

Our prior study confirmed that health care providers (HCPs) were susceptible to breakthrough infection, specifically them with hypertension. The most effective vaccines, by far, are known to increase the production of neutralizing antibodies which will later prevent infection. One of the strategies implemented is heterologous prime-boost vaccination.

Several previous studies have proven this method is more effective in enhancing vaccine action in preclinical studies. However, research on humans' immune responses using this method is still being carried out.[3] Heterologous prime-boost vaccination is a vaccine method by inserting the same nucleotide or antigen expressed by different vectors for primary or booster/repeat vaccination. According to WHO (2021), other reasons for using heterologous vaccines include reducing vaccine adverse reactions, increasing immunity to the SARS-CoV-2 virus, and strengthening vaccine effectiveness. Prior research on the heterologous prime-boost vaccine, in particular the combination of exogenous (inactivated vaccines) and endogenous (mRNA vaccines), had demonstrated considerable improvements in the immunogenicity of the HIV-1, influenza, and particularly the SARS-CoV-2 vaccines.[4,5]

As above mentioned, the use of a heterologous vaccine for booster dose is to anticipate the emergence of SARS-CoV-2 infection from various variants, especially Omicron, that is so contagious.[6-13] By far, several studies on the effect of booster vaccine in preventing Omicron infection have shown varying results. There are no clear studies stating whether to use homologous or heterologous vaccines for omicron variations.[14-16] In Indonesia, this condition is a dilemma because vaccine availability is also limited there are no clear references that compare the two types of vaccines. In this study, we reviewed preceding literature about the administration of booster vaccine with two different platforms and how it prevents Omicron infection so that we are right in giving vaccine boosters.

MATERIALS AND METHODS

Materials

We performed an electronic literature search from PubMed, Springer, and the Cochrane Library to identify studies exploring the use of heterologous COVID-19 vaccine regimen. The keywords used were (heterologous) AND (prime-boost) AND (inactivated) AND (SARS-CoV-2) AND (Omicron) AND (vaccine) AND (neutralizing antibody) AND (T cell response) AND (IgG subtypes). The last search was conducted from November 21st 2021 until June 30th 2022.

Methods

Protocol trial, review, comparative study, experimental study, case report, pre proof, and systematic review were eliminated. The relevant studies were collected and screened as shown in Figure 1 and Figure 2.

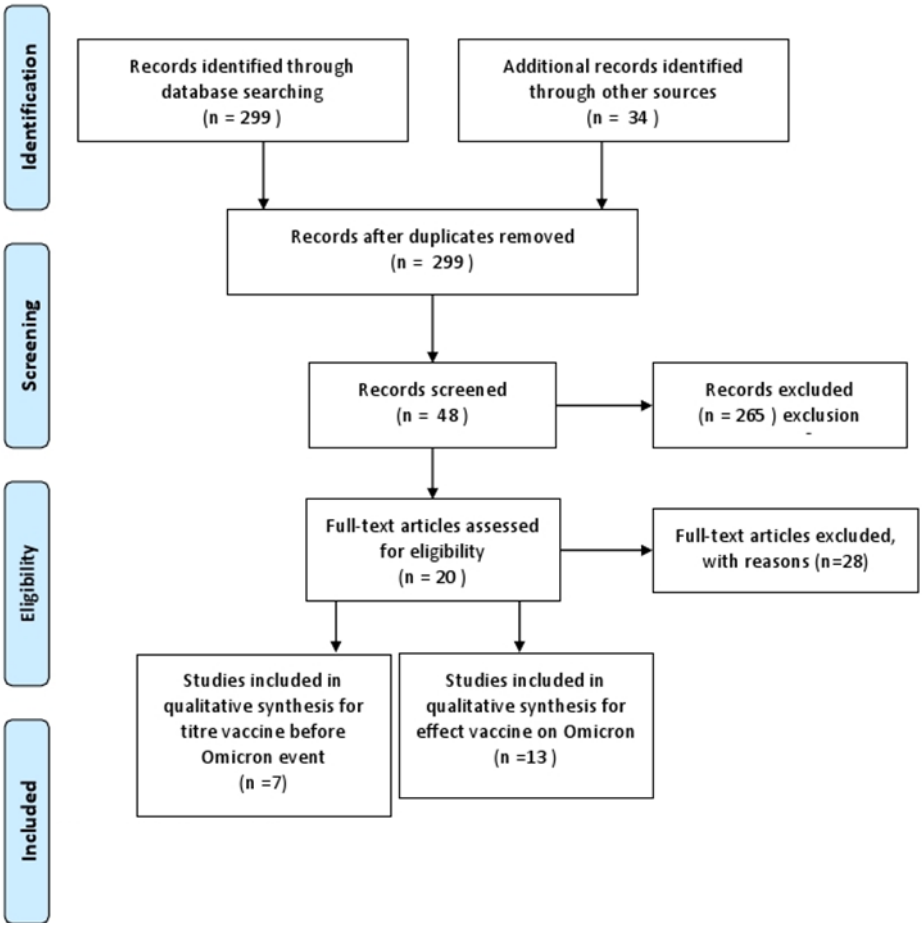

Figure 1. Literature Selection

We made a descriptive comparison between immunological parameters after heterologous and the homologous vaccine. We included the author's name, the year of study, the country of research and publication, the types of vaccine, and the final result. We give (+++) for an increase in immunological parameters more than >100x; (++) if 50-100x; and (+) when <50x.

RESULTS AND DISCUSSION

We derived 20 studies from the literature search and summarized them in Table 1 and 2. Of these subsequent studies, the mRNA vaccine was mostly used as the heterologous booster vaccine. Table 1 compares the immune response after heterologous vaccine with the homologous vaccine. Seven studies showed that heterologous vaccines provided an enhanced receptor-binding domain (RBD) antibody, neutralizing antibody, and spike-specific Th1 type T cell responses better than homologous vaccines.

Thirteen studies above stated that booster vaccines, both heterologous and homologous, boosted protection against Omicron variants, despite decreasing neutralizing antibody titers. Heterologous booster provides superior protection compared to homologous ones in preventing Omicron infection. Cheng study in 2022 stated that the majority of people receiving three CoronaVac treatments by failed to produce Omicron-neutralizing antibodies.

Table 1. The comparison of immune response between heterologous vaccine and homologous vaccine before Omicron.

Study	Platform vaccine	Heterologous			Homologous		
		Antibody RBD	Antibody Neutralizing	Spike T cells	Antibody RBD	Antibody Neutralizing	Spike T cells
Atmar et al. 2021	mRNA/mRNA vs mRNA/viral Vector	+++	+++	Not exam	++	++	Not exam
Xinxue Liu et al. 2021	Chad/ChAd or BNT/BNT vs Chad/BNT or BNT/Chad	+++	+++	+++	++	++	++
Joana Barros-Martins et al. 2021	ChAd/BNT vs ChAd/ChAd	+++	+++	+++	++	++	++
Tensbuch et al. 2021	ChAdOx1 nCoV-19 / BNT162b2	Not exam	+++	Not exam	Not exam	++	Not exam
Kant et al. 2021	ChAdOx1/ChAdOx1 vs ChadOx1/ BBV152 ChadOx1	+++	+++	Not exam	++	++	Not exam
Benning et al. 2021	ChAdOx1 nCoV-19 / BNT162b2	++	++	Not exam	++	++	Not exam
Hilus et al. 2021	BNT/BNT or ChAdOx/ChadOx vs ChAdOx/BNT	++	++	+++	++	++	++

Table 2. Effect vaccine booster for omicron event.

Author	Vaccine booster	Effect to Omicron
Ai et al., (2022)	BBIBP-CorV vs ZF2001	Reduced potency of geometric mean neutralizing titers (GMTs), higher GMTs in heterologous booster group.
Wang et al, (2022)	BBIBP-CorV vs ZF2001	Homologous or heterologous vaccine reduces the omicron escape from neutralization even though the levels are decreased.
Poh et al., (2022)	mRNA-1273 vs BNT123b2	A stronger neutralizing response to the Omicron variant was induced by the heterologous mRNA-1273 booster vaccine in older people than by the homologous BNT123b2 vaccine.
Zuo et al., (2022)	inactivated vaccine (CoronoVaccine, BBIBP-CorV) vs mRNA (BNT162b2, mRNA1273)	In people who have received two doses of an inactivated vaccine and a booster dose of an mRNA vaccine, the levels of specific antibodies, responses from memory B and T cells, and neutralization activities against the SARS-CoV-2 virus and VOC, including the novel Omicron form, have significantly increased.
Wang et al., (2022)	Inactivated vaccine against RBD recombinant subunit vaccine (Zifivax) (I-I-S) (CoronaVac or BBIBP-CorV)	In comparison to homologous booster(I-I-I), heterologous booster (I-I-S) has a greater ability to neutralize various VOCs, including omicron.

Author	Vaccine booster	Effect to Omicron
Du et al., (2022)	Recombinant protein subunit vaccines, inactivated vaccines, vector vaccines, and mRNA vaccines (BNT162b2 and mRNA-1273), as well as inactivated vaccines (BBIBP-CorV and CoronaVac) (ZF2001 vaccine)	The mRNA vaccinations were generally very effective against the Omicron variety, especially the mRNA-1273 vaccine. Furthermore, it didn't seem like heterologous booster immunization regimens were worse than homologous booster vaccination regimens.
Au and Cheung (2022)	mRNA vaccine (BNT162b2 vaccine and mRNA-1273 vaccine), inactivated vaccine (BBIBP-CorV and CoronaVac), vector vaccine (ADZ1222 vaccine and Ad26.COV2.S vaccine)	Three dosing regimens of homologous and heterologous drugs effectively reduce omicron infection. Any original vaccine that includes an mRNA booster provides high levels of protection comparable to a three doses mRNA regimen.
Suah et al., (2022)	BNT162b2, CoronaVac, and AZD1222	Homologous BNT162b2 boosting was less successful than heterologous boosting for CoronaVac and AZD1222 primary immunization patients.
Cheng et al., (2022)	CoronaVac or BNT162b2	Homologous or heterologous booster doses of BNT162b2 improve neutralizing antibody levels against the Omicron variety after two doses of either CoronaVac or BNT162b2. Most participants took three doses of CoronaVac without producing any Omicron-neutralizing antibodies.
Fang et al. (2022)	mRNA vaccine	After a single dose in animal models, the heterologous Omicron LNP-mRNA booster induced a more potent anti-Omicron antibody response than the WT booster.
Ai et al., (2022)	homologous booster group for BBIBP-CorV and a heterologous booster group for BBIBP-CorV/ZF2001	A marked decline in pVNT titre against Omicron after 14 days following booster doses of homologous or heterologous vaccine when compared to the prototype. When compared to the BBIBP-CorV homologous group, the GMT of the BBIBP-CorV/ZF2001 heterologous group was significantly higher.
Perez-Then., et al (2022)	CoronaVac plus BNT162b2	In comparison to the original strain and the Delta variation, neutralizing antibody titers for Omicron were decreased by 7.1-fold and 3.6-fold, respectively.
Costa Clemens et al., (2022)	A third homologous dose of CoronaVac vs a recombinant adenoviral-vectored ChAdOx1 nCoV-19 vaccine (AZD1222, AstraZeneca), an mRNA vaccination (BNT162b2, Pfizer-BioNTech), or an mRNA vaccine (Ad26.COV2-S, Janssen).	The live virus neutralization titres against both the delta and omicron versions are increased by heterologous boosting. After an mRNA spike, the highest antibody concentrations are seen.

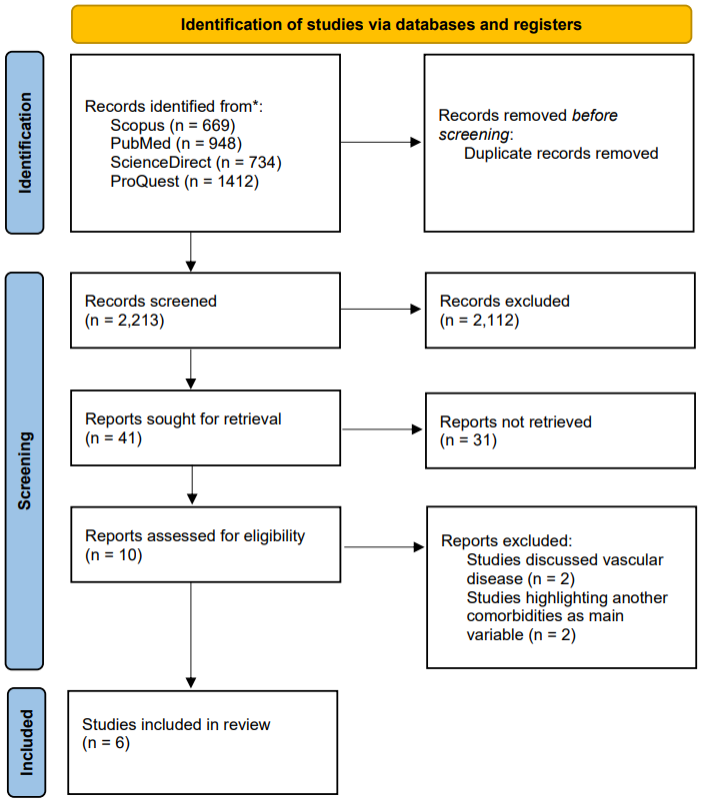

Figure 2. Schematic Workflow of Studies' Finding.[11]

Table 3. Characteristics of Selected Studies

Author	Year	Location	Sample Size	Ab	Vaccine	Dose	Measurement (Weeks after Dose 2)	Age (Years)	Male (%)	BMI (kg/m^2)	Hyper-tension (%)	Dia-betes (%)	Smokers (%)
Watanabe et al[13]	2021	Japan	68	IgS	BNT162b2	2	1-4	29.0 (17.0)	39.5	22.4 (5.5)	15.3	2.4	31.7
Ebinger et al[14]	2022	USA	843	IgS	BNT162b2	2	1, 2, 8, 16, 24, 32, 40	45.0 (13.0)	30.0	-	15.2	-	-
Delgado et al[15]	2022	Spain	2174	IgS	BNT162b2	2	12	45.9	19.9	24.1	8.1	-	22.2
Soegiarto et al[16]	2022	Indonesia	101	IgG	CoronaVac	2	4, 12, 20	47.7 (18.9)	59.5	-	23.7	17.8	10.9
Parthymou et al[17]	2022	Greece	712	IgS	BNT162b2	2	3, 12	50.8 (11.4)	37.6	26.7 (4.9)	16.2	7.0	34.4
Rifai et al[18]	2022	Indonesia	155	IgG	CoronaVac	2	8, 24	39.0 (9.2)	48.3	27.9 (7.3)	18.7	-	-

Table 4. Results of Selected Studies

Author	Vaccine	Results
Watanabe et al[13]	mRNA	Hypertensive patients presented lower antibody response compared to normotensive (650 ± 1192 vs 1911 ± 1364, p = 0.001). Hypertensive patiens shown significant beta coefficient on univariate and multivariate analysis with -1033.16 (p = 0.005) and -973.27 (p = 0.036) respectively.
Ebinger et al[14]	mRNA	Hypertensive patients shown significant beta coefficient on multivariate analysis with -0.17 and SE of 0.08 (p = 0.041).
Delgado et al[15]	mRNA	Hypertensive patients shown insignificant fold changes with -1.02 (p = 0.8584).
Soegiarto et al[16]	Inactivated	Hypertensive patients shown significant beta coefficient on multivariate analysis with -11.208 (p = 0.038). Patients with history of cardiovascular diseases shown non-significant beta coefficient on multivariate analysis with -10.040 (p = 0.969)

Parthymou et al[17]	mRNA	Hypertensive patients shown insignificant beta coefficient on multivariate analysis with -0.0454 (p = 0.3276).
Rifai et al[18]	Inactivated	Patients with high systolic blood pressure and high diastolic blood pressure shown significant correlation with lower antibody response with R coefficient of -0.172 (p = 0.016) and -0.139 (p = 0.043) respectively second months after vaccination, and R coefficient of -0.284 (p = 0.046) and -0.475 (p = 0.006) respectively six months after vaccination.

The Dynamics of Antibody Level Following Homologous vs Heterologous Vaccine

The development of vaccines currently focuses on maximizing the immune response targeting RBD. It is assumed that antibodies bound to this domain can prevent the virus from entering the host cell. Other epitopes of protein S can also be targets of vaccines that can produce significant effects. Polyclonal antibodies against protein S epitopes besides RBD may also inhibit viral binding.[17]

According to a prior study, 88-97% of participants who got the second dosage of CoronaVac at 14-day intervals had antibodies that selectively bind to RBD on day 28 after treatment. Meanwhile, in the 28-days interval group, 92-100% of participants had an increase in RBD-specific binding antibodies. Furthermore, neutralizing antibodies were detected in all participants 21 days following the second dose of CoronaVac.[18,19]

Selecting a booster vaccine with variable work mechanisms (heterologous) is expected to increase the immunity against SARS-CoV-2 virus infection. Research on the administration of the third dose of Moderna has also begun to determine its effectiveness by measuring antibody titers. An observational study was conducted on a group of healthy adults in Germany who used a combination of the ChAdOx1 nCoV-19 vaccine (AstraZeneca), an mRNA booster vaccine, and BNT162b2 (Pfizer) or mRNA-1273 (Moderna). Of the 216 subjects, the participants were divided into 3 groups; 97 subjects in the heterologous group (AstraZeneca - Pfizer/Moderna), 55 subjects in the homologous AstraZeneca group, and the mRNA homolog group with 62 subjects involved.[20]

The results of the heterologous vaccine group, in which mRNA was used as the third dose, showed that the concentrations of spike-specific IgG protein, neutralizing antibody, and spike-specific CD4 T cells were significantly higher than the AstraZeneca homolog group or mRNA. CD8 T cell levels were also significantly higher in the heterologous vaccine group.[20] Researchers performing a similar experimental study concluded that the heterologous vaccines can generate stronger humoral and cellular immune responses against SARS-Cov-2 infection with the sufficient reactogenicity profile.[20-23]

Zhang's study in 2021 was conducted on a group of mice with immune characteristics after the third booster with various types of vaccines. Previously, the group of rats had been given two inactivated virus (INA) vaccines. Humoral and cellular immune responses (T cells) were observed after administration of recombinant RBD vaccine (rRBD), Ad5-vectored adenovirus (rAd), mRNA vaccine and INA vaccine. Neutralizing antibody (NAb), which targets the spike protein, was also observed in the mice group. This study concluded that the heterologous vaccine, a combination of INA with booster rRBD, rAd, and mRNA, increased NAb antibody titres and Th-1 type T cell response. The mRNA and rAd vaccines showed the highest NAb titers and T cell responses. The increased response of Th-1 cells can be seen from the high levels of IFN-γ and IL-2.[21]

Other studies showed that increase in RBD, Nab, and spike T-cell responses was observed after mRNA vaccine as the booster for adenovirus vaccine in the majority of the adult population, especially in healthcare

workers.[20,24-31] Kant *et al.* (2021) revealed that administering inactivated virus and viral vector vaccine induced high neutralizing immune response against alpha, beta, and delta variant of SARS-COV-2.[32]

Good Responders vs Non/Less Responders

According to numerous research, those over 60 are more likely to have COVID-19 infection and experience worse outcomes, especially those who already have coexisting illnesses. Typically, this risk increases with age.[33-35] Older individuals are less responsive to the vaccine due to the aging of immune cells. The innate and adaptive immune systems' cellular and molecular components can be affected by modifications associated with aging in general.[35,36] Various types of vaccines have been developed since the outbreak continued spreading. Similarly, multiple studies have indicated that administering vaccinations containing mRNA, adenovirus vectors, or inactivated viruses can generate neutralizing antibody responses in older persons. A study showed that CoronaVac is highly immunogenic in adults aged above 60. Neutralizing antibody responses observed in groups of individuals receiving two vaccines at doses of 3µg or 6µg had similar results. The seroconversion rate and Geometric Mean Titer (GMT) of the neutralizing antibody were low before the second dose in the study's initial phase. In this trial, the GMT range for subjects who got doses of 3 g and 6 g after the second dosage was 42.2 to 64.4, and the seroconversion rate was 95%.[37]

Nonetheless, many studies still do not include groups of individuals who are immunocompromised, such as patients receiving immunosuppressants, patients in immunodeficiency states, organ donor recipients, and patients with malignancies undergoing chemotherapy with cytotoxic agents. Patients with malignancy usually have 10-30 times higher mortality rate than normal individuals.[38]

Several studies have shown a decrease in the immune response to both mRNA vaccines and primary infection of COVID-19 in immunocompromised individuals. However, this may differ depending on the type of treatment received by the patient.[39-42] For example, B-cell depleting antibodies for patients with autoimmune disorders or patients with chronic lymphocytic leukemia are thought to reduce humoral immune responses and vaccination effect. However, patients receiving anti-TNF therapy are still able to receive the vaccine.[40, 41, 42] Donor recipients are known to show poor antibody responses to mRNA vaccines. Similar to those who have solid or hematological malignancies, patients in this situation typically have a drop in antibody responses following the first vaccine but an improvement following the second immunization.[39] In immunocompromised patients (kidney transplant and CLL patients), the third dose of homologous vaccine mRNA induced an average increase in SARS-Cov-2 anti-spike IgG levels.[43]

Factors Affecting Each Group of Responder

In our previous study, hypertension has been noted as a factor lowering vaccine titers even after two doses of inactivated vaccine. It also was known to elevate the risk of breakthrough infection.[44] The following study on mRNA vaccine boosters after two doses of inactivated vaccine is still underway.

According to other literatures, patients with the haemtological disease are less likely to respond to the SARS-CoV-2 virus vaccine. Agha *et al*. (2021) showed that 46% of patients with haematological malignancies did not respond after four weeks of the second dose of SARS-CoV-2 mRNA vaccine.[45] Moreover, in patients with chronic lymphocytic leukemia, only about 23% of patients experienced seroconversion. Another study compared the antibody response to the third dose of mRNA vaccine (Pfizer/Moderna) with AstraZeneca in

patients taking rituximab. The factor that causes a reduced response is the lack of B lymphocytes following the administration of immunosuppressant such as rituximab.[46]

Age is also an influential factor. A study conducted on groups of individuals with an age range of 18 – 59 years had seroconversion results of 97% and GMT 44.1.[18] However, in patients over 60, seroconversion and neutralizing antibody were lower at the first dose. Another study also compared the immune response in the age group of 80 and above and the younger age group, after the first vaccination. Patients above 80 had less binding IgG or IgA than the younger age group. The age group over 80 years old had decreased levels of interferon- and interleukin-2 production by SARS-CoV-2 spike-specific T cells. However, elderly patients had larger levels of SARS-CoV-2 spike-specific memory B cells following the second dosage of the vaccination.[47] This signifies that a good immune response occurred in the age group under 60, and a poor one occurred in the younger group.

Regrettably, the factors affecting the effectiveness of this booster are not extensively discussed in our study. We also did not conduct any quantitative analysis due to the unavailability of the specific software. Nonetheless, we managed to depict how booster vaccines, both heterologous and homologous, promote a better immune response. Follow-up studies on the influential factors affecting boosters' effectiveness are beneficially required.

The Impact of Booster Vaccine on Omicron Infection

Numerous theories have been put out to explain how Omicron, which has a high transmission rate, might evade the booster shot. Neutralizing antibody titers for Omicron were lower than those for the original strain and the Delta variation by 7.1-fold and 3.6-fold, respectively.[48]

In contrast to two weeks of the second dosage, the mRNA booster vaccine caused a >40-fold loss in neutralizing capacity against the Omicron version, according to animal experiments.[49] Mice were given either a homologous booster with LNP-mRNA or a heterologous booster with Omicron LNP-mRNA as a booster injection after two doses of the mRNA vaccines. Two weeks following the booster injection, compared to the day before the booster, the antibody response to Omicron jumped 40-fold. The heterologous Omicron LNP-mRNA booster evoked neutralizing titers 10–20 fold higher with equal titers against the Omicron variation compared to the homologous booster against that variation.[49]

According to Wi Ying Au and colleagues' investigation, COVID-19 infections brought on by the omicron variant can be successfully reduced by both homologous and heterologous three-dose regimens. Heterologous booster provides superior protection compared to homologous on Omicron.[50] The majority of recipients of three doses of CoronaVac did not produce neutralizing antibody responses to Omicron, according to just a research by Samuel M. S. Cheng et al.[51]

STRENGTH AND LIMITATION

The strength of this study was that this is the first literature discussing the administration of two COVID-19 vaccines with different platforms with a comprehensive manner based on previous human and animal trials in various countries. Whereas this study came out with a limitation to be conducted at the time when no trial on the combined effectiveness of two COVID-19 vaccine platforms was available, therefore, a quantitative study could not be performed.

CONCLUSIONS

As this pandemic still causes a continuous health burden, the vaccine has been one of

the worldwide significant steps in overcoming it. After two doses of vaccination, a booster vaccine with heterologous with mRNA-based is thought to improve the cellular and humoral immune systems, enhancing RBD antibody, NAb, and spike-specific Th1-type T cell responses.

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This study did not receive funding.

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest.

AUTHOR CONTRIBUTION

Writer, literature searcher, collecting data from literature: BAM, Conceptor and supervision: GS, review and supervision: LW and DP.

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