Immune responses to the ChAdOx1 nCoV-19 and BNT162b2 vaccines and to natural COVID-19 infections over a three-month period

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Summary

The antibody responses induced by BNT162b2 were much higher than those induced by ChAdOx1 and similar in the responses to natural infections. T cell responses were maintained in the BNT162b2 vaccinees, but not in the ChAdOx1 vaccinees after 3 months.

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Foot note

Conflict of interest: There were no conflicts of interest for any of the authors.

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Abstract

Background: There are limited data directly comparing immune responses to vaccines and to natural infections with COVID-19. This study assessed the immunogenicity of the BNT162b2 and ChAdOx1 nCoV-19 vaccines over a 3-month period and compared the immune responses with those to natural infections.

Method: We enrolled healthcare workers (HCWs) who received BNT162b2 or ChAdOx1 nCoV-19 vaccines and COVID-19-confirmed patients, and then S1-IgG and neutralizing antibodies and T cell responses were measured.

Results: A total of 121 vaccinees and 26 patients with confirmed COVID-19 were analyzed. After the 2nd dose, the BNT162b2 vaccine yielded S1-IgG antibody responses similar to natural infections (2241 ± 899 vs. 2601 ± 5039, p=0.676), but significantly stronger than the ChAdOx1 vaccine (174 ± 96, p <0.0001). The neutralizing antibody titer generated by BNT162b2 was 6-fold higher than that generated by ChAdOx1, but lower than that by natural infection. T cell responses persisted for the 3 months in the BNT162b2 and natural infection but decreased in the ChAdOx1.

Conclusions: Antibody responses after the 2nd dose of BNT162b2 are higher than after the 2nd dose of ChAdOx1 and like those occurring after natural infection. T cell responses are maintained longer in BNT162b2 vaccinees than in ChAdOx1 vaccinees.

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Key words: COVID-19, 2nd dose**,** BNT162b2, ChAdOx1 nCoV-19, antibody, T cells

Introduction

Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are expected to end the Coronavirus Diseases-19 (COVID-19) pandemic. The lipid nanoparticle-formulated mRNA-based vaccine, BNT162b2, developed by BioNTech/Pfizer has been reported to be 95% effective in preventing COVID-19 [1]. The ChAdOx1 nCoV-19 vaccine developed by Oxford University/AstraZeneca, which is a replication-deficient chimpanzee adenovirus vector-based vaccine, has been reported to be 70.4% effective [2]. Separate studies reported that BNT162b2 and ChaAdOx1 nCoV-19 elicited strong antibody responses and robust spike protein specific $CD8^+$ and $CD4^+$ T cell responses [3-8]. In our previous study, antibody responses to BNT162b2 after the 1^{st} vaccination of a homogeneous population were faster and stronger than those to ChAdOx1 nCoV-19 but spike-specific T cell responses were similar [9]. However, there are limited comparisons of the detailed kinetic immunogenicity across different platformed, second doses completed ChAdOx1 and BNT162b2. Many studies have reported rapid waning of IgG antibodies within 3-4 months in patients naturally infected with COVID-19 [10-13], and our previous findings were consistent with those studies [14]. However, studies directly comparing immune responses to natural infection and vaccines have also been limited. In this study, we examined immune responses, both humoral and cellular, to the BNT162b2 and ChAdOx1 nCoV-19 vaccines over a 3-month period and compared the antibody and T cell responses induced by the vaccines with those generated by natural COVID-19 infection.

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Materials and Methods

Study participants and the specimens

A nationwide vaccination program against COVID-19 is ongoing in South Korea. Our study enrolled HCWs who received the ChAdOx1 nCoV-19 vaccine (AZ) or the BNT162b2 vaccine (PF) at a tertiary care hospital in Seoul, South Korea, between March 5th and March 25th, 2021. In accord with the policy of the Korean government, the BNT162b2 vaccine was assigned to high-risk HCWs in direct contact with COVID-19 patients, and the ChAdOx1 vaccine was assigned to those involved in general patient care. All participants agreed to peripheral blood sampling, and blood sampling was carried out once before vaccination, for baseline serology. Thereafter, blood samples were taken from the participants vaccinated with NT162b2 at 3 weeks after the first dose, 2 weeks after the second dose (5 weeks after the first dose), and 12 weeks after the first dose. The blood samples collected from the participants vaccinated with the ChAdOx1 nCoV-19 vaccine were collected at 3, 8, and 12 weeks after the first dose, and 2 weeks after the second dose (14 after the first dose).

COVID-19 naturally infected patients admitted to Asan Medical Center were enrolled between March 2020 and February 2021. COVID-19 infection was confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR) for the RdRp, N, and E genes of SARS-CoV-2 (Allplex™ 2019-nCoV assay, Seegene, Seoul, South Korea). All participants agreed to peripheral blood sampling, which was carried out on the day of hospital admission, and 1 month and 2 months, and either 3 or 4 months after symptom onset. The study was reviewed and approved by the Institutional Review Board of Asan Medical Center (IRB No. 2020-0297 and IRB No. 2021-0170). Informed consents were taken from all participants.

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Measurement of antibody responses

SARS-CoV-2 S1-specific IgG and IgM antibody titers were measured using an enzyme-linked immunosorbent assay (ELISA) developed in-house, details of which are described in a previous report (8). The data are presented as International Units per milliliter (IU/ml), which is standardized with reference pooled sera from International Vaccine Institute (Seoul, South Korea).To determine cut-off values for the ELISA, the mean and standard deviation (SD) of negative control plasma were measured, and cut-off values were defined as mean IU plus three-fold the SD value; the cut-off value was 10 IU/ml for IgG, as reported previously [15, 16].

We also measured plasma levels of neutralizing antibodies using a microneutralization (MN) assay. Briefly, a 100-tissue culture infective dose 50 (100 $TCID_{50}$) of SARS-CoV-2 (βCoV/Korea/KCDC/2020 NCCP43326) was mixed with an equal volume of diluted plasma specimen, incubated at 37°C for 30 minutes, and added to Vero cells. After 96 hours, the cytopathic effect of SARS-CoV-2 on the infected cells was measured. Neutralizing antibody titer was calculated as the reciprocal of the highest dilution of test plasma giving 50% neutralization (ID_{50}). The MN assay was performed in a Bio Safety Level (BSL)-3 laboratory in Institut Pasteur Korea (Seongnam, Republic of Korea).

Measurement of T cell responses

An IFN-gamma enzyme-linked immunospot (ELISPOT) assay was performed to measure the SARS-CoV-2-specific T cell response of PBMCs isolated from participants' blood samples. T cells were stimulated with overlapping peptides of SARS-CoV-2 spike protein (Miltenyi Biotec, Bergisch Gladbach, Germany), and numbers of spot-forming cells (SFC) per 5.0×10^5 PBMCs were counted with an automated ELISPOT reader (AID iSPOT, Autoimmun Diagnostika GmbH, Strassberg, Germany).

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Statistical analysis

Statistical analyses were performed with SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA), and graphs were plotted with GraphPad Prism 8. Depending on normality of the data, we used the Chi-squared test or Fisher's exact test to analyze categorical variables, and Student's *t*-test or the Mann–Whitney *U* test for continuous variables. All tests of significance were two-tailed, and *P* values < 0.05 were considered statistically significant.

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Results

Baseline characteristics of the study participants

A total of 129 HCWs were enrolled in this study; 93 (72%) were vaccinated with ChAdOx1, 36 (28%) with BNT162b2, and 8 of the ChAdOx1 vaccinees dropped out; thus 85 ChAdOx1 and 36 BNT162b2 vaccinees were finally analyzed. The baseline characteristics of the participants are shown in Table 1. Median age was higher in the ChAdOx1 participants (36 vs. 32, $P = 0.006$; Table 1). After the second dose of vaccine, local and systemic reactogenicity as severity grade were significantly higher in the ChAdOx1 participants than the BNT162b2 participants ($P = 0.037$ and $P < 0.001$, respectively; Table 1).

Twenty-six patients with confirmed COVID-19 were classified according to disease severity: 1 as asymptomatic, 1 as mild, 8 as moderate, 12 as severe, and 4 as critical. Detailed baseline characteristics and clinical outcomes of the patients are shown in Table 2.

S1-IgG antibody responses

SARS-CoV-2 S1 protein-specific IgG antibody (S1-IgG) titers were measured in 36 of the plasma samples from the participants injected with the BNT162b2 vaccine at baseline, and at 5 and 12 weeks, and in 35 of the plasma samples at 3 weeks after the first vaccination. S1-IgG titers were significantly higher 2 weeks after the second dose (5 weeks after the first dose; mean ± SD, IU/ml, 2241 ± 899) than at 3 weeks after the first dose (351 ± 180, $p < 0.0001$). They then decreased by 12 weeks after the first dose (834 ± 467, $p < 0.0001$, Fig. 1A).

S1-IgG was measured in 84 plasma samples from ChAdOx1 nCoV-19 vaccinees at baseline, 85 at 3 and 8 weeks, 82 at 12 weeks, and 83 at 14 weeks after the first vaccination. S1-IgG titers declined between 3 and 12 weeks after the first vaccination (at 3 weeks, 142 ± 139; at 12 weeks, 42 ± 29; $p < 0.0001$, Fig. 1B). At 2 weeks after the second dose (14 weeks after the first dose), S1-IgG was higher than at 12 weeks but not significantly different from at 3 weeks (at 14 weeks, 174 ± 96; between 12 and 14 weeks, $p < 0.0001$; between 3 and 14 weeks, $p = 0.067$, Fig. 1B).

For the naturally infected patients, S1-IgG was measured in 21 plasma samples on admission (median, 6 days; range, 0-13 days after symptom onset), 24 samples at 4 weeks after symptom onset (median, 30 days; range, 15-44 days), 18 samples at 8 weeks after symptom onset (median, 54 days; range, 47-74 days), and 26 samples at 15 weeks after symptom onset (median, 105 days; range, 81-140 days). The highest S1-IgG titers were measured at 4 weeks (2601 ± 5039); they then declined to 15 weeks (457 ± 620, $p = 0.022$, Fig. 1C).

At 4 weeks after symptom onset, the naturally infected patients had almost the same antibody levels as 2nd dose BNT162b2 vaccinees at 5 weeks (2601 ± 5039 vs. 2241 ± 899, $p = 0.676$), but significantly higher than at 2 weeks after the 2nd dose of ChAdOx1 nCoV-19

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(174 ± 96at 14 weeks, p <0.0001). At 3 months after the 1st vaccination or natural infection, S1-IgG antibody of ChAdOx1 nCoV-19 (174 ± 96at 14 weeks) was significantly lower than BNT162b2 (834 ± 467at 12 weeks, p < 0.0001) or natural infection (457 ± 620at 15 weeks, p = 0.0001, Fig. 1D).

Virus neutralizing antibody responses

SARS-CoV-2 virus neutralizing antibody titers were measured in the plasmas of 31 BNT162b2 and 37 ChAdOx1 nCoV-19 vaccinees 3 weeks after the 1st dose, and in the plasma of 36 BNT162b2 and 81 ChAdOx1 nCoV-19 vaccinees 2 weeks after the 2nd dose. Also, the neutralizing antibody titers were measured in the plasmas of 18 natural infected patients at 4 weeks after symptom onset (peak response). After the 1st dose, the neutralizing antibody titer of the BNT161b2 vaccinees was about 1.6-fold higher than that of the ChAdOx1 nCoV-19 vaccinees (183.1 ± 155.6 vs. 116.6 ± 116.2, p = 0.036, Fig. 1E). After the 2nd dose, it was about 6-fold higher than that of the ChAdOx1 nCoV-19 vaccinees (2544 ± 2547 vs. 447 ± 341, p <0.0001), but lower than that of natural infected patients at 4 weeks (vs. 4708 ± 3270, p = 0.010). Neutralizing antibody titer was significantly correlated with S1-IgG antibody titer (Pearson r = 0.747, p < 0.0001; Supplementary Fig. 1).

Interferon-gamma-producing T cell responses

SARS-CoV-2 spike protein-specific IFN-γ-producing T cell responses were measured in 35 PBMC samples from the participants injected with BNT162b2 at baseline and at 5, and 12 weeks, and in 33 PBMC samples at 2 weeks after the 1st dose. T cell responses had increased significantly by 2 weeks after the 1st dose, whereas by 2 weeks after the 2nd dose they had not (mean ± SD, 2 weeks, 104.6 ± 97.8 vs. 5 weeks, 156.3 ± 113.6; p = 0.638; Fig. 2A). After

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that they remained roughly constant until 12 weeks after the 1st vaccination (5 weeks vs. 12 weeks, p = 0.639; 2 weeks vs. 12 weeks, p = 0.982; Fig. 2A).

IFN-γ-producing T cell responses were measured in 29 PBMC samples from the participants injected with ChAdOx1 nCoV-19 at baseline, and at 12 and 14 weeks, and in 27 PBMC samples 2 weeks after the 1st dose. T cell responses declined between 2 weeks and 12 weeks after the first dose (2 weeks vs. 12 weeks, 121.2 ± 104.3 vs. 34.3 ± 46.9, p = 0.0008; Fig. 2B). By two weeks after the second dose (14 weeks), the T cell responses had not significantly increased (44.93 ± 33.11, p = 0.614).

The T cell responses were measured in 18 PBMC samples at 4 weeks and 24 PBMC samples at 15 weeks after symptom onset from the COVID-19 natural infected patients. T cell responses maintained between 4 weeks and 15 weeks after symptom onset (4 weeks vs. 15 weeks, 78.1 ±83.8 vs. 77.7 ± 119.1, p = 0.990; Fig. 2C).

Two weeks after the first doses, the T cell responses of the BNT162b2 and ChAdOx1 nCoV-19 were similar (p = 0.509, Fig. 2D) and like that of the natural infection at 4 weeks after symptom onset (vs. BNT162b2; p = 0.522, vs. ChAdOx1; p = 0.386). At 3 months after the first dose, the T cell responses of the BNT162b2 vaccinees (at 12 weeks) was significantly higher than that of the ChAdOx1 nCoV-19 vaccinees at 14 weeks (108.7 ± 89.8 vs. 44.93 ± 38.11, p = 0.006), but comparable with that of the natural infection at 15 weeks after symptom onset (77.7 ± 119.1, p = 0.078).

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Discussion

In this study we assessed the immunogenicity of 2nd dose-completed BNT162b2 and ChAdOx1 nCoV-19 vaccines and compared the antibody and T cell responses induced by the vaccines with those evoked by natural infection with COVID-19. After the 2nd dose, S1-IgG antibody responses to BNT162b2 vaccine were similar to those of naturally infected patients and significantly higher than those to ChAdOx1 nCoV-19 vaccine. Neutralizing antibody after the 2nd dose was also significantly higher in BNT162b2 vaccinees than in ChAdOx1 nCoV-19 vaccinees, but lower than in natural infection. S1-IgG antibody declined over 3 months in both BNT162b2 vaccinees and naturally infected patients. Three months after the 1st dose, the S1-IgG antibody response to BNT162b2 was highest, and the response to ChAdOx1 was lower than to the other groups. With both vaccines, the 2nd doses did not elicit significant IFN-γ-producing T cell responses. The T cell response to BNT162b2 was more-or-less maintained, but that to ChAdOx1 decreased by 3 months after the 1st dose. The T cell responses to natural infection was constant for 3 months after the infection.

In our previous study, the 1st dose of BNT162b2 elicited a higher antibody response than ChAdOx1 nCoV-19 [9]. The differences between the S1-IgG and neutralizing antibody responses to the two vaccines increased after the 2nd dose (Fig. 1). After the 2nd dose, BNT162b2b elicited a similar S1-IgG antibody response to that in the naturally infected patients, but the response to ChAdOx1 was significantly lower. The spike glycoprotein of SARS-CoV-2 binds a receptor, angiotensin converting enzyme 2 (ACE2), through a domain that is part of S1, and mediates cell entry [17, 18]. The spike protein is a key target for virus neutralizing antibodies [19] and a prime candidate for vaccine development. The ChAdOx1 nCoV-19 vaccine contains the full-length spike protein along with the leader sequence of

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tissue plasminogen activator [20]. The BNT162b2 vaccine also encodes the full-length spike protein, which is stabilized in the prefusion conformation by mutations of residues 986 and 987 to prolines [21, 22]. This structural difference between the spike proteins may affect antibody production, and the difference between the adenovirus-vector-based platform and the mRNA-based platform may also partly explain the discrepancy in antibody response between the two vaccines.

To the best of our knowledge, there are very limited data directly comparing SARS-CoV-2-specific T cell responses to the different COVID-19 vaccine platforms after the 1st and 2nd doses of vaccine. Our study revealed that the spike protein-specific IFN-γ-producing T cell response to the BNT162b2 vaccine was more stable over 3 months than that to the ChAdOx1 nCoV-19 vaccine. T cells may play a major role in the resolution of COVID-19 [23], but the effects on long-term memory T cells and their effects on long-lasting immunity are unclear. Nevertheless, current studies have shown that T cell responses remain robust up to 6 or 12 months after exposure to SARS-CoV-2 [24, 25], even though they are accompanied by waning of antibody responses. Jung et al. also reported that SARS-CoV-2 spike, membrane, and nucleocapsid protein specific IFN-γ-producing T cell responses were sustained over 200 days after the infection [26]. Thus, vaccine-induced T cell responses may well contribute to long-term immunity. Although our findings indicate that the BNT162b2 vaccine elicits more durable SARS-CoV-2-specific T cell responses than the ChAdOx1 nCoV-19 vaccine, further studies are needed to assess which vaccine platform may be superior in terms of long-term immunity against SARS-CoV-2.

In both BNT162b2 vaccinees and natural-infected patients, S1-IgG antibody declined significantly at 3 months after vaccination / infection. Other studies have reported results consistent with ours, namely, waning of spike-IgG antibody to the BNT162b2 vaccine [27, 28] and to natural COVID-19 infections [11, 12, 24]. However, the previous study reported

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that antibody waning dynamics were various among natural-infected patients with rapid waning, slow waning, and persistent groups [29]. So, further detailed kinetic studies are needed on the different waning patterns of vaccine-induced immunity in terms of longevity. In addition, S1-IgG antibody levels induced by the ChAdOx1 nCoV-19 vaccine declined between 3 weeks and 12 weeks after the 1st dose, although we did not observe a further decline after the 2nd dose. However, this waning immunity was reversed after the 2nd dose of ChAdOx1 nCoV-19 vaccine, which was given in accordance with Korean national vaccine policy based on evidence that a 3-month interval between doses may be beneficial for protection against COVID-19 [30]. In contrast, even though the 2nd dose was delayed, the ChAdOx1 vaccine induced a lower S1-IgG antibody titer at 3 months after the 1st dose than either BNT162b2 or natural infection. Meanwhile, Goel et al. found that spike-specific IgG antibody responses decreased by half at 28-33 days after mRNA vaccinations, but spike-specific memory B cell responses did not decline up to 6 months [31]. It is worth noting that various immunologic factors in addition to the antibody response may affect vaccine effectiveness against symptomatic or severe COVID-19. Hence, further studies of vaccine effectiveness as well as of the immunologic properties of the various COVID-19 vaccine platforms are needed.

The gradual reduction in antibody titers may affect the efficacy of the vaccines, especially to infections by variants. A current prime concern about COVID-19 is the emergence and spread of diverse variants of SARS-CoV-2. The B.1.617.2 (delta) variant, which is already dominant worldwide, has several spike protein mutations [32] that may affect immune responses to the key antigenic regions of this receptor-binding-protein [33]. Indeed, neutralizing antibody activity against the delta variant in BNT162b2 recipients is reported to be 5.8 times lower than that against wild-type SARS-CoV-2 [34]. Furthermore, the effectiveness of the mRNA vaccines in nursing home residents fell from 75% to 53% after

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the emergence of the delta variant [35]. Additional studies of the effect of the reduced efficacies of the different COVID-19 vaccine platforms against the delta variant are urgently needed.

Limitations of the present study are the relatively small number of enrolled participants and the differences in vaccine schedules and sampling times. Despite these limitations, our study provides clear comparative data on the immune responses to 2nd dose-completed BNT162b2 and ChAdOx1 nCoV-19 vaccines as well as to natural COVID-19 infections. The antibody responses induced by the BNT162b2 vaccine were much higher than those induced by the ChAdOx1 vaccine and similar in magnitude to the responses to natural infections. The antibody responses to the vaccines, like those to natural infections, waned after 3 months. T cell responses were maintained in the BNT162b2 vaccinees and natural infected patients, but not in the ChAdOx1 vaccinees. Further research into the induction of long-term immunity is needed, specially to manage emerging variants.

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Figure legends

Figure 1. Antibody responses over a three-month period after vaccination with the BNT162b2 and ChAdOx1 nCoV-19 vaccines, and after natural infection with COVID-19

(A) SARS-CoV-2 S1-specific IgG antibody titers induced by BNT162b2 vaccine from before vaccination to 12 weeks after the 1st dose. (B) SARS-CoV-2 S1-specific IgG antibody titers induced by ChAdOx1 nCoV-19 vaccine from before vaccination to 14 weeks after the 1st dose. (C) SARS-CoV-2 S1-specific IgG antibody titers in COVID-19-confirmed patients from within two weeks after symptom onset to 15 weeks after symptom onset. (D) SARS-CoV-2 S1-specific IgG antibody titers induced by BNT162b2 and ChAdOx1 nCoV-19 vaccines and COVID-19 natural infections over the 3 months after 1st dose vaccination / infection. (E) Neutralizing antibody titers at 3 weeks after 1st dose and 2 weeks after 2nd dose vaccinations with BNT162b2 and ChAdOx1 nCoV-19 vaccines and at 4 weeks after natural infection.

Figure 2. Cell-mediated immune responses over the three months after vaccination with BNT162b2 and ChAdOx1 nCoV-19 vaccines and after natural infection with COVID-19

(A) IFN-gamma-producing T cell responses induced by BNT162b2 vaccine from before vaccination to 12 weeks after the 1st dose. (B) IFN-gamma-producing T cell responses induced by ChAdOx1 nCoV-19 vaccine from before vaccination to 14 weeks after the1st dose. (C) IFN-gamma-producing T cell responses induced by natural infection with COVID-19 up to 15 weeks after symptom onset. (D) IFN-gamma-producing T cell responses over 3 months after the 1st dose of vaccinations and after natural infection. SFC: spot-forming cells.

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Table 1. Baseline characteristics of the study participants

Variables	ChAdOx1 (n=85)	BNT162b2 (n=36)	*P* value
Age at vaccination, years, median (range)	36 (21, 64)	32 (24, 53)	0.006
Age range			0.062
20s	22 (26)	17 (47)	
30s	33 (39)	15 (42)	
40s	20 (24)	3 (8.3)	
50s	8 (9.4)	1 (2.8)	
60s	2 (2.4)	0 (0)	
Sex			0.12
Female	66 (78)	23 (64)	
Male	19 (22)	13 (36)	
Occupation			0.001
Office worker	20 (24)	0 (0)	
Doctor	25 (30)	12 (33)	
Nurse	34 (40)	24 (67)	
Paramedic	5 (6.0)	0 (0)	
Local reaction after 2nd dose			0.037
Grade 0	11 (13)	7 (20)	
Grade 1	61 (73)	17 (49)	
Grade 2	10 (12)	9 (26)	
Grade 3-4	1 (1.2)	2 (5.7)	
Systemic reaction after 2nd dose			<0.001
Grade 0	26 (31)	7 (20)	
Grade 1	30 (36)	5 (14)	
Grade 2	23 (28)	13 (37)	
Grade 3-4	4 (4.8)	10 (29)	

Data represent n (%) unless indicated otherwise.

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Table 2. Demographic and clinical characteristics of COVID-19 patients

Characteristic	Asymptomatic (n= 1)	Mild (n = 1)	Moderate (n = 8)	Severe (n = 12)	Critical (n=4)	*P* value
Age, median (range)	35 (35, 35)	70 (70, 70)	35 (33, 70)	62 (35, 80)	76 (76, 89)	0.020
Sex						0.003
Female	1 (100)	1 (100)	8 (100)	7 (58)	0 (0)	
Male	0 (0)	0 (0)	0 (0)	5 (42)	4 (100)	
Underlying disease						
Diabetes mellitus	0 (0)	0 (0)	0 (0)	1 (8.3)	0 (0)	>0.99
Hypertension	0 (0)	1 (100)	3 (38)	6 (50)	1 (25)	0.7
Cardiovascular disease	0 (0)	1 (100)	2 (25)	2 (17)	1 (25)	0.6
Chronic kidney disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Chronic lung disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Chronic liver disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Solid cancer	0 (0)	0 (0)	0 (0)	0 (0)	3 (75)	0.003
Hematologic malignancy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Obesity	0 (0)	0 (0)	1 (12)	2 (17)	0 (0)	>0.99
Smoking	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Pregnancy	0 (0)	0 (0)	1 (12)	0 (0)	0 (0)	0.5
Treatment						
Remdesivir	0 (0)	1 (100)	2 (25)	6 (50)	4 (100)	0.070
Convalescent plasma	0 (0)	0 (0)	0 (0)	3 (25)	1 (25)	0.5
Steroid	0 (0)	1 (100)	3 (38)	5 (42)	4 (100)	0.2
Barcitinib	0 (0)	0 (0)	0 (0)	0 (0)	1 (25)	0.12
Tocilizumab	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-
Mortality	0 (0)	0 (0)	0 (0)	1 (8.3)	3 (75)	0.020
Hospital day, median (range)	9 (9, 9)	24 (24, 24)	9 (9, 24)	11 (9, 24)	60 (60, 140)	0.014

Data represent n (%) unless indicated otherwise.

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Figure 1

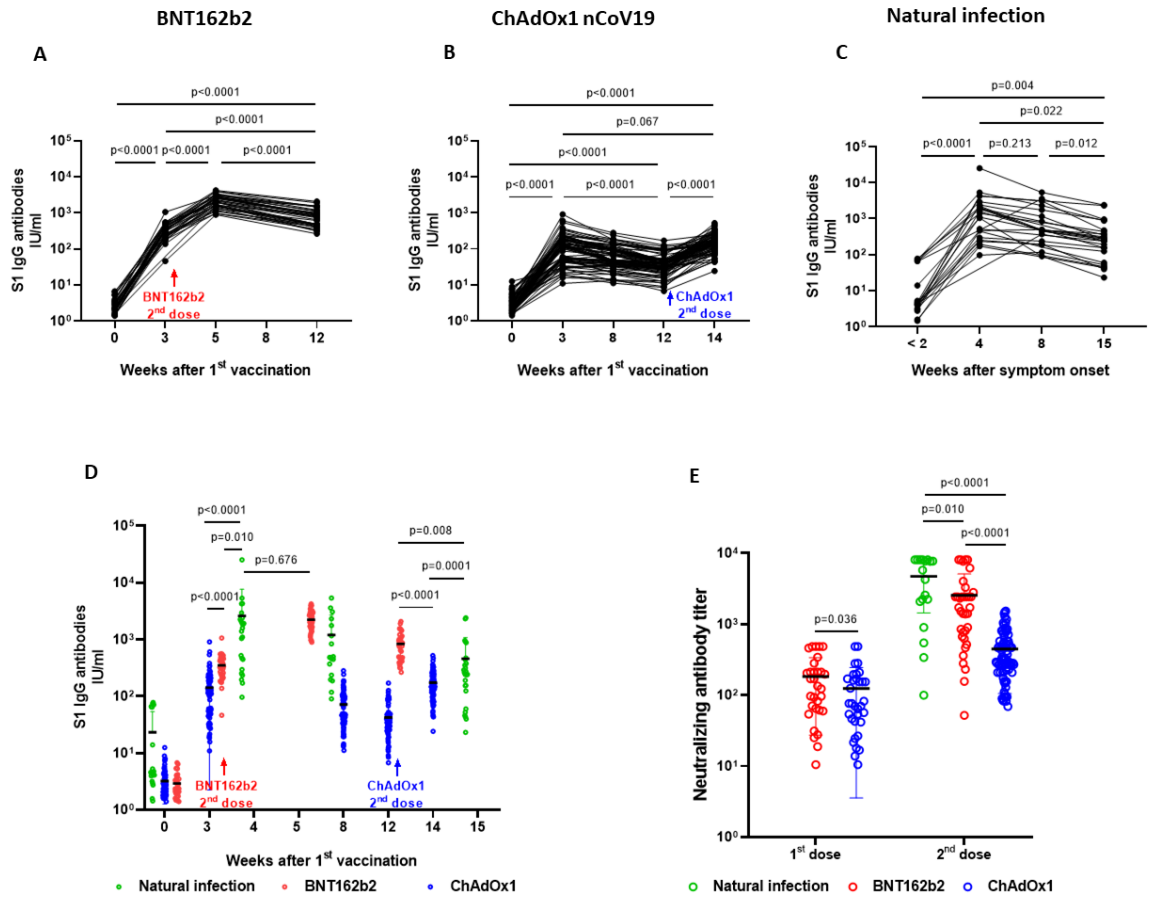

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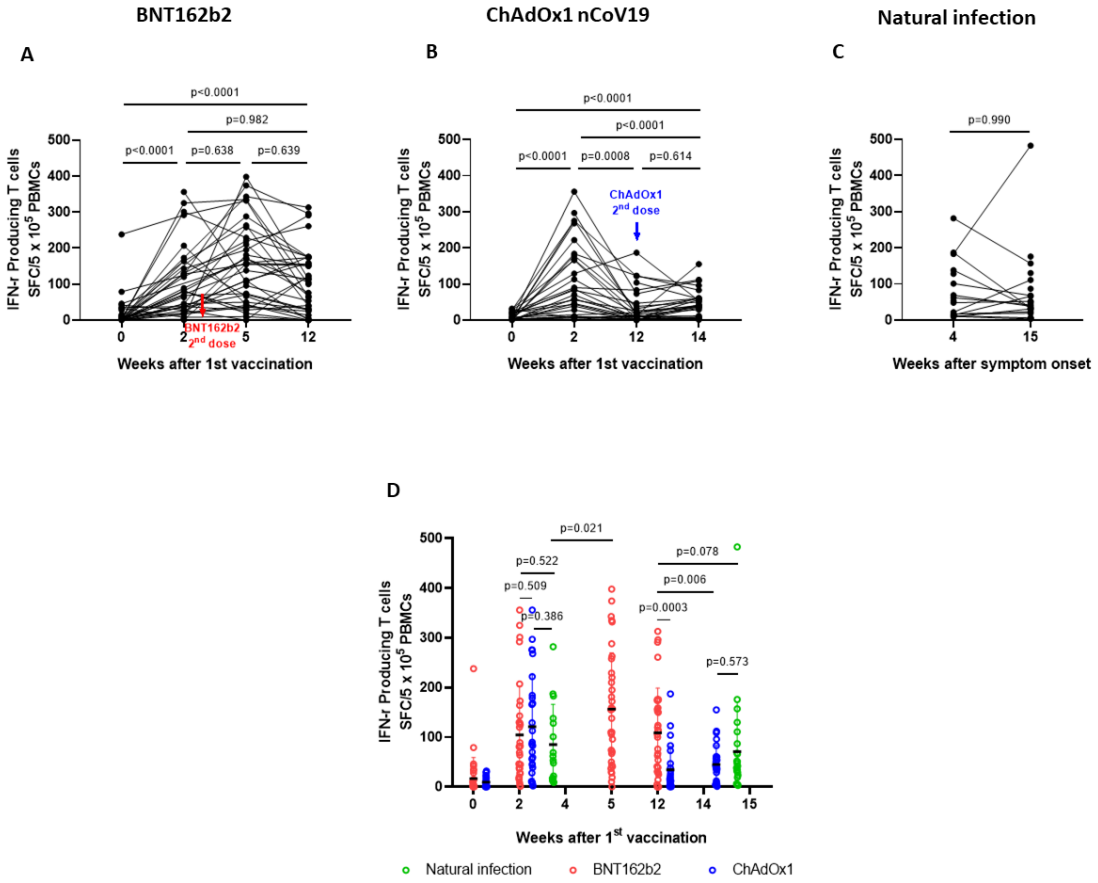
Figure 2



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