Antibody response to variants during Omicron outbreak after BNT162b2 booster in Korean healthcare workers

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Abstract

In South Korea, the booster shot for COVID-19 was carried out amid concerns about the effectiveness of the existing vaccine. The virus neutralization test (sVNT) inhibition (%) score for the wild-type and delta variant significantly and uniformly increased (97%, 98%; $p < 0.001$) but it was decreased for the omicron after the BNT162b2 booster dose (75%; $p < 0.001$). In 41 HCWs (39.0%), infected with the omicron, no difference in immunogenicity, adverse events, and effectiveness between homogeneous and heterogeneous boosters were observed. In cohort 2, 58 HCWs included, at the fourth month of the booster dose, sVNT inhibition to omicron was significantly increased in the omicron-infected group (95.13%) compared to the non-omicron-infected (mean of 48.44%; $p < 0.001$). It is difficult to respond to the current vaccines to the Omicron variant adequately. Developing a variant-response vaccine should be prioritized, especially for the additional vaccination for HCW or previously infected persons.

Introduction

In Korea, the COVID-19 vaccination program was implemented in February 2021. BNT162b2 (Pfizer Biotech) and ChAdOx1-nCoV-19 (Oxford/AstraZeneca) were started at first, followed by mRNA-1273 (Modena) and JNJ-78436735 (Janssen) in the second quarter of 2021. With the nathinal wide schedule for vaccination, our medical center started immunizing with the BNT162b2 and the ChAdOx1 in March 2021, and to evaluate the vaccine effectiveness in healthy healthcare workers study of analyzing the neutralizing antibodies were conducted [1]. As a result, both vaccines (BNT162b2 and ChAdOx1) showed a 100% antibody production rate after the second dose, but the ChAdOx1 showed a significant decrease of the protective immune response, compared to the BNT162b2 with more than 68% cutoff of the sVNT inhibition.

According to reports from the Korea Centers for Disease Control and Prevention (KCDC), in December 2021, the first vaccination rate was 83.7% of the total population in Korea, and the second was 81.2%. However, variants of the alpha (B.1.1.7), beta (B.1.351), gamma (P.1.), and delta (B.1.617.2) shows the reduced effectiveness of the existing vaccine. The omicron (B.1.1.529), the most recent dominant variants appeared in November 2021, shows that it neutralizes the vaccine effect. Collectively, emerging with continues appearance of new variants require the need for extra booster dose [2].

Six months after the second dose vaccination, all medical staff at the center were given a booster dose with the BNT162b2. There has been reported showing the side effects of cross-inoculation by booster dose, and its effectiveness to prevention is not still determined. There is also remained questions how effective the current vaccine would be against variants.

The current study aimed to compare the level changes of the neutralizing antibody production after booster and to analyze the neutralizing antibody production level responding to the delta and omicron variants together. It was also examined whether there was a difference in side effects due to cross-

inoculation. Finally, we further estimated the changes of neutralizing antibody efficiency against the omicron variant after infection due to the rapid spread of Omicron infection after booster dose.

Results

Total 105 HCWs were enrolled in this study after one for refusing the sampling and the nine for leaving the company, from originally 115 HCWs participants in the previous study,. The mean age was 42.39 (24–72) years old, and the percentage of women was 78.1%. None history of allergy was 88.6%, and the experience of adverse reactions to previous COVID vaccines were 88.6%. Group participants for ChA/ChA/BNT and BNT/BNT/BNT were 57 and 48, respectively (Fig. 1, Supplementary Table 1).

Each group for the ChA/ChA/BNT and the BNT/BNT/BNT comprised 45 (78.95%) and 37 (77.08%) females and 41.35 (12.68) and 43.62 (9.56) years of mean (SD) ages, respectively (Table 1). Most participants had no history of allergy or anaphylaxis to drugs or foods (94.74% in the ChA/ChA/BNT and 81.25% in the BNT/BNT/BNT). There were statistical differences in occupational groups within the hospital between the two groups ($p < 0.001$). As the BNT162b2 vaccine was supplied prior to the ChAdOx1, first vaacinated HCWs including doctors and nurses were in the BNT/BNT/BNT group. There was no difference for the adverse reactions to the first and second COVID vaccines between the two groups ($p = 0.0635$ and 0.2735, respectively).

Table 1
Clinical characteristics of the study population by group

Characteristic	ChA/ChA/BNT group (N = 57)	BNT/BNT/BNT group (N = 48)	p-value
Age, years			0.1605
Mean+/-SD (range)	41.35 ± 12.68 (24–72)	43.62 ± 9.56 (25–60)	
Sex			> 0.99
Male	12(21.05%)	11(22.92%)	
Female	45(78.95%)	37(77.08%)	
Previous allergy/anaphylaxis history			0.045
None	54(94.74%)	39(81.25%)	
Drug/Food	2(3.51%)	5(10.42%)	
Anaphylaxis to drug/food	0(0.00%)	2(4.17%)	
Vaccine allergy	0(0.00%)	2(4.17%)	
Vaccine anaphylaxis	1(1.75%)	0(0.00%)	
Occupation in hospital			< 0.001
Administrative worker	7(12.28%)	0(0.00%)	
Doctor	0(0.00%)	6(12.50%)	
Facility services staff	11(19.30%)	0(0.00%)	
Support staff	30(52.63%)	13(27.08%)	
Researcher	9(15.79%)	3(6.25%)	
Nurse	0(0.00%)	25(52.08%)	
Other	0(0.00%)	1(2.08%)	
Previous COVID vaccine Adverse reaction			
1st vaccine dose AE	54(94.74%)	39(81.25%)	0.0635
2nd vaccine dose AE	47(82.46%)	44(91.67%)	0.2735
• P-value[1] = Two sample t-test, P-value[2] = Wilcoxon rank sum test (Mann-Whitney U test) for continuous variable			
• P-value[1] = Chi-squared test, P-value[2] = Fisher's exact test for categorical variable			

Serology results

The sVNT inhibition (%) scores to the wild-type significantly and evenly increased when the booster dose (mean (SD) 97.28 (4.37) %, median 97.91%, Q1/Q3 97.4/97.96) given, which sampled at 1 month after shots, compared to two (mean (SD) 81.67 (20.25) %, median 91.95%, Q1/Q3 73.86/96.32) or six months (mean (SD) 57.5 (25.42) %, median 58.29%, Q1/Q3 36.31/78.72) after the second dose ($p < 0.001$) (Fig. 2).

In order to analyze the neutralizing antibody responses to the wild-type, delta, and omicron variants, sVNT inhibition was first measured in a control group that had not received any COVID-19 vaccine and had never been infected with COVID-19. All subgroups of wild-type, delta, and omicron had negative serologic test results ($p = 0.432$; Fig. 3A).

After booster vaccination, the neutralizing antibody efficiency against the wild-type and the delta variant were both high as 97% and 98%. However, the efficiency to the omicron was significantly decreased with 75%, compared to the wild-type or delta variant ($p < 0.001$). These differences were also observed equally in the BNT/BNT/BNT ($p < 0.001$) and the ChA/ChA/BNT group ($p < 0.001$) (Fig. 3B).

Comparison between groups

Comparing the difference of neutralization efficiency between the groups, sVNT inhibition in the ChA/ChA/BNT (mean (SD) 96.83 (5.88) %, median 97.77%, Q1/Q3 97.33/97.91) and the BNT/BNT/BNT (mean (SD) 97.83(0.64) %, median 97.96%, Q1/Q3 97.91/98.05) ($p = 0.2086$) showed both higher efficiency, but no significant differences (Table 2).

Table 2
Serology results one month after booster of vaccine

	ChA/ChA/BNT group (N = 57)	BNT/BNT/BNT group (N = 48)	
Wild Type			
Seropositive, No (%)	57 (100.0)	48 (100.0)	
sVNT inhibition (%)			
Mean ± Std	96.83 ± 5.88	97.83 ± 0.64	0.2086
Median	97.77	97.96	< 0.001
Q1, Q3	97.33, 97.91	97.91, 98.05	
Range	53.27 ~ 98.06	94.73 ~ 98.15	
Delta variant			
Seropositive, No (%)	57 (100.0)	48 (100.0)	
sVNT inhibition (%)			
Mean ± Std	98.00 ± 2.18	98.18 ± 0.86	0.5658
Median	98.44	98.35	0.0424
Q1, Q3	98.28, 98.59	98.24, 98.43	
Range	84.10 ~ 98.65	92.88 ~ 98.62	
Omicron variant			
Seropositive, No (%)	52 (91.23)	46 (95.83)	
sVNT inhibition (%)			
Mean ± Std	72.18 ± 24.05	79.06 ± 21.40	0.1242
Median	81.44	85.76	0.0938
Q1, Q3	66.46, 88.59	70.59, 95.06	
Range	8.67 ~ 98.06	0.80 ~ 98.02	
sVNT, surrogate virus neutralization test; Std, standard deviation			

The delta variant did not show significant differences of sVNT inhibition between the two groups, but the higher neutralizing antibody efficiency was observed after booster vaccination (mean (SD) 98.00 (2.18) % vs. 98.18 (0.86) %, respectively, $p = 0.5658$).

For the omicron variant, no significant difference of VNT inhibition between the two groups were observed, but lower and dispersed neutralizing antibody efficiency was shown, compared to wild or delta

variants after booster dose (mean (SD) 72.18 (24.05) % vs. 79.06 (21.40) %, respectively, $p = 0.1242$).

Adverse events

Adverse events of systemic or injection site after booster dose are shown in Table 3. Within 28 days after booster vaccination, 49 participants in the ChA/ChA/BNT (85.96%) and 46 in the BNT/BNT/BNT group (95.83%) reported the adverse events ($p = 0.11$). The most common reported adverse reaction in the two groups was injection site pain (68.4% and 60.4%, respectively). Systemic symptoms in the BNT/BNT/BNT were reported slightly more than ChA/ChA/BNT, followed by myalgia (58.3% vs. 52.6%), fatigue (47.9% vs. 33.3%), fever (35.4% vs. 17.5%), headache (33.3% vs. 28.1%), arthralgia (25.0% vs. 12.3%), and chills (22.9% vs. 14.0%). Most side effects were reported that occurred between 6–12 hours after the booster dose and persisted for 24–48 hours in approximately 50% of cases. The onset ($p = 0.42$) or duration ($p = 0.26$) of adverse events between the two groups has no differences. BNT/BNT/BNT group showed the significantly more medications taken to alleviate the side effects (79.2% vs. 54.4%; $p = 0.01$), and the most taken medication was the acetaminophen (70.8% vs. 47.4%), followed by ibuprofen (14.6% vs. 7.0%), anti-histamines (4.2% vs. 0%), and steroids (2.1% vs. 0%). Both groups had few adverse events requiring a hospital visit (93.8% vs. 100%; $p = 0.09$).

Table 3
Adverse reactions within 28days after Booster vaccine dose

	ChA/ChA/BNT group (N = 57)	BNT/BNT/BNT group (N = 48)	p-value
Any AE	49 (85.96%)	46 (95.83%)	0.1055
Systemic AE**			
Fever	10 (17.5%)	17 (35.4%)	
Chills	8 (14.0%)	11 (22.9%)	
Myalgia	30 (52.6%)	28 (58.3%)	
Headache	16 (28.1%)	16 (33.3%)	
Nausea	0	5 (10.4%)	
Fatigue	19 (33.3%)	23 (47.9%)	
Joint pain	7 (12.3%)	12 (25.0%)	
Dyspnea	1 (1.8%)	3 (6.3%)	
Dizziness	2 (3.5%)	3 (6.3%)	
Itching	3 (5.3%)	1 (2.1%)	
Dysmennorrhea	0	2 (4.2%)	
Lymphadenopathy	0	4 (8.3%)	
Abdominal pain	1 (1.8%)	1 (2.1%)	
diarrhea	1 (1.8%)	1 (2.1%)	
Anaphylaxis*	0	0	
Injection site AE**			
Pain	39 (68.4%)	29 (60.4%)	
Heating sense or Redness	7 (12.3%)	10 (20.8%)	
Swelling	6 (10.5%)	8 (16.7%)	
Timing of AE after vaccination			0.4172
Within 3hours	5(8.77%)	5(10.42%)	
3–6 hours	9(15.79%)	4(8.33%)	
6–12 hours	19(33.33%)	22(45.83%)	

*anaphylaxis is diagnosed by a doctor; **allow double dosin

	ChA/ChA/BNT group (N = 57)	BNT/BNT/BNT group (N = 48)	p-value
12–24 hours	11(19.30%)	8(16.67%)	
24–48 hours	4(7.02%)	6(12.50%)	
After 48 hours	1(1.75%)	1(2.08%)	
Duration of AE			0.2636
< 24 hours	10(17.54%)	7(14.58%)	
24–48 hours	26(45.61%)	24(50.00%)	
48–72 hours	7(12.28%)	12(25.00%)	
72 hours – 5 days	4(7.02%)	1(2.08%)	
More than 5days	2(3.51%)	2(4.17%)	
Use of medication**			
Any	31(54.39%)	38(79.17%)	0.0139
Acetaminophen	27(47.37%)	34(70.83%)	
Ibuprofen	4(7.02%)	7(14.58%)	
Anti-histamine	0(0.00%)	2(4.17%)	
Steroid	0(0.00%)	1(2.08%)	
Visit to hospital			0.0923
None	57 (100%)	45 (93.75%)	
Outpatient clinic	0 (0%)	2 (4.17%)	
Emergency room	0 (0%)	1 (2.08%)	
Admission	0 (0%)	0 (0%)	
*anaphylaxis is diagnosed by a doctor; **allow double dosin			

Binary logistic regression analysis was performed to predict adverse reactions after a booster dose of COVID-19, and variables including sex, age, previous vaccine type, previous allergy history, primary vaccine side effects, and secondary vaccine side effects. The risk factor for adverse reactions to the booster vaccine was age, and the probability of significance was 0.037. As the age increased by 1, the probability of adverse reactions from the booster vaccine decreased by 0.943 times (Supplementary Table 2).

Vaccine-effectiveness for omicron variant after booster

Vaccine effectiveness of booster against the omicron variant was observed. Of the 105 HCWs enrolled in the study, 41 (39.0%) were confirmed to be infected with the omicron variant. The period from booster dose administration to confirmation of the omicron infection was 90.9 ± 20.68 days (mean ± SD) (Fig. 4). There were 18 cases (31.6%) in the ChA/ChA/BNT and 23 cases (47.9%) in the BNT/BNT/BNT. There was no statistical difference in effectiveness for the omicron variant between the two groups ($p = 0.1314$). However, when comparing the time to infection of the omicron variant between the groups, the ChA/ChA/BNT group showed the averaged 74.67 ± 14.68 days, which significantly shorter than 103.61 ± 15.04 days in the BNT/BNT/BNT group ($p < 0.001$). The follow-up period was 134.65 ± 3.77 days in the BNT/BNT/BNT group and 116.54 ± 0.98 days in the ChA/ChA/BNT group, respectively.

Changes in immune response before and after the omicron infection

Using blood samples from 58 HCWs who voluntarily consented to further analysis, we investigated how the presence or absence of the omicron infection alter sVNT inhibition at 127.31 ± 9.77 days after booster vaccination. In total of 58 HCWs, 33 had confirmed the omicron infection, and 25 were uninfected (Table 4). At follow-up, sVNT inhibition was significantly reduced in the non-omicron-infected group (mean (SD) 48.44 (33.64) %, median 48.1%, Q1/Q3 21.07/80.39), compared to the omicron-infected (mean (SD) 95.13 (3.47) %, median 96.48%, Q1/Q3 93.46/97.73) ($p < 0.001$). In the omicron-infected group, there was no difference of sVNT inhibition between subgroups divided by one within a month and more than month after infection (Table 4). Thirty-three patients infected with the omicron showed that the sVNT inhibition was significantly elevated after omicron infection ($p < 0.001$) (Fig. 5A). In contrast, twenty-five HCWs of the uninfected with omicron had a significant decrease of the omicron sVNT levels at four months after booster dose, compared to 1 month ($p = 0.002$; Fig. 5B). The sVNT inhibition against the omicron was measured by adding the difference of the inoculated vaccine types to the presence or absence of the omicron infection and the whole samples were subsequently divided into four groups; BNT/BNT/BNT group-non-infected COVID-19 (n = 14), BNT/BNT/BNT group-infected COVID-19 (n = 20), ChA/ChA/BNT group-non-infected COVID-19 (n = 11), and ChA/ChA/BNT group-infected COVID-19 (n = 13) (Fig. 6). No differences were observed between vaccine types in each of the four groups. Within the group of the BNT/BNT/BNT, sVNT inhibition of the omicron in the presence of COVID-10 showed a significantly higher than uninfected (absence) with $p < 0.001$ differences, but ChA/ChA/BNT group has a tendency without significance

Table 4
Comparison of serological results of Omicron variant between SARS-CoV-2 infected and uninfected subjects after booster vaccination

Group	SARS-CoV-2 uninfected subjects (N = 25)	SARS-CoV-2 infected subjects (N = 33)		P-value
		< 30 days after infection (N = 13)	> 30 days after infection (N = 20)	
sVNT inhibition (%)				
Mean ± Std	48.44 ± 33.64	94.7 ± 3.67	95.41 ± 3.40	< 0.001
Median	48.1	96.11	96.76	< 0.001
Q1, Q3	21.07, 80.39	93.31, 97.73	94.34, 97.69	
Range	-4.02 ~ 98.22	87.59 ~ 98.19	86.70 ~ 98.40	

Discussion

The current study showed that the booster dose of BNT162b2 as third shot significantly enhanced the humoral immunogenicity in the wild-type of HCWs. The sVNT inhibition score measured at two months after the second dose (82%) was further reduced to six months after the second dose (58%), but this was significantly improved by the third dose (97%), which measured four weeks after final administered with booster. These results are consistent with recent reports [3, 4, 5] showing that booster shot improved the inhibition of sVNT. The comparison between the ChA/ChA/BNT group and the BNT/BNT/BNT group showed that there was no difference in immunogenicity between homogeneous and heterogeneous boosters, which was the same in the occurrence of adverse reactions. This result was somewhat different from the recent result that the heterologous boosting produced neutralizing antibody similar to or better than homogenous boosting, but it consistently showed that there was no difference in reactogenicity and no issue of safety [6].

The neutralizing activity against the omicron variant was significantly lower than the delta with the booster dose (75% vs. 98%, $p < 0.001$). Our results are supported by recent study shown that the neutralizing activity for omicron was 6 to 23-times lower than delta in the booster with Pfizer [7]. In December 2021, the UK Health Security Agency (UKHSA) announced delta variant prevention rates in the ChA/ChA/BNT group was 94% and the BNT/BNT/BNT was 93%, but omicron variant showed the rates of 71% in the ChA/ChA/BNT group and 76% inthe BNT/BNT/BNT [8]. Although the current study for sVNT inhibition values used a surrogate antibody, it was shown that the ChA/ChA/BNT group (98%) and the BNT/BNT/BNT group (98%) for delta variant, and ChA/ChA/BNT group (72%) and the BNT/BNT/BNT group (79%) for omicron variant. Surprisingly, the efficacy of the neutralizing antibody in our study was

consistent with the effectiveness of the vaccine reported by UKHSA. It could be considered that sVNT test used for prediction the vaccine effectiveness. We also observed that both homogeneous and heterogeneous boosters have similar results with low sVNT levels of omicron.

Interestingly, 41 participants in this study had omicron infection, and it was investigated that the omicron infection was confirmed in a shorter period from the last administration in a heterogenous booster than a homogenous booster (75 vs. 104 days, $p < 0.001$). This result can be considered as if the early vaccine efficiency against the omicron in the ChA/ChA/BNT group was lower than that in the BNT/BNT/BNT. However, revisiting the date passed at the infection status of omicron showed that the time difference between homogeneous boosters and heterogeneous was unclear. Thus, we consider that the reduced effectiveness of the booster vaccine is probably related to increased omicron transmissibility rather than enhanced immunologic escape after the booster vaccination, as suggested by Dr. Yu et al. [9].

This is the first study to examine the change of neutralizing antibody efficiency after a breakthrough omicron infection after the third booster vaccination. In addition, we compared the change in neutralizing antibody efficiency in the group without breakthrough infection in the cohort corresponding to the same conditions. There was a significant decrease in the sVNT inhibition level 4 months after the third booster vaccine, but a dramatic increase was observed in breakthrough infection. According to the announcement by the Korea Centers for Disease Control and Prevention (KCDC) on July 19, 2022, 2.8% of confirmed COVID-19 patients were reinfected, and 97% were the first infections [10]. Our results support the evidence for the COVID-19 resurgence. The inhibition level of neutralizing antibody against omicron in the breakthrough omicron-infected group (95%) was almost identical to wild-type (97%) or delta variant (98%) after the third booster vaccination. Of course, there are variables such as cross-immune reactions, but additional research is required to determine whether there will be a uniform or increased high neutralizing antibody efficiency as the wild-type after the fourth booster dose using the original vaccine in the non-infected group.

This study used a surrogate virus neutralization test, which showed a correlation with the gold standard for cell culture-based neutralization assays [1, 4, 11, 12]. Delta and omicron variants were evaluated in the same way using the sVNT. Although there are few studies using sVNT for novel variants [13], a recent study showed that the neutralizing efficacy of the antibody against the delta, which measured by sVNT was strongly correlated with pseudotyped virus neutralization tests (pVNT) [14]. sVNT kits used in these studies is able to detect functionally neutralizing antibodies in patients after vaccination and COVID-19 infection without the conventional labor and time-intensive laboratory procedures. These results may serve as a basic tool for evaluating the efficacy of vaccines against various strains using sVNT in the future.

Although this study has the advantage of being real-world data on a group of HCWs in Korea, it has some limitations. First, sample size from a single center are relatively small. Allocation to each vaccine group was not random, and there was an imbalance between occupations. Due to the characteristics of HCWs, a relatively more number of young women were included. In addition, the follow-up period of the ChA/ChA/BNT and the BNT/BNT/BNT group was also different because the time of booster vaccination

differed by one month depending on the presence of allogeneic and heterogeneous booster vaccines. At last, cellular immune responses that may affect cross-immune responses have not been evaluated.

Recently, the rapid transmission of BA.2, BA.4, and BA.5 in omicron sub-lineages with additional mutations were reported. The controversy over the pros and cons of the fourth additional vaccination using the original vaccine is also emerging. Determining the effectiveness of the quaternary vaccine will depend on which of the two prevail: immune evasion or waning immunity. A booster dose using the original vaccine may help those who have weakened immunity over time or due to disease or age. However, a different approach may be necessary for those infected with omicron or healthy health care workers enrolled in our study.

Existing original vaccines are inferior to the omicron variant in the efficacy of neutralizing antibodies and the vaccine's effectiveness. The development of an omicron-specific vaccine should be given priority, but it is necessary to devise a method to select the people who need the fourth shot as boost using the original vaccine before a new vaccine is released.

Methods

Study design and participants

This study was initially designed as a cross-sectional study. From 23 to 25 November and 23 to 24 December 2021, total 2,133 HCWs at the Soon Chun Hyang University Bucheon Hospital received BNT162b2 (Pfizer) as a booster vaccination. Among them, 115 HCWs who already participated in the previous study about the primary and secondary vaccination and voluntarily wanted to participate in the current study were enrolled (Fig. 1). All participants had no history of COVID-19 infection or suspected symptoms at the time of registration.

Blood samples of participants were collected at four weeks after the booster dose. The samples were analyzed with the commercial virus neutralization test kit (Genscript Biotech Corporation, Piscataway, NJ, USA), which used in the previous study [1]. Participants who consented to the study were given a self-administered questionnaire for adverse events of a booster vaccination. The data included the following information: sex, age, date of vaccination, history of COVID-19, drug AEs, allergy, types and duration of adverse events, use of medication (acetaminophen, ibuprofen, opioid), and visit to an outpatient clinic or emergency room.

While the study was ongoing, the omicron variant was rapidly emerging in Korea, thus the additional evaluation for the neutralizing antibodies' efficiency of the booster vaccine against the delta and omicron variants were substituted. In addition, the study protocol was modified and additional blood sampling to compare the change in neutralizing antibody efficiency after the omicron infection and the change in omicron neutralizing antibody efficiency between omicron-infected and uninfected subjects were

performed. The sampling was limited to HCWs who voluntarily consented at least three months after the booster dose.

The study was approved by institutional review board (IRB) of Soon Chun Hyang University Bucheon Hospital (IRB No. 2021-12-017). Written consent was obtained from all enrolled participants.

Cohorts

Cohort 1 is for evaluation the neutralizing antibody efficiency against the wild, delta, and omicron variants one month after the booster vaccine, and cohort 2 is a group for further study of the change in neutralizing antibody efficiency against the omicron variant four months after the booster dose.

Groups

The BNT/BNT/BNT group was defined as a booster dose with BNT162b2(Pfizer) after two doses of BNT162b2 vaccine (Pfizer) 3 weeks apart. The ChA/ChA/BNT group was defined as a booster dose with BNT162b2(Pfizer) after two doses of ChAdOx1 vaccine (AstraZeneca/Oxford) 12 weeks apart.

Serological assays

To evaluate for neutralizing activity against the SARS-CoV-2 wild type and the variants of B.1.617.2 (delta) and B.1.1.529 (omicron), ELISA-based surrogate virus neutralization test (sVNT) were used. All detailed methods were described in the previous study [1].

Statistical analysis

Statistical analyses were performed with Graphpad Prism software (version 9.3.1), and R software (version 4.0.2). All measurements and calculation data were presented as the mean ± standard deviation (SD), median, IQR, range for continuous variables, and frequency (percentage) for categorical variables. Nonparametric Kruskal-Wallis compared two or more independent groups for the continuous variables. For comparison the independent groups' variables, independent two-sample t-tests or chi-square tests were used. For the one subject variable, a paired t-test was used. Related-samples Wilcoxon signed rank test was used to compare paired samples at two-time points. All tests used were two-tailed, with $p < 0.05$ considered statistically significant.

Declarations

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Figures

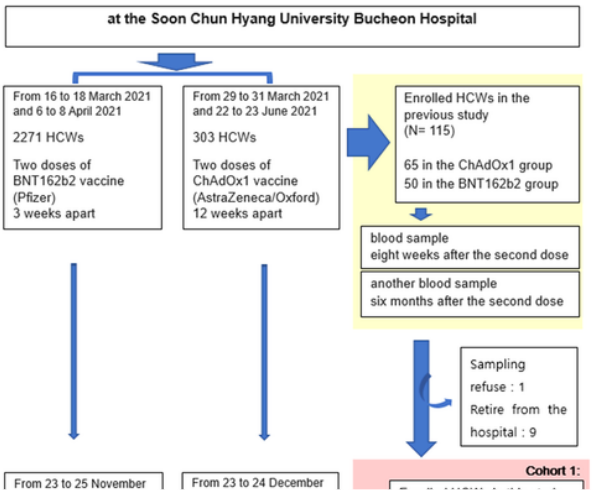


Figure 1

Flowchart of COVID-19 Vaccine study in health care workers (HCW) cohorts at the Soon Chun Hyang University Bucheon hospital health.

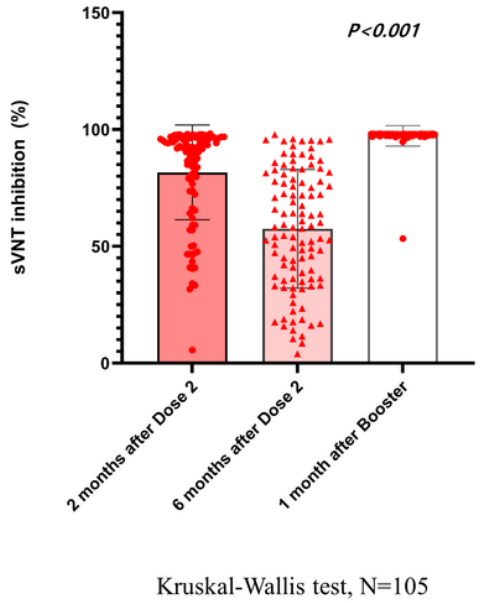


Figure 2

Changes of vaccine-induced neutralization efficiency in second doses of vaccination only or boostor vaccination in HCWs. Titers were measured at two months and six months (i.e. just before the booster of the BNT162b2 vaccine) after second doses vaccination or one month after the booster dose.

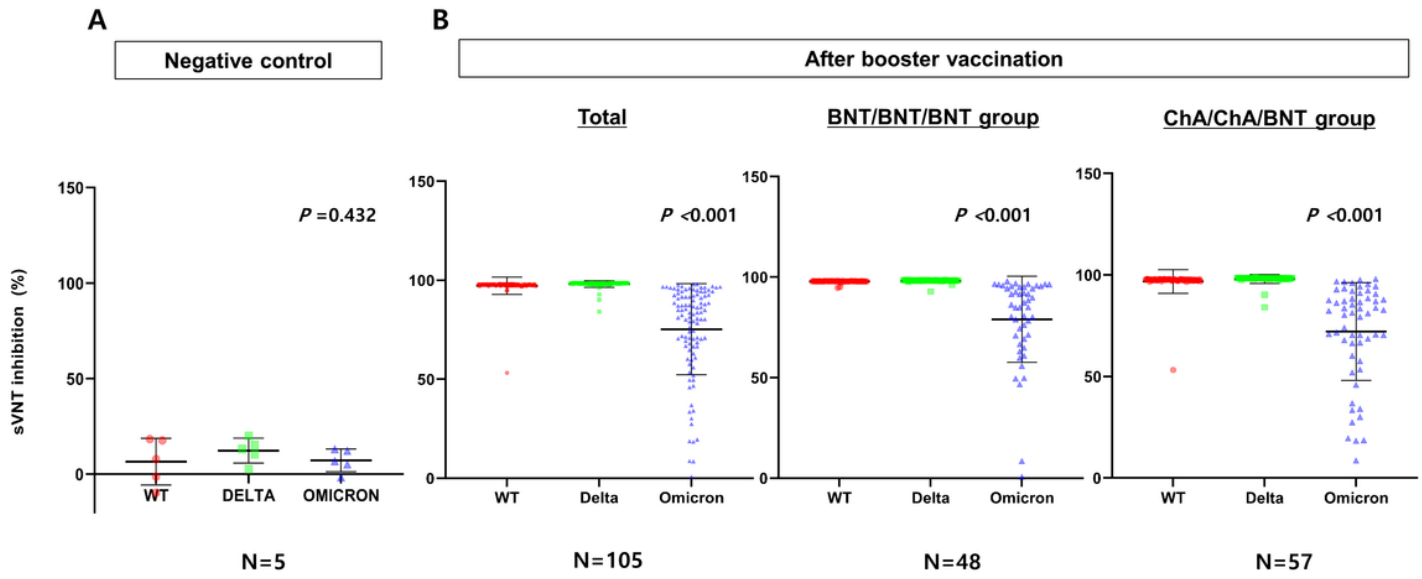
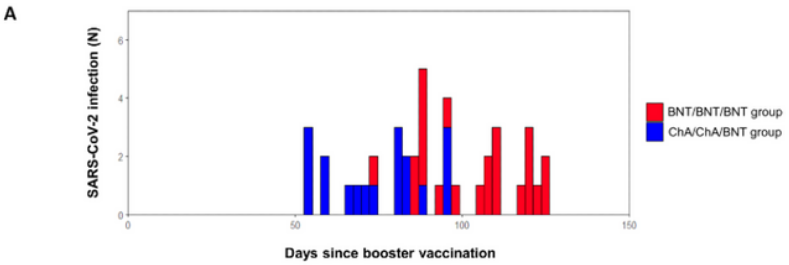


Figure 3

Neutralization efficiency to Wild-type, the Delta, and Omicron variant after booster dose. Neutralizing antibody level measured by percentage inhibition of sVNT readings at (A) negative control (unvaccinated) and (B) 4 weeks after booster vaccination.



	Total (N=41)	ChA/ChA/BNT group (N=18)	BNT/BNT/BNT group (N=23)	P-value
Period from booster dose to confirmation of Omicron variant infection	90.9±20.68	74.67±14.68	103.61±15.04	<0.001

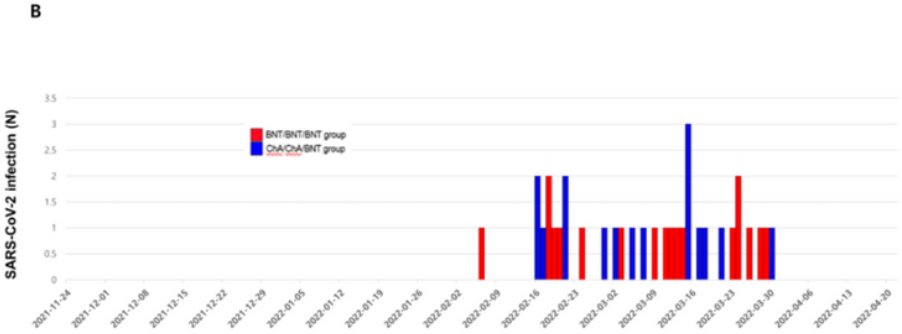


Figure 4

A daily number of SARS-CoV-2 infections according to the period from booster vaccination to breakthrough infection (A) and over time after booster vaccination (B).

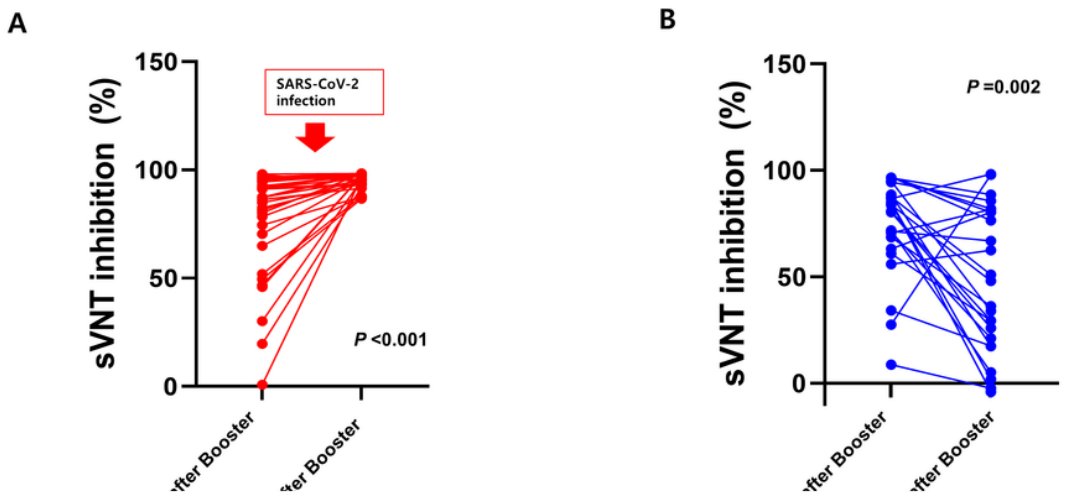


Figure 5

The pattern changes of sVNT inhibition (%) scores between omicron infected (A) and uninfected individuals (B). Subsequent titers were measured 127.31 ± 9.77 days after booster vaccination in both groups (n=33, n=25)

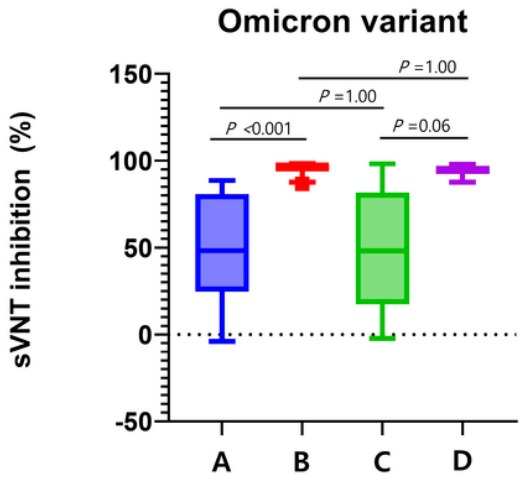


Figure 6

Neutralizing antibody level measured by sVNT inhibition of omicron in four groups. Each of the four groups consists of uninfected or infected with omicrons in the BNT/BNT/BNT or ChA/ChA/BNT group, respectively. Sebsequent titers were measured 128.61±9.15 days after booster vaccination. A: BNT/BNT/BNT group-non-infected COVID-19 (n=14), B: BNT/BNT/BNT group-infected COVID-19 (n=20), C: ChA/ChA/BNT group-non-infected COVID-19 (n=11), D: ChA/ChA/BNT group-infected COVID-19 (n=13).

Supplementary Files

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- SupplementaryTable.docx