Article

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Antibody Response after a Booster COVID-19 Vaccine Mixing in Vietnam

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Background: The booster vaccine is essential for maintaining the antibody against the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) virus. This study sought to evaluate the antibody response after booster coronavirus disease 2019 (COVID-19) vaccines and compare the immunogenic by different vaccine combination strategies.
Methods: A cross-sectional study in Hanoi, Vietnam was conducted on 679 adult participants who received two doses of vaccines with any combination of AstraZeneca, Pfizer, and Moderna during the COVID-19 vaccination campaign in 2021. The SARS-CoV-2 S1/S2 Immunoglobulin G (IgG) antibody concentrations were measured by the LIAISON SARS-CoV-2 S1/S2 IgG and presented as arbitrary units.
Results: We found that the median (interquartile range (IQR)) of IgG level among those who completed two doses of Moderna and Pfizer was 484.55 (284.80) AU/mL and 349.00 (362.50) AU/mL, respectively. Meanwhile, the counterpart of AstraZeneca was 110.00 (128.10) AU/mL. Mixing two doses of AstraZeneca-Pfizer has higher odds of having high IgG level than two doses of Pfizer (Odds Ratios (OR) = 2.94, 95% Confidence Intervals (CI): 1.57–5.51), AstraZeneca (OR = 28.50, 95% CI: 15.00–54.14).
Conclusions: We found that the matching two doses of mRNA vaccines are more immunogenic as compared to the DNA vector vaccines. Furthermore, mixing AstraZeneca-Pfizer has higher antibody quantities as compared to matching vaccines, while lower the rate of advert events.

Keywords: COVID-19 vaccination; mixing; matching; antibody response; Vietnam

Introduction

The global efforts to combat the coronavirus disease 2019 (COVID-19) pandemic have led to the rapid development and distribution of various COVID-19 vaccines. These vaccines have proven to be effective in preventing COVID-19 and reducing its severity [1]. However, the emergence of new severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) variants and the waning of immunity over time have necessitated the use of booster vaccinations to bolster and extend protection [2]. The current research field has been exploring the antibody response following booster COVID-19 vaccinations, with a particular emphasis on vaccine mixing and matching [3,4].

Many studies have investigated the antibody response after administering booster COVID-19 vaccinations, illuminating the effectiveness and potential advantages of mixing and matching different vaccines [3,5]. Recent findings have shown that booster doses markedly elevate antibody levels and offer extra protection against SARS-CoV-2 virus infection [6,7]. Nevertheless, the optimal strategy for booster vaccinations, including the use of mixed (heterologous) vaccine combinations, continues to be a subject of debate and investigation.

A growing body of research suggests that mixed boosters (heterologous) may be more effective than receiving the same vaccine (homologous). For example, the UK's COV-BOOST study (ISRCTN 73765130) in phase II, evaluated several boosters (ChAdOx1, BNT162b2, mRNA-1273, NVX-CoV2373, VLA2001, and CVnCov) in individuals initially primed with ChAdOx1 or BNT162b2 vaccinations. After receiving two doses of BNT162b2, all groups, except those given VLA2001, observed an increase in antibody and neutralizing responses, observed an increase in antibody and neutralizing responses, with the most robust response occurring in the group that received mRNA boosters [8]. In the US MixNMatch trial with phase I/II, three boosters (BNT162b2, mRNA-1273, or Ad26.COV2.S) were tested on people who initially received BNT162b2, mRNA-1273, or Ad26.COV2.S, resulting in nine combinations [9]. According to preliminary findings, all homologous and heterologous booster com-

binations exhibited an acceptable safety profile and raised binding and neutralizing titers of antibodies against the SARS-CoV-2 pseudo-virus in adults. It's important to note that heterologous boosters produced larger titers than homologous boosters. All groups, except the homologous Ad26.COV2.S-boosted subgroup showed an increase in spike-specific T-cell responses [9].

Conversely, other studies argue for the efficacy of homologous booster regimens, emphasizing the preservation of immune memory and the potential for stronger and more focused immune responses against the specific target antigen. These studies suggest that using the same vaccine for boosters may result in a more predictable and consistent immune response, particularly in terms of neutralizing antibody production [6,10].

This study focuses on examining the antibody response after booster COVID-19 vaccines in Hanoi, Vietnam, with an emphasis on the effects of combining different vaccines. By evaluating the immune response in the study population, we aim to shed light on the effectiveness of booster doses and the potential benefits of mixing various COVID-19 vaccine types.

Materials and Methods

The study was conducted in accordance with the Declaration of Helsinki and approved by the Council of Ethics in Biomedical Research of the National Institute for the Control of Vaccine and Biologicals (No. 0126/2022/KDQG-HDYD) before commencing official data collection. All study participants provided written informed consent, and their information was kept confidential and solely used for research purposes.

Participants

Participants in the study were required to be 18 years of age or older and have received the COVID-19 vaccine (Pfizer-BioNTech, Astra Zeneca, Moderna, Cambridge, MA, USA) between April and December 2021 in the National Institute of Control for Vaccines and Biologicals (NICVB), Hanoi, Vietnam. Inclusion criteria involved receiving two doses of the vaccine, whether the same or a different variety, at NICVB and providing written informed consent for research participation. Participants who received the vaccine were screened beforehand, ensuring they were not at risk for underlying medical conditions, and received no medical or other treatment during the study.

Participants were instructed to return to the NICVB within 14–28 days after the second vaccination dose for blood specimen testing. Those who did not adhere to the protocol were excluded from the study. A total of 679 vaccine recipients were included in this study, with an average age of 46 years (ranging from 20 to 78 years old). Blood samples were collected, the serum was refrigerated after blood collection, and antibody testing was completed within two days.

To record adverse events, a structured questionnaire was developed. Common adverse event following the first and second vaccine doses was documented through telephone interviews conducted by nurses. Serious adverse events, including cases of shock, were recorded by medical doctors during the 30-minute monitoring period after vaccination.

SARS-CoV-2 Antibody Measurement

Each blood specimen was examined for antibodies against SARS-CoV-2 using the LIAISON® SARS-CoV-2 S1/S2 Immunoglobulin G (IgG) assay (DiaSorin S.p.A., Saluggia, Italy). The LIAISON® SARS-CoV-2 S1/S2 IgG is a chemiluminescence immunoassay (CLIA) designed for the qualitative detection of IgG antibodies to SARS-CoV-2 in human serum, and plasma (sodium heparin, lithium heparin, and potassium Ethylene Diamine Tetra Acetic (EDTA)). The analyzer automatically calculates SARS-CoV-2 S1/S2 IgG antibody concentrations, which are expressed as arbitrary units (AU/mL) and grades the results accordingly. A concentration of <15 AU/mL was considered negative and that of ≥ 15 AU/mL was deemed positive.

Data Analysis

The data collected were input and cleaned using the Epidata 3.1 software (The EpiData Association, Odense, Denmark). Data analysis was carried out using STATA 16 (StataCorp LP, College Station, TX, USA) and R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics, including frequencies and percentages, were used to characterize the demographic attributes of the participants. Antibody quantities were presented as the median and interquartile range (IQR). The antibody response was also categorized into high and low IgG levels, with the median value serving as the cutoff point. To compare the clinical variables between groups associated with the vaccine and those not associated with the vaccine, various statistical tests were employed. As the data of the IgG level was not distributed normally, the non-parametric tests were applied. The Mann-Whitney U-test was used to compare IgG levels between two groups (i.e., gender, adverse effects), while the Kruskal Wallis test was applied to compare the IgG levels among three groups or more (i.e., age groups, combination of vaccines). Factors associated with a high antibody response were examined using logistic regression. Both unadjusted and adjusted logistic regression models were employed to analyze the association between high levels of IgG and the mixing and matching vaccine strategy. A significance level of $p < 0.05$ was applied.

Table 1. Descriptive statistics and associations of selected factors with Immunoglobulin G (IgG) levels (AU/mL) post-administration of two doses of coronavirus disease 2019 (COVID-19) vaccines (n = 679).

Variable, n (%)	n (%)	IgG Level (AU/mL) Median (IQR)	Value of test	*p*-value
Age groups			$\chi^2 = 3.84$	0.15
18–34 years old	120 (17.67%)	294.50 (403.40)		
35–54 years old	453 (66.72%)	282.00 (375.80)	df = 2	
55–73 years old	106 (15.61%)	285.50 (332.60)		
Gender				
Male	405 (59.65%)	266.00 (374.60)	z = –2.393	0.0167*
Female	274 (40.35%)	323.50 (374.00)		
Adverse effects				
No	360 (53.02%)	282.50 (383.30)	z = –0.413	0.68
Yes	319 (46.98%)	289.00 (369.60)		
Combining two doses			$\chi^2 = 281.073$	0.0001***
Astra-Pfizer	95 (13.99%)	468.70 (263.70)		
Astra-Astra	255 (37.56%)	110.00 (128.10)		
Moderna-Moderna	146 (21.50%)	484.55 (284.80)	df = 3	
Pfizer-Pfizer	183 (26.95%)	349.00 (362.50)		

Note: *p-value less than 0.05; ***p-value less than 0.001. IQR, interquartile range.

Results

Characteristics of the Participants and Quantities of IgG Level

The characteristics of participants according to the IgG levels are presented in Table 1. Generally, most of the participants were males and aged between 35–54 years. The results highlighted a significant difference in IgG level by gender, with a p-value of less than 0.05 (p = 0.0167). Concerning age groups, subjects aged 18–34 years were more likely to have a higher IgG level than those in the 55–73 years old group (Median (IQR): 294.50 (403.40) vs. 285.50 (332.60) AU/mL), although this difference was not statistically significant. The rate of experiencing at least one advert event was 46.98%. There were statistically significant differences in the mean IgG levels among different vaccination strategies. The highest median IgG level was observed in recipients of two matching doses of Moderna (Median (IQR): 484.55 (284.80) AU/mL), followed by those who received a combination of Astra-Pfizer (Median (IQR): 468.70 (263.70) AU/mL) (Table 1).

In this study, the largest proportion of individuals in the lower IgG group had received two doses of AstraZeneca (65.96%). On the other hand, individuals who had received two doses of Pfizer or two doses of the Moderna vaccine accounted for over 30% of the high IgG group (32% and 34.57% for two doses of Pfizer and two doses of Moderna recipients, respectively). Interestingly, the study revealed that over 20% of individuals who received a combination of AstraZeneca and Pfizer vaccines were classified in the high IgG group (22.57%). Meanwhile, a remarkably similar percentage of those who were administered two doses of Pfizer vaccines fell into the low IgG group (21.58%) (Fig. 1).

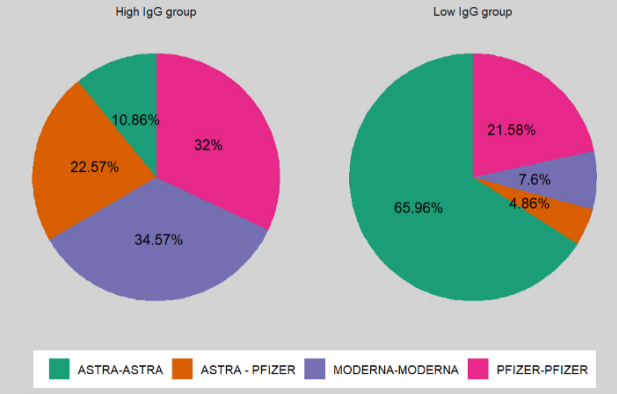

Fig. 1. The Proportion of IgG levels by Vaccine Types (n = 679).

Regarding advert events, the same five types of side effects—fever, headache, fatigue/muscle pain, injection site pain, and shock—were observed following both vaccine doses for each participant, with shock only occurring after the first dose (Fig. 2). The Astra-Pfizer group had the lowest frequency of adverse events among all the vaccination strategies, with no reported cases of shock. The frequency of some common adverse events was fatigue/muscle pain (n = 7), fever (n = 5), headache (n = 5), pain at the site (n = 35) (Fig. 2). In contrast, the Moderna-Moderna and Pfizer-Pfizer strategies exhibited a significantly higher frequency of adverse events, including shock cases (Fig. 2).

Antibody Quantities Following Matching and Mixing COVID-19 Vaccines

After receiving two doses of vaccines, the Astra-Astra combination exhibited the lowest IgG levels, with approxi-

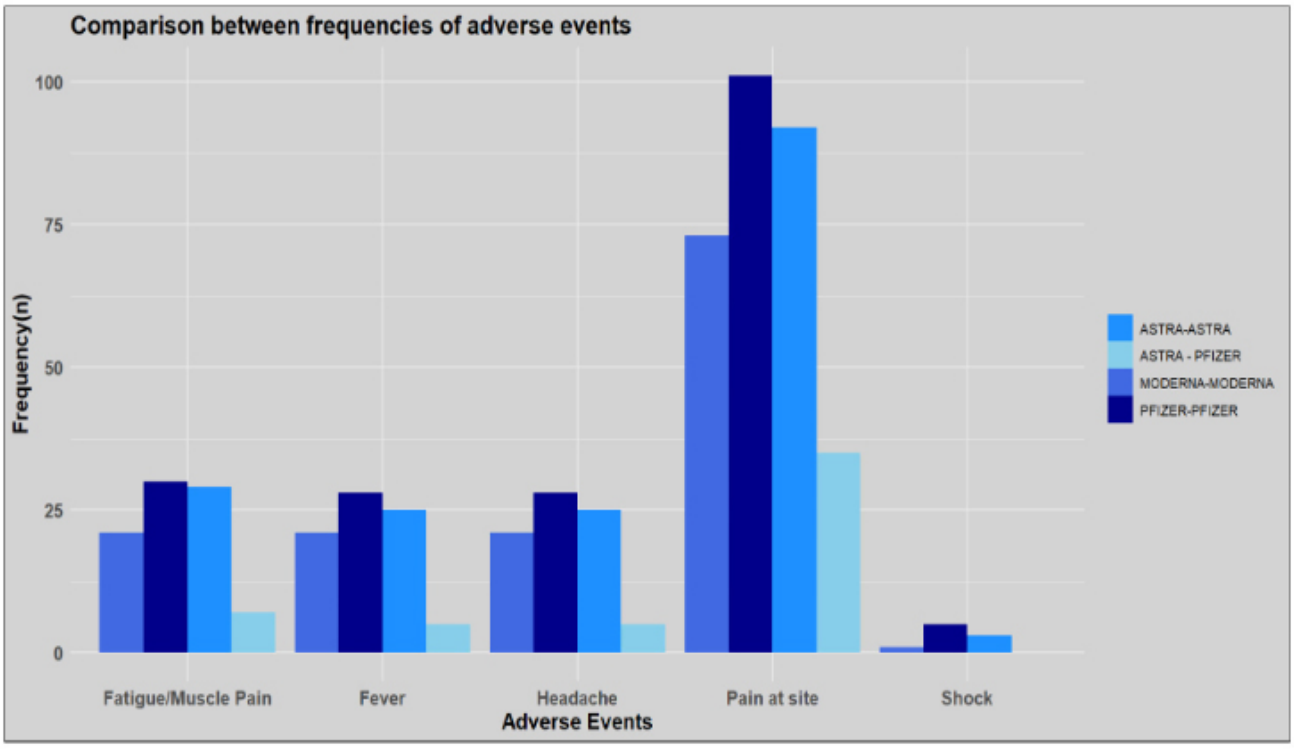

Fig. 2. Frequency of adverse events among recipients following complete two doses of COVID-19 vaccines with different combinations of vaccine types (n = 679).

mately one-third of those in the Pfizer-Pfizer group (110 vs. 349 AU/mL) (Table 1, Fig. 3). The Pfizer-Pfizer combination displayed lower IgG levels compared to the other two combinations (Moderna-Moderna and Astra-Pfizer) (Table 1, Fig. 3).

Table 2 presents the factors associated with post-immunization IgG levels. In the unadjusted model, a statistically significant difference in IgG levels was observed among individuals receiving three matching vaccination strategies ($p < 0.001$). After adjusting for age and gender, these differences remained statistically significant. Further adjustment for adverse events, statistically significant differences in IgG levels persisted among these three matching vaccine strategies. Notably, individuals receiving two doses of Moderna, or two doses of Pfizer had approximately 28.39 and 9.72 times higher odds, respectively, of having high IgG levels.

When comparing the mixing vaccine strategy (Astra-Pfizer) with the matching vaccine, a statistically significant difference was observed in the rate of high IgG levels favoring the mixing strategy. In the adjusted model (Model 3), the Astra-Pfizer mixed vaccines were associated with higher odds of having high IgG level when compared to matching two doses of AstraZeneca (Odds Ratios (OR) = 28.5, 95% Confidence Intervals (CI): 15.0–54.14), and Pfizer (OR = 2.94, 95% CI: 1.57–5.51) (Table 2).

Discussion

COVID-19 vaccines, such as those based on mRNA technology (e.g., Pfizer-BioNTech and Moderna) or adenovirus vectors (e.g., Oxford-AstraZeneca and Johnson & Johnson), stimulate the immune system to recognize and initiate a response against the SARS-CoV-2 spike protein [11]. This protein is crucial for viral entry into human cells. After vaccination, B cells are activated, which results in the production of antibodies that are specifically targeted at the spike protein [12]. These antibodies can neutralize the virus by preventing its attachment to host cells and subsequent infection. This study aimed to assess the antibody response after the mixing and matching of two doses of COVID-19 vaccination in Hanoi, Vietnam. We found that the antibody response was highest among those who received two matching doses of the Moderna vaccine, followed by those who received a combination of two different vaccines, and finally, those who received two matching doses of the Pfizer vaccine (Table 1, Fig. 3).

In terms of the antibody response to the matching vaccine, the present study found that the matching two doses of mRNA vaccines (i.e., Moderna and Pfizer) were more immunogenic compared to matching two doses of DNA vector vaccines (i.e., AstraZeneca). The IgG levels for those who completed two doses of Moderna and Pfizer were (Median (IQR)) 484.55 (284.80) and 349.00 (362.50) AU/mL, respectively. Meanwhile, the median (IQR) of IgG level for

Table 2. Odds Ratios (OR) and 95% Confidence Intervals (CI) for IgG levels concerning matching and mixing vaccines, pre- and post-adjustment for additional variables (n = 679).

	Low versus high level of IgG n (%)		Model 1		Model 2		Model 3	
	Low level (126.33 ± 72.21)	High level (523.00 ± 181.32)	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Between matching								
Astra-Astra	217 (85.10)	38 (14.90)	1		1		1	
Moderna-Moderna	25 (17.12)	121 (82.88)	27.64 (16.19–48.90)	<0.001	27.83 (16.25–49.42)	0.0165	28.39 (16.52–50.63)	0.0230
Pfizer-Pfizer	71 (38.80)	112 (61.20)	9.01 (5.76–14.35)		9.43 (5.99–15.15)		9.72 (6.12–15.75)	
Mixing versus matching								
Astra-Astra	217 (85.10)	38 (14.90)	1		1		1	
Astra-Pfizer	16 (16.84)	79 (83.16)	28.19 (14.89–53.38)	<0.001	28.21 (14.89–53.47)	<0.001	28.50 (15.00–54.14)	<0.001
Moderna-Moderna	25 (17.12)	121 (82.88)	1		1		1	
Astra-Pfizer	16 (16.84)	79 (83.16)	1.02 (0.51–2.03)	0.955	1.04 (0.52–2.08)	0.904	0.97 (0.48–1.96)	0.940
Pfizer-Pfizer	71 (38.80)	112 (61.20)	1		1		1	
Astra-Pfizer	16 (16.84)	79 (83.16)	3.13 (1.69–5.78)	<0.001	2.97 (1.60–5.53)	0.001	2.94 (1.57–5.51)	0.001

Note: A logistic regression model was performed by STATA 16 statistical software to explore factors related to high-level rates. Model 1 is an un-adjusted model; Model 2 was adjusted for age (continuous), gender (male, female); Model 3 was further adjusted for adverse events (yes, no).

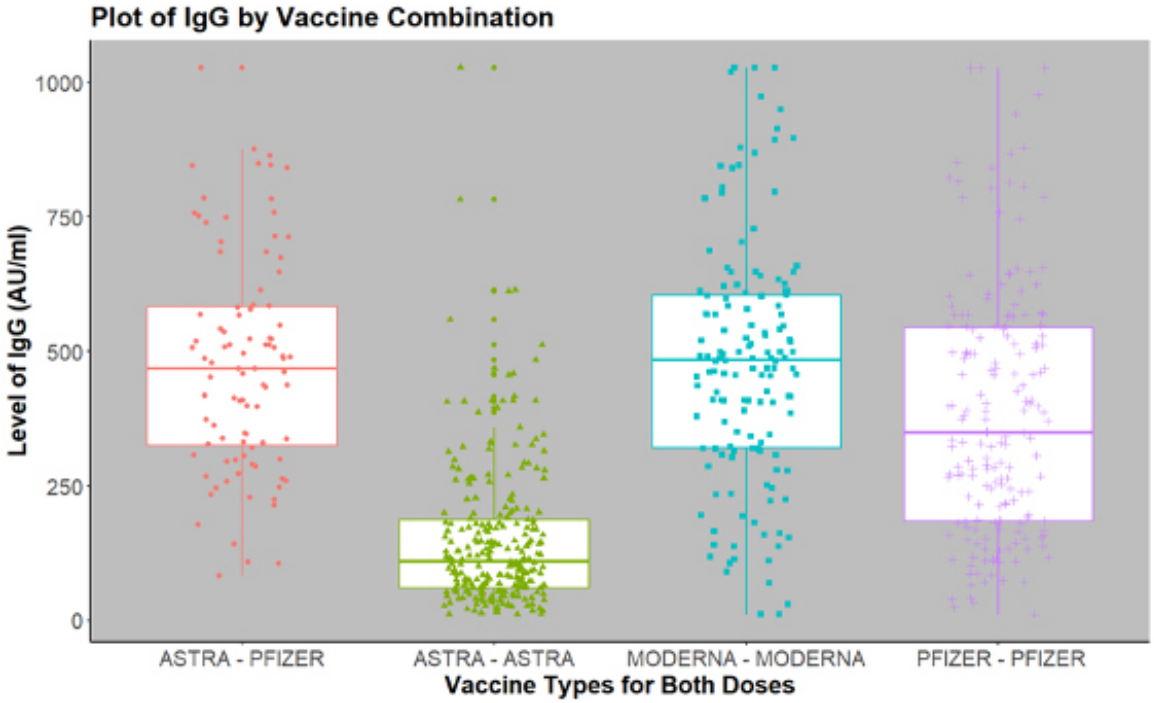

Fig. 3. Comparison of IgG levels (AU/mL) after completing two doses of COVID-19 vaccines across different combinations of vaccine types (n = 679).

AstraZeneca recipients was 110.00 (128.10) AU/mL (Table 1, Fig. 3). The likelihood of having a high IgG level was 28.39 times higher for those who received two matching doses of Moderna and 9.72 times higher for those who received two matching doses of Pfizer (Table 2). These findings align with a recent study in Germany that compared the antibody response after using different mixing and matching vaccines for the prevention of COVID-19 [13]. The results indicated that mRNA vaccines were the most immunogenic after two doses. DNA-vectored vaccines, including AstraZeneca and Sputnik-V, demonstrated reduced but still considerable antibody expression and viral neutralizing abilities after two doses [13]. Similarly, a recent living meta-analysis also showed that the three doses of mRNA vaccine were the most effective strategy in reducing COVID-19 hospitalization in non-delta and non-omicron groups [14]. The explanation for this could be the mechanism of the mRNA vaccine. Previous evidence suggested that the mRNA vaccine induces robust T cell responses, including $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells

[15–17]. These T cells play a crucial role in recognizing and eliminating virus-infected cells. However, there is a scarcity in the direct comparison of the T cell responses between mRNA vaccines versus DNA vector vaccines. Future studies may seek to elucidate this issue.

Comparing the effects of mixing and matching vaccines, the present study's results suggested that combining a DNA vector vaccine with an mRNA vaccine is more immunogenic than the matching vaccines. When compared to matching vaccines, mixing Astra-Pfizer vaccines increased the likelihood of having higher IgG levels than matching AstraZeneca (OR = 28.50, 95% CI: 15.00–54.14), Pfizer (OR = 2.94, 95% CI: 1.57–5.51), except Moderna (Table 2). These findings corroborate the efficacy of mixing vaccines, as observed in recent studies [8,18]. For example, the Com-COV study conducted in the United Kingdom compared various combinations of the Oxford-AstraZeneca and Pfizer-BioNTech vaccines. The study found that individuals who received the mixed dose regimen exhibited higher antibody levels compared to those who received two doses of the same vaccine [8].

Several factors contribute to the higher antibody quantities observed with mixed dose regimens. Firstly, different vaccines employ distinct technologies, which may trigger diverse immune responses. When various vaccine platforms are utilized, the immune system is exposed to a broader range of viral components, potentially leading to a more robust and diverse antibody response [19,20]. Furthermore, the interval between the two doses also plays a critical role. Studies have suggested that a longer gap between doses allows for increased antibody production due to enhanced activation of memory B cells and affinity maturation [21,22]. Mixed dose regimens often involve a longer interval between the two doses, providing additional time for the immune system to generate a stronger response. Another factor contributing to enhanced antibody levels with mixed doses is the concept of heterologous prime-boosting. When two different vaccines are administered, the initial dose primes the immune system, while the subsequent dose acts as a booster, reinforcing the immune response [23]. This strategy may result in a more robust and durable antibody response.

In the present study, we only analyzed the mixing of AstraZeneca and Pfizer vaccines, as other combinations had small sample sizes and were therefore excluded from the analysis (the number of recipients for Astra-Moderna and Moderna-Astra were 4 and 1, respectively). The other mixing vaccine strategies might show different results compared to combining a DNA vector vaccine and an mRNA vaccine. However, existing evidence demonstrates the superiority of mixing an mRNA vaccine with a DNA vector vaccine. The living meta-analysis by Au *et al.* [14] (2022) highlighted that a mixing vaccine strategy in which a booster dose of mRNA is provided to recipients of two doses of adenovirus vector vaccines was effective in the prevention of COVID-19. Similarly, Adjobimey *et al.* [13] (2022) also suggested that, compared to homologous vaccination, heterologous immunization involving AstraZeneca DNA vector vaccines and mRNA vaccines is more successful in inducing neutralizing antibodies.

When considering adverse events, mixing vaccines appears to be the preferable option. While both the mixing Astra-Pfizer and matching Moderna-Moderna groups exhibit the best immune response due to their higher mean IgG levels compared to the other groups, the mixing vaccine Astra-Pfizer presents a significant advantage as it has the lowest frequency of adverse events among all the vaccination strategies, with no reported cases of shock. In contrast, the matching Moderna-Moderna group has a considerably higher frequency of adverse events, including cases of shock (Fig. 2). Indeed, in the logistic model that was adjusted for advert events, Astra-Pfizer had higher odds of achieving a high IgG level compared to matching two doses of Moderna (Table 2). Although our previous analysis indicated a weak association between shock and vaccine types [24], decision-makers and vaccine recipients should consider the mixing vaccine strategy, as it achieves high IgG levels while having the lowest frequency of adverse events.

In light of the discussed research, the study has brought forth three salient points that underline its strengths. Firstly, the mRNA vaccines, particularly Moderna and Pfizer, have exhibited superior immunogenicity compared to DNA vector vaccines, such as AstraZeneca. This implies that the mRNA vaccines were found to stimulate stronger antibody responses, aligning with prior research indicating that these types of vaccines can trigger more potent T-cell responses [25,26]. Secondly, the research emphasized that a combination of DNA vector and mRNA vaccines resulted in greater immunogenicity than using homologous vaccines. This finding holds significant implications it reinforces the concept of mixing vaccines, as evidenced in various other studies. The superior immune response can be attributed to various factors, including the introduction of diverse viral components to the body, the extension of the interval between doses, and the application of the heterologous prime-boost strategy. Lastly, the strategy of combining AstraZeneca and Pfizer vaccines not only led to a robust immune response but also had the added advantage of a reduced frequency of adverse events compared to other vaccination strategies. This finding suggests that mixing vaccines could be a more viable option for individuals aiming to achieve high levels of IgG antibodies while concurrently reducing the likelihood of adverse effects. In summary, these points showcase the study's strengths and contribute to the growing body of evidence supporting strategic vaccine combinations for enhanced immunogenicity and safety.

This study has some limitations. First, we did not calculate the positive or negative rate with the antibody testing. Instead, we reported the antibody quantities as the contin-

uous value would be more useful in terms of statistics and for comparing between vaccines. Second, we did not measure the time relapse and the antibody quantities. Time relapse might affect the antibody quantities [3]. However, in this study, almost all the participants returned for blood testing within the specified interval of 14–28 days, following the study protocol. Hence, the variation between time relapse might not affect the antibody response. Third, we only tested for antibody response after the second dose of the vaccine, not after the first dose. This makes it impossible to assess the change in antibody response after the first and second doses. Fourth, as we included only the participants naïve with COVID-19, we cannot assess add on the impact of COVID-19 infection on the vaccination strategies. Future studies may be interested in evaluating the immunogenicity of mixing and matching vaccines among people previously infected with COVID-19 and quantifying the antibody response based on the time since infection. Finally, we did not collect the medical history and comorbidity information of the vaccine recipients. Future studies may need to investigate the immune response of these specific populations.

Conclusions

In conclusion, we found that the matching two doses of mRNA vaccines (i.e., Moderna and Pfizer) are more immunogenic when compared to DNA vector vaccines (i.e., AstraZeneca). Furthermore, mixing two doses of different COVID-19 vaccines results in higher antibody levels compared to matching vaccines, along with a lower rate of adverse events. These findings support the recommendation of specific vaccine combinations for booster doses, offering valuable insights into optimizing vaccination strategies.

Availability of Data and Materials

All the data available is provided in this paper.

Author Contributions

THT, HVP and TDN contributed to the study conception and design. THD, BKN and TLP acquired and analyzed the data. THT, HVP, TDN and TLP drafted the initial manuscript and revised the final manuscript. THD, and TDN support the improvement of the manuscript after the review process. THD, BKN and TDN revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Council of Ethics in Biomedical Research of the National Institute for the Control of Vaccine and Biologicals (No. 0126/2022/KDQG-HDYD). Informed consent was obtained from all subjects involved in the study.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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