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Impact of the COVID-19 vaccine booster strategy on vaccine protection: a pilot study of a military hospital in Taiwan

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Purpose: The global fight against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has led to widespread vaccination efforts, yet the optimal dosing schedule for SARS-CoV-2 vaccines remains a subject of ongoing research. This study aims to investigate the effectiveness of administering two booster doses as the third and fourth doses at different intervals to enhance vaccine protection.

Materials and Methods: This study was conducted at a military regional hospital operated by the Ministry of National Defense in Taiwan. A cohort of vaccinated individuals was selected, and their vaccine potency was assessed at various time intervals following their initial vaccine administration. The study participants received booster doses as the third and fourth doses, with differing time intervals between them. The study monitored neutralizing antibody titers and other relevant parameters to assess vaccine efficacy.

Results: Our findings revealed that the potency of the SARS-CoV-2 vaccine exhibited a significant decline 80 days after the initial vaccine administration. However, a longer interval of 175 days between booster injections resulted in significantly higher neutralizing antibody titers. The individuals who received the extended interval boosters exhibited a more robust immune response, suggesting that a vaccine schedule with a 175-day interval between injections may provide superior protection against SARS-CoV-2.

Conclusion: This study underscores the importance of optimizing vaccine booster dosing schedules to maximize protection against SARS-CoV-2. The results indicate that a longer interval of 175 days between the third and fourth doses of the vaccine can significantly enhance the neutralizing antibody response, potentially offering improved protection against the virus. These findings have important implications for vaccine distribution and administration strategies in the ongoing battle against the SARS-CoV-2 pandemic. Further research and large-scale trials are needed to confirm and extend these findings for broader public health implications.

Keywords: SARS-CoV-2, COVID-19 vaccine, Booster dose, Neutralizing antibodies

Introduction

Coronavirus disease 2019 (COVID-19), caused by the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), manifested global disease rate impact by the end of 2019. SARS-CoV-2 belongs to the beta subfamily of the Coronavirinae family. It is an enveloped, single-stranded, positive-sense RNA virus that is unstable during transcription and prone to single nucleotide variations [1,2]. As the number of muta-

tions increased, transmission efficiency accelerated rapidly, leading to decreased vaccine potency. Seven types of coronaviruses are known to cause human infections [3]. SARS-CoV-2 primarily relies on its surface spike protein (S protein) as a bridge to enter cells. The S protein consists of two subunits, S1 and S2. SARS-CoV-2 first binds to angiotensin-converting enzyme 2 (ACE2) [1,2] on human respiratory system epithelial cells via the receptor-binding domain (RBD) of the S1 subunit. After binding, the cellular transmembrane protease serine 2 protease and furin protease help cleave the S1 and S2 subunits. S1 is then cleaved and triggers endocytosis by regulating the binding of S2 on the virus to the cell membrane [3-6]. This leads to subsequent inflammatory reactions [7]. Vaccine engineers used cryo-electron microscopy to observe the dynamic state of the S-domain and the process by which the S protein subunit conformation undergoes transformation, combines with the host ACE2 receptor, and mediates entry into host cells [8-10]. The S protein plays a key role in determining whether the virus can penetrate the cells. The S protein can also induce strong antiviral immunity to produce a high neutralizing antibody titer, which blocks viral invasion into host cells [11-15].

Antibodies have three primary functions: (1) neutralization, wherein neutralizing antibodies recognize specific viruses and bind to them to prevent pathogens or toxins from invading cells; (2) activation of the complement system, which destroys the bacterial cell wall via cytolytic action; and (3) the regulation of phagocytosis (opsonization) [6,16,17]. Clinically, neutralizing antibody titers in serum can be used as the basis for confirming infection. Once an individual receives a SARS-CoV-2 vaccine, helper T cells are activated, which in turn activate killer T cells that seek out spike proteins and stimulate B cells to produce antibodies that bind to the virus and inhibit infection. Vivaldi et al. [18] conducted a large-scale cohort study to investigate the relationship between vaccine protection and anti-S-protein immunoglobulin G (IgG), IgA, and IgM titers. Their research revealed a strong correlation between anti-S-protein IgG/A/M, neutralizing antibody titers, and S peptide-stimulated interferon-γ concentration [18]. To combat the SARS-CoV-2 pandemic, three main types of vaccines have been developed by international pharmaceutical companies: (1) viral DNA adenovirus vector vaccines, such as those created by AstraZeneca and Johnson & Johnson; (2) messenger RNA (mRNA) vaccines, such as those created by Moderna and Pfizer-BioNTech; and (3) protein subunit vaccines comprising recombinant spike proteins, such as those created by Medigen (Taipei, Taiwan) and Novavax. Anti-S-protein antibody IgG concentrations have been shown to highly correlate with ID50 neutralization in a validated pseudoviral assay and significantly correlate with protection efficacy, especially against wild-type, Alpha, and Delta variants [19]. The level of anti-S-protein IgG antibodies can also predict the possibility of a breakthrough infection in the 5-month period following full vaccination [18]. A recent study by the UK Health Services indicated that anti-S IgG produced following a natural infection may protect against re-infection for up to 6 months [20]. Additional investigative research has shown that the levels of neutralizing antibody and IgG-binding antibody can be used as determinants of vaccine protective efficacy [21,22].

A number of recent publications have indicated that a third vaccine dose can induce a higher neutralizing antibody level and slower waning of protection compared to receiving only a second dose, but a significantly higher Omicron variant infection rate 4 months after the third vaccination has also been reported [23]. Barouch [24] reported that the half-life of neutralizing antibodies after the third dose is only 60 days. The high initial serum neutralizing antibody titers induced by mRNA vaccines wane after 3–6 months, and decline further by 8 months [24]. Most studies have concluded that the levels of IgG and neutralizing antibodies wane approximately 4 months after the third dose. Another study by Magen et al. [25] indicated that a second booster dose reduces the short-term risk of COVID-19 outcomes for those who had received the first booster dose 4 months earlier. Hence, a second booster dose is required to address the threat of the Omicron variant [25]. It was recently reported that three-quarters of Sinovac/Sinopharm vaccine recipients had no protection against Omicron variants. Two doses of the AstraZeneca or Pfizer/BioNTech vaccines were found to be less protective, but still reduced hospitalizations by 63% and 74%, respectively [26].

Depending on the different mechanisms of vaccination, there are many dissertations regarding the effectiveness of the vaccine booster dose, but the results remain inconclusive. Thus, we aimed to investigate the antibody titers of personnel who visited a military regional hospital in eastern Taiwan after they had received different vaccines and evaluate the effectiveness of booster doses. We also assessed whether vaccination policies are reasonable and similar to the current World Health Organization (WHO) guidelines.

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Materials and Methods

Case collection method

In this study, we chose a regional hospital to investigate vaccine efficacy and designed a questionnaire to collect the basic profiles of candidates. The questionnaire included several items, such as sex, age, body mass index (BMI), date of vaccination, and type of vaccine received. We were particularly interested in examining the effects of the interval between the first and second booster doses.

This research was initiated on June 20, 2022, after review and approval by the Institutional Review Board (IRB) of the Tri-Service General Hospital (IRB approval no., B202205156). The study was conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from all subjects involved in the study. The project host explained the relevant sampling methods, rights, obligations, sample collection, and relevant information to vaccine recipients at the outpatient department of the National Army Hualien General Hospital and obtained informed consent. Fifty patients were accepted in the study, including 30 males and 20 females (male-to-female ratio, 3:2).

Laboratory preparation

To estimate the neutralizing antibody titer after vaccination, an anti-SARS-CoV-2 (B.1.1.529) neutralizing antibody titer serologic assay kit (Spike RBD) and an Omicron virus-free neutralizing antibody assay kit (ACRO Biosystems, Newark, DE, USA) were used to measure the anti-SARS-CoV-2 neutralizing antibody levels via using a competitive enzyme-linked immunosorbent assay (ELISA) method [27-29]. As per the manufacturer's instructions, 5 mL of blood was collected using a green-top tube (containing Na-heparin anticoagulant), which was centrifuged at 1,300 rpm for 10 minutes at low speed. After centrifugation, 2 mL of plasma was withdrawn and stored at -20°C. ELISA plates were pre-coated with ACE-2, and horseradish peroxidase-labeled RBD reagent was mixed with the test samples and then placed in the plates to observe the subsequent reaction. After the reaction, the plates were washed with wash buffer and then were subsequently detected by measuring the absorbance spectrophotometrically at 450 nm through using a microplate reader. The optical density (OD) of the assay signal decreased in proportion to the concentration of anti-SARS-CoV-2 neutralizing antibodies. An equation for percent inhibition was provided by the ACRO Biosystems manual, as follows:

$$Percent\ inhibition = \left(1 - \frac{OD_{450nm}\text{-}OD_{630nm}\ of\ Sample}{OD_{450nm}\text{-}OD_{630nm}\ of\ Negative\ control}\right) \times 100\%$$

where OD_{450nm} and OD_{630nm} mean the optical density under the wavelength at 450 nm and 630 nm. The manufacturer sets an inhibition cut-off value=20%. A positive result depends on the percent inhibition of sample ≥cut-off value, meaning that the neutralizing antibody is detected. From the equation, the optical density is inversely proportional to the amount of SARS-CoV-2 neutralizing antibody in the sample.

Statistical methods

Graphpad Prism software (GraphPad Software, San Diego, CA, USA) for analysis of variance (ANOVA) and Student t-tests were used to verify whether there were significant differences in the values between groups. ANOVA was used to evaluate whether the means of multiple groups of samples were equal.

Results

In this study, the 50 people who received the second booster dose to complete vaccination comprised 30 males and 20 females, with a male-to-female ratio of 3:2 (Table 1). The age range was 25–55 years. Among those receiving the fourth dose (also known as the second booster dose), 27 received the Moderna vaccine, 16 received the Pfizer/BioNTech vaccine, and seven received the Novavax vaccine. The investigated hospital did not administer Taiwan's domestic Medigen vaccine for the initial or booster doses.

The overall inhibition rate among the 50 participants gradually decreased according to the mutant strain (BA.1, BA.2, and BA.5) (Fig. 1). These data indicated that the protective ef-

Table 1. Characteristics of the study participants

Characteristic	Value
Age (yr)	42.71±8.64 (47–83)
Body mass index (kg/m^2)	24.05±3.58 (21–27.05)
Gender	
Male	3
Female	2
Interval between the fourth booster dose of COVID-19 (day)	84.22±13.71 (89.25–91)
Interval between the third and the fourth booster dose of COVID-19 vaccination (day)	175.10±19.04 (162–181)

Values are presented as mean±standard deviation (interquartile range) or number.
COVID-19, coronavirus disease 2019.

fect against the BA.1 mutant strain was less than 30%, whereas the protective effect against the newer BA.5 mutant strain was only 20% (ANOVA p-value=0.0032). We also conducted statistical analysis between groups BA.1 and BA.5. Which revealed a significant statistical difference in group BA.1 versus BA.5 (p-value=0.005). When sex was included as a variable, the neutralizing antibody titers were higher for males than females, regardless of the mutant strain (BA.1, BA.2, or BA.5); however, the difference was not statistically significant (Fig. 2A). We also analyzed the data according to age. Based on the age distribution, 45 years appeared to be a meaningful cut-off. Neutralizing antibody titers were higher in participants aged <45 years. However, no significant differences were observed (Fig. 2B). According to the numerical distribution of neutralizing antibody titers obtained in individual cases, we found that the titers decreased significantly approximately 80 days after the second booster immunization. However, these differences were not statistically significant (Fig. 3A). When comparing the interval from the first booster to the second booster injection across all mutant strain groups, the neutralizing antibody titers were greater for subjects with a first-to-second booster interval longer than 175 days than for those with an interval shorter than 175 days. These data were significantly different, especially in the BA.1 and BA.5 groups (Fig. 3B). We also analyzed the data according to BMI, but found no numerical or statistical differences in these variables. Another interesting phenomenon was observed in this study. Those receiving the Novavax vaccine as the second booster dose produced neutralizing antibody titers that were slightly higher than those produced by individuals receiving the mixed and matched viral vector vaccines and mRNA vac-

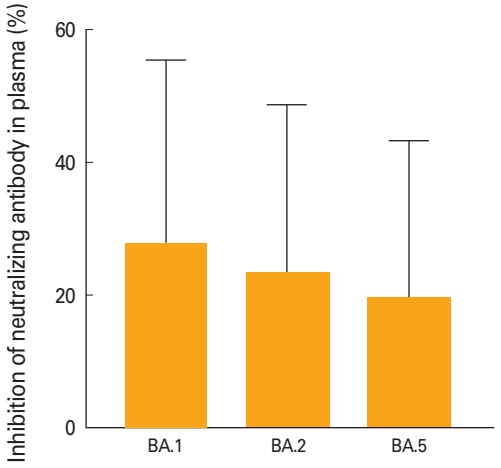
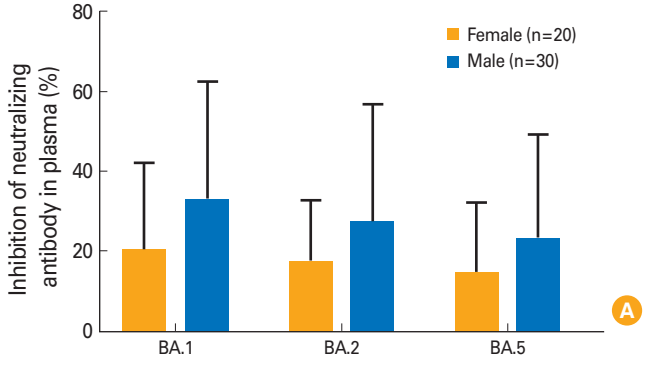
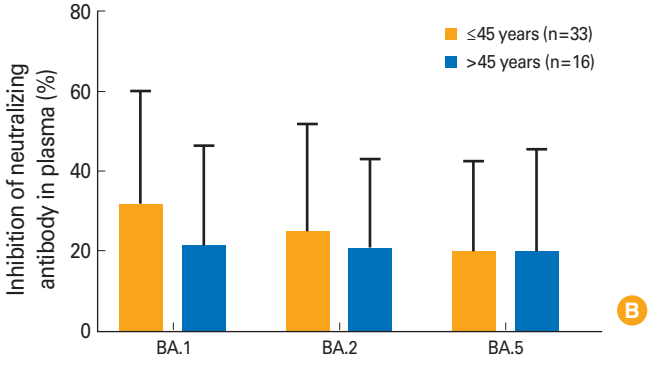


Fig. 1. Percent inhibition of neutralizing antibodies against BA.1, BA.2, and BA.5 variants. The data show a percentage of approximately 28.06% for BA.1 and 23.58% for BA.2. The percentage of antibodies against BA.5 decreased to 19.7%, indicating a decrease in inhibition with new generations of mutant strains. Turkey's test had been conducted between groups BA.1 and BA.5. A significant statistical difference was found in group BA.1 versus BA.5 (p-value=0.005).



	BA.1	BA.2	BA.5
p-value	0.1086	0.1751	0.1934
	NS	NS	NS



	BA.1	BA.2	BA.5
p-value	0.2270	0.5946	0.9796
	NS	NS	NS

Fig. 2. (A) In this study, 30 males and 20 females were recruited as research cases. The effect of gender on the vaccine suppression rate is worth exploring. When we use gender as an analysis variable. The results of the statistical analysis showed that: (1) a gradual decrease in percent inhibition with new virus variants and (2) that the inhibition was stronger for males than females. However, there was no statistically significant difference. **(B)** When we collected the data and then analyzed the results by age as a variable, we found that 45 years old is an obvious cut-off point. The percent suppression of neutralizing antibodies was higher in those under 45 years of age than in those over 45 years of age, but there was no statistically significant difference. In the BA.1 group, the titer for the over 45 years group was only 67.6% of the titer of the under 45 years group (p=0.2270). However, there were no significant differences in titer according to age in the BA.2 group (p=0.5946) or the BA.5 group (p=0.9796). NS, not significant.

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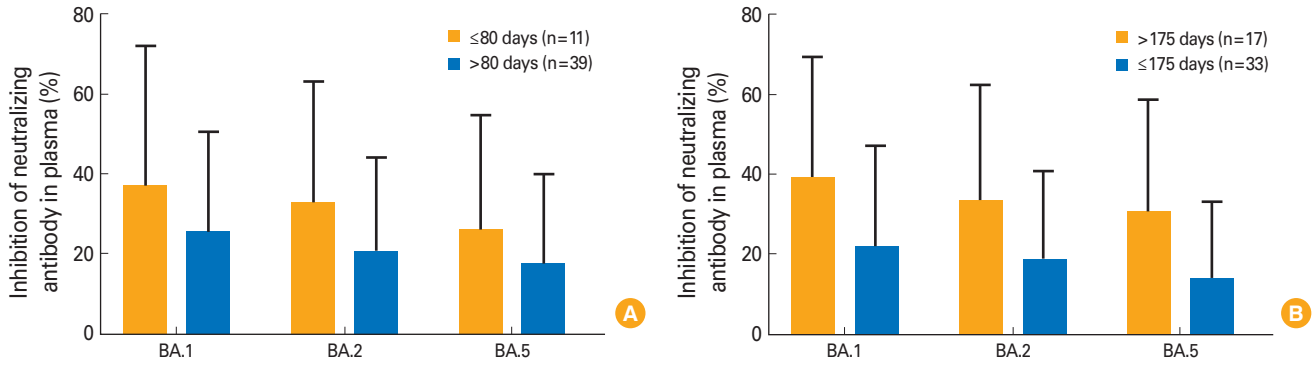
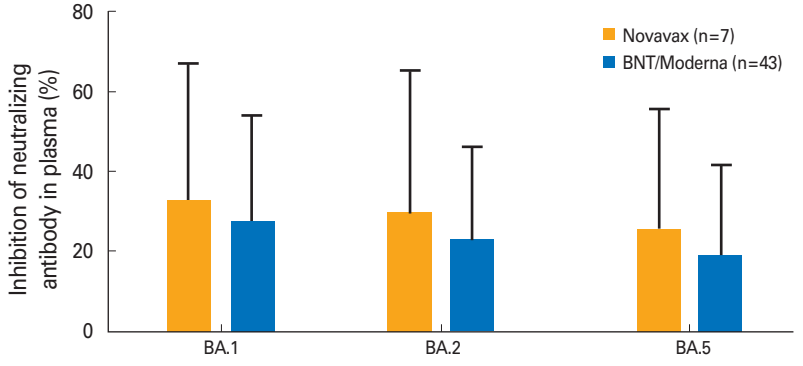


	BA.1	BA.2	BA.5
p-value	0.1997	0.1638	0.2968
	NS	NS	NS

	BA.1	BA.2	BA.5
p-value	0.0404	0.0527	0.0160
	*	NS	*

Fig. 3. (A) The Central Epidemic Command Center (CECC) of Taiwan encouraged our population to received further vaccine 12 weeks after a previous vaccination. As the results of our analysis according to the number of days post-vaccination. The results showed: (1) a gradual decrease in percent inhibition with new virus variants and (2) the neutralizing antibody inhibition percentage reached a watershed at 80 days after vaccination, after which the neutralizing antibody titer began to show a significant downward trend. However, there were no statistically significant differences. The ratio of inhibition at >80 days/<80 days was approximately 67.6% (p=0.1997) in the BA.1 group, 63.4% in the BA.2 group (p=0.1638), and 67.6% in the BA.5 group (p=0.2968). This result indeed compatible to the policy of CECC to maintain the level of neutralizing antibody. **(B)** Higher neutralizing antibody titers obtained after a revaccination with the booster after 120–180 days was identified by the World Health Organization. In our study, subsequent inhibition was significantly higher when the interval between the two doses of booster injections exceeded 175 days than when the interval was less than 175 days. Although according to previous studies and this study, the immunosuppressive effect of the vaccine gradually decreases after approximately 80 days, after increasing the injection interval, the titer of neutralizing antibodies elicited was higher than it was after 80 days of injection. This result was statistically significant for the BA.1 and BA.5 groups. These results are also in line with those of previous studies conducted in other countries. The ratio of inhibition after >175 days/<175 days was approximately 174% (p=0.0404) in the BA.1 group, 178% in the BA.2 group (p=0.0527), and 241% in the BA.5 group (p=0.0160). NS, not significant. *p<0.05 (statistically significant).



	BA.1	BA.2	BA.5
p-value	0.6302	0.5114	0.5015
	NS	NS	NS

Fig. 4. Although we only recruited seven candidates to receive Norvavax vaccination in our study, the data still demonstrated the difference in our analysis according to the type of vaccine. The percentage inhibition of neutralizing antibodies was higher in the Novavax group than in the messenger RNA vaccine group (Pfizer-BioNTec). However, the results were not statistically significant. Our results indicated that the number of Novavax cases was too small to allow a comparison. We hypothesize that the power of suppression is similar to recent studies that found high rates of protection in Hispanic/Latino populations even at high exposure rates. However, the current situation in the Asian ethnic group is still unclear. NS, not significant.

cines (Fig. 4). However, no significant differences were observed.

We recruited 50 candidates with an average age of 42.71 years and a male to female ratio of 3:2. The average interval from the last booster vaccination to the examination was 84.22 days and the average interval between the first and second booster dose was 175.1 days. The candidates were relative healthy medical workers. No obvious chronic medical history or co-disease was recorded.

Discussion

Because SARS-CoV-2 emerged at the end of 2019 and caused a global pandemic in a short period of time, it has caused social unrest, economic collapse, and a heavy medical burden for many countries worldwide. The Ministry of Health and Welfare of Taiwan also declared the disease caused by SARS-CoV-2 infection as a severe infectious disease on January 15, 2020, and announced it as the fifth category of legal infectious disease [30]. Since the pandemic entered the country, people's livelihoods, the economy, and medical burdens have been overwhelming. To reduce the risk of severe illness and death after infection, the most effective and large-scale strategy to reduce the rate of severe illness during a pandemic is to use passive immunity to stimulate the immune system to produce antibodies, so that when an individual actually comes into contact with the pathogen, they can quickly produce an immune response to avoid infection. Vaccination is an important component in pandemic prevention. However, after the emergence of the Delta variant and the subsequent Omicron variant, two full doses of the original vaccine no longer provided sufficient protection. Before next-generation or bivalent vaccines became available in the market, the governments of various countries actively advocated the administration of a first or second booster dose to compensate for declining vaccine protection.

According to recent studies, although the Omicron variant has a strong immune escape ability, the risk of hospitalization is lower for this variant than the Delta variant. The risk of reinfection is significantly higher with Omicron variants than prior variants. The use of an mRNA vaccine as the first booster dose not only increases the neutralizing antibody titer against the Wuhan strain HU-1, but also significantly maintains the neutralizing antibody titer against Omicron variants (including BA.1 and BA.2 sub-variants). According to the data analysis reported by Chenchula et al. [31], patients who received the second and third doses (the first booster dose) had an 81% lower risk of hospitalization than unvaccinated patients after Omicron infection [32]. Israeli studies have shown that the first booster dose of an mRNA vaccine significantly increases the neutralizing antibody titer and reduces the risk of infection or severe disease caused by the Delta variant. However, a first or second booster dose cannot prevent Omicron infection [31,33]. Furthermore, mixing viral vector vaccines with mRNA vaccines produces significantly higher titers of neutralizing antibodies, even for the Beta and Delta variants [34]. Another Israeli study also noted a significant reduction in the severity of SARS-CoV-2 infection after the first booster dose of the Pfizer/BioNTech vaccine. The Government of Israel observed an epidemic of SARS-CoV-2 infection at the time. Currently, the number of hospitalizations is increasing, but the total number of severe cases remains low. More Israeli studies have found that the absolute risk of SARS-CoV-2-associated hospitalization versus severe cases (first booster versus second booster) is approximately 3:1. All of these investigations indicated that the rate of severe disease was significantly reduced following the administration of the second booster dose [25,31,35]. The Central Epidemic Command Center encourages people over the age of 18 years who have received two doses of the vaccine before October 31, 2021, and have an interval of 12 weeks from the previous dose, to receive a third dose (the first booster/supplemental dose). The command center recommends the booster vaccine for all people who meet the following criteria: (1) 18 years of age or older, (2) completion of two doses of vaccination (regardless of the brand), and (3) a time interval of 3 months after receiving the second vaccine dose.

Higher neutralizing antibody titers were observed in female patients than in male patients. However, this difference was not statistically significant. According to the distribution of our data, 45 years of age appeared to be a reasonable watershed age. We found that people under the age of 45 years achieved higher neutralizing antibody titers than those over the age of 45 years, regardless of whether the second booster dose was an mRNA vaccine or the Novavax vaccine. Moreover, those in the booster group with a second-dose-to-booster interval greater than 175 days demonstrated more resistance to neutralizing antibodies than those with an interval less than 175 days. These findings were statistically significant. Therefore, we conclude that the booster dose stimulated greater protection after 175 days. One of the Israeli studies investigated here also suggested that a fourth dose of the BioNTech vaccine was effective in reducing the short-term risk of SARS-CoV-2–related outcomes among persons who had received a third dose at

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least 120 days earlier [25]. Relevant studies in other countries have also determined that an interval between the second and first booster dose of more than 4 months (112 days) can reduce the short-term risks and post-infection complications [25]. In the future, when the Health Administration Department formulates a third booster injection, the vaccination interval should be extended to achieve more significant effects. Another study found that protection gradually declined approximately 80 days after vaccination. Combining these two results, the following inferences can be drawn. To maintain effective protection, the 84-day vaccination interval stipulated by the Central Epidemic Prevention Command Center of the Taiwanese government is reasonable. However, revaccination (booster) is recommended after 175 days.

Among the 50 patients studied, seven subjects chose to receive the Novavax vaccine as their second booster dose. We found that protection against neutralizing antibodies was higher than among those who chose the Novavax vaccine as the second booster dose than those who did not. However, the number of patients was too small to produce a statistically significant difference in the statistical analysis. At the end of the study, there were 10 breakthrough infections in the mRNA-vaccinated group (10/43) compared to none (0/7) in the Novavax-vaccinated group. Currently, global research on the efficacy of the Novavax vaccine is limited to Caucasian populations. Some studies have suggested that 100% protection can still be achieved in Hispanic/Latino populations, even at high exposure rates [36,37]. Therefore, further studies are warranted. Moreover, there is a lack of large-scale research data on the protective capacity of Novavax vaccines in Asian populations. Although the results of this study did not demonstrate statistically significant differences, they are still valuable and may encourage health authorities to consider the use of the Novavax vaccine for booster doses [38].

Conclusions

This study aimed to evaluate the effectiveness of first and second booster vaccinations. However, we recruited only 50 participants because many breakthrough infections were excluded. We observed a significant decline in vaccine protection 80 days after the second booster dose. The vaccine elicited higher neutralizing antibody titers in cases younger than 45 years than in cases older than 45 years. In addition, the neutralizing antibody titers obtained with an injection interval of more than 175 days were higher than those obtained in subjects with an injection interval of less than 175 days, and these three parameters showed statistically significant differences. Thus, the government's policy of recommending 84-day vaccination intervals is reasonable. However, the neutralizing antibody titer induced by this strategy may only be maintained at the previous level. Administration of the next dose 175 days later resulted in higher neutralizing antibody titers, which also echoes the current WHO recommendations for revaccination with the booster after 120–180 days.

Before the end of the study, 10 breakthrough infections were recorded in 50 patients after they had been recruited and had their blood drawn. Candidates who received a second booster dose were still not immune to the infection. However, the infection symptoms of these 10 cases were limited to typical upper respiratory tract symptoms, and none of the infection cases required hospitalization or became seriously ill. This phenomenon suggests that receiving a booster dose does not help prevent infection, but does help reduce the risk of post-infection complications.

Limitations

This study has two limitations. First, the Central Epidemic Command Center encourages booster dose vaccination regardless of whether the two primary doses were used. However, a detailed assessment of the baseline efficacy of each vaccine is difficult. Second, when we conducted the study, the Novavax vaccine had only recently been imported into Taiwan. Therefore, we included only seven patients who received the Novavax vaccine. In this study, neutralizing antibody titers were slightly higher among subjects receiving a combination of viral DNA vectors and mRNA vaccines, although the difference was not statistically significant. However, by the end of the experiment, none of the seven patients had a breakthrough infection. Some studies have suggested that 100% protection can be achieved in Hispanic/Latino populations, even at high exposure rates [36-38]. We assume that the results of our experiment are similar to those of studies conducted in other countries. However, there were not enough cases to determine whether the protection provided by the Novavax vaccine achieves the same results in Asian populations. There is still a need for a large-scale study on the protective capacity of the Novavax vaccine among Southeast Asian populations. In addition, the patients recruited in this study were under 55 years old, and there were no chronic diseases available for research, such as hypertensive heart disease, cancer, neurological disorders, and end-stage kidney disease, and so forth, so the efficacy of the vaccine in these groups cannot be determined full discussion [39].

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