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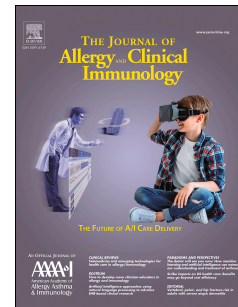
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Comparative analyses of IgG/IgA neutralizing effects induced by three COVID-19 vaccines against variants of concern

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Conflict of interest:

The authors declare no conflict of interest.

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ABSTRACT

Background: Only a few studies directly compared virus-specific antibodies and their neutralizing capacity against SARS-CoV-2 wild type and circulating variants of concern, despite the reported high efficacy of mRNA- and vector-based vaccines.

Objective: Here we assessed SARS-CoV-2-S1-specific antibodies of BNT162b2, mRNA-1273 and ChAdOx1 vaccinated as well as convalescent COVID-19 patients and furthermore determined the neutralization ability against SARS-CoV-2 wild type and B.1.1.7 (Alpha), B.1.1.7 E484K (Alpha E484K), B.1.351 (Beta) and B.1.617.2 (Delta) variants.

Methods: Serum samples of 107 fully vaccinated or convalescent individuals were analyzed for anti-SARS-CoV-2-S1 IgG and IgA as well as for total anti-SARS-CoV-2 RBD Ig. Furthermore, neutralization capacity as NT50 and NT90 values against SARS-CoV-2 wild type virus and circulating variants were determined.

Results: We observed a robust IgG response in all participants, however the highest titers were detected in mRNA-based vaccine recipients. In case of serum IgA responses, the difference between mRNA- and vector-based vaccines or convalescent patients was even more pronounced. Interestingly, all three vaccines could neutralize all tested VOCs in addition to wild type virus, but in some individuals only low or no neutralization especially against Alpha-E484K and Delta variant was detected.

Conclusion: Critically, we here studied the efficacy of various COVID-19 vaccines and found that mRNA-1273 had the highest neutralization abilities compared to BNT162b2- and ChAdOx1 vaccinees. COVID-19 convalescent patients demonstrated the most heterogeneous range of antibody titers and neutralization ability, rendering assessment of protection difficult. Furthermore a significant, positive relation between antibodies and NT50 values for immunized and convalescent individuals was determined.

Capsule summary:

Here we determined IgG/IgA responses and neutralization titers in individuals immunized with three major COVID-19 vaccines and in unvaccinated convalescent patients. mRNA-based vaccinees demonstrated superior variants of concern neutralization, while convalescent patients presented lower humoral protection.

Key Messages

- mRNA-1273 showed highest neutralization compared to BNT162b2- and ChAdOx1 vaccinees
- COVID-19 convalescent patients demonstrated lower range of antibody or neutralization titers
- Significant, positive relation between antibodies and NT50 values

Keywords:

SARS-CoV-2, variants of concern, vaccines, IgG and IgA antibodies, virus neutralization

Abbreviations

Ab	antibody, immunoglobulin
BAU	binding antibody unit
BNT162b2	BioNTech/Pfizer COVID-19 vaccine
CDC	Center of Disease Control
ChAdOx1	AstraZeneca COVID-19 vaccine
CI	confidence interval
COVID-19	Coronavirus disease 19
dpi	day post infection
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
HRP	horse radish peroxidase
Ig	immunoglobulin, antibody
IgA	immunoglobulin A
IgG	immunoglobulin G

95	MAC	membrane attack complex
96	MERS-CoV	Middle East respiratory syndrome-related coronavirus
97	MOI	multiplicity of infection
98	mRNA	messenger ribonucleic acid
99	mRNA-1273	Moderna COVID-19 vaccine
100	NT50	neutralization titer, reduction of 50%
101	NT90	neutralization titer, reduction of 90%
102	RBD	receptor binding domain
103	RoA	qualitative results area
104	RU	relative units
105	S1	SARS-CoV-2 spike protein region 1
106	SARS-CoV-1	severe acute respiratory syndrome coronavirus type 1
107	SARS-CoV-2	severe acute respiratory syndrome coronavirus type 2
108	VOI	variants of interest
109	VOC	variants of concern
110	WT	wild type

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INTRODUCTION

The current COVID-19 pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is ongoing, causing a high burden of mortality and morbidity among the global population (1). In 2020 large-scale phase III clinical trials have demonstrated safety and efficacy of the first EMA-approved vaccines, including BNT162b2 by BioNTech/Pfizer, mRNA-1273 by Moderna and ChAdOx1 by AstraZeneca (2-4) and promising results from other candidate trials rapidly followed (5-7). Viral vector-based ChAdOx1 demonstrated 70.4% efficacy against symptomatic SARS-CoV-2 infections while mRNA-based BNT162b2 and mRNA-1273 vaccine trials concluded in 95% and 94.1% (2-4), which exceeded by far the FDA and EMA requirements for approval, defined as 50% point estimate efficacy (8, 9). As vaccines entered the stage to change the course of the pandemic, new SARS-CoV-2 variants with the potential of higher transmission and more severe infection emerged. These new virus variants acquired mutations primarily in the spike protein of the virus, especially in the receptor binding domain (RBD), which have to be closely monitored. Changes in the RBD region could potentially have disadvantages associated with reduction of antibody (Ig) binding and neutralization or treatment efficacy, increased transmissibility, disease severity or diagnostic impact. According to the CDC, variants for which there is evidence of the aforementioned risks are defined as variants of concern (VOC) or variants of interest (VOI). Early in the pandemic, a variant carrying the D614G mutation rapidly became the dominant lineage in North America and Europe and was associated with an increased infectivity (10). Late 2020, a lineage emerging from UK, defined as B.1.1.7 or Alpha variant, with a N501Y mutation, was found to be more infectious and transmissible, but whether disease severity is impacted is still not clear (11, 12). Currently, the phylogenetic landscape has tremendously changed with the emergence of B.1.617.2 or Delta variant, shown to be more transmissible and suspected to increase disease severity (13, 14). Concerns further arose after evidence was presented, showing emerging variants escape from SARS-CoV-2-specific antibodies (15, 16). Recent studies highlighted a reduced neutralization of Alpha variant and B.1.351 (Beta variant) by convalescent- and BNT162b2 or ChAdOx1 vaccinated individual sera (15, 16). Of note, only few reports on mRNA-1273 induced neutralization on variants have been published and were mostly performed using

pseudotyped viruses harboring mutant SARS-CoV-2 spike proteins, but not whole virus isolates (17-19). Specific acquired RBD mutations defined as E484K mutation, notably found in the two VOC B.1.351 and P.1 (Gamma variant), were associated with a reduced neutralization capacity by vaccine-elicited sera (15, 17, 20). Cases of Alpha variant carrying the escape mutation E484K were found first in the United Kingdom in February 2021. As the Alpha variant was already associated with higher transmission, the combination with an escape mutation raised concerns and is still classified as VOC by the Public Health England (21). So far, the variant has not replaced other major variants, however, careful assessment of vaccine- as well as COVID-19 induced immunity has to be made, due to their risk of causing local outbreaks.

Here we investigated humoral immune responses and virus neutralization abilities from COVID-19 recovered patients and vaccinated individuals. To this aim, we assessed IgG, IgA and total SARS-CoV-2-specific antibody titers and furthermore determined the neutralization ability of COVID-19 vaccinated and recovered individuals against infectious clinical isolates of SARS-CoV-2. Vaccinated participants received one of the three vaccines approved in EU/EAA countries at the time of the study, BNT162b2 by Pfizer/BioNTech, mRNA-1273 by Moderna or ChAdOx1 by AstraZeneca. Convalescent COVID-19 patients were tested positive for SARS-CoV-2 wild type (WT) only. Serum was analyzed for anti-SARS-CoV-2-S1 IgG and IgA as well as for total anti-SARS-CoV-2 RBD Ig. Furthermore, neutralization capacity as NT50 values from each vaccine group or COVID-19 recovered group was assessed against SARS-CoV-2 WT virus and circulating variants B.1.1.7 (Alpha), B.1.1.7 E484K (Alpha E484K), B.1.351 (Beta) and B.1.617.2 (Delta).

METHODS

Ethics Statement

Written informed consent was obtained from all donors of leftover nasopharyngeal/oropharyngeal specimens and serum samples by the participating clinics. The Ethics Committee of the Medical University of Innsbruck approved the use of anonymized leftover specimens of COVID-19 patients (ECS1166/2020) and healthy donors (ECS1166/2018) for scientific purposes.

Human samples

In this study 87 persons fully vaccinated with ChAdOx1 (n=33), BNT162b2 (n=31) or mRNA-1237 (n=23) as well as 29 COVID-19 convalescent patients were included. The average age of all patients was 46 years (22 – 86 years) and the percentage of female and male patients included in the study was 52.6% and 47.4%, respectively. The average sampling day of vaccinated persons after their second dose was day 39 (day 21 – 104). The average sampling day for COVID-19 convalescent patients after diagnosis with SARS-CoV-2 WT virus, defined as the time (days) between positive PCR testing and blood sampling, was 130 days (22 – 206 days). All included COVID-19 patients were diagnosed with mild disease severity, which did not require any treatment or hospitalization. Detailed information of each individual from the different groups (ChAdOx1, BNT162b2 or mRNA-1237 vaccinated persons as well as convalescent patients) regarding age, sex, sampling days, inclusion in neutralization experiments is presented in Tables 1 – 4.

Viruses

Clinical specimens for SARS-CoV-2 (Alpha E484K and Delta) from COVID-19 positive swabs (Ethics statement, ECS1166/2020) and SARS-CoV-2 viruses (WT, Alpha and Beta) from repositories (BEI Resources, Manassas, VA, USA; CFAR/NIBSC; Nr-52281, Nr-54000, NR-54009) were propagated according to the manufacturer's instructions and used subsequently in neutralization assays.

ELISA

Serum and plasma samples from vaccinated or COVID-19 convalescent participants were retrieved from blood samples in serum or EDTA collection tube by centrifugation at 300 g for 5 min and serum or plasma fractions were carefully collected and stored at -80 °C until use. Sera were analysed by ELISA to assess SARS-CoV-2-specific Ig by three commercially available tests according to the manufacturer's instructions: SARS-CoV-2 Ab ELISA (WS-1096; Wantai Biological, Beijing, China), Anti-SARS-CoV-2 QuantiVac ELISA IgG (EI 2606-9601-10 G; Euroimmun, Lübeck, Germany) and Anti-SARS-CoV-2 ELISA IgA (EI 2606-9601 A; Euroimmun, Lübeck, Germany). SARS-CoV-2 Ab ELISA is a qualitative assay and detects all Ig against RBD and for the detection of anti-SARS-

CoV-2 IgA and IgG against S1 protein the anti-SARS-CoV-2 ELISA IgA and the QuantiVac ELISA IgG were used. In order to obtain qualitative results, areas for positive (total Ig $\geq$ 1.1 RoA), borderline (1.1>total Ig $\geq$ 0.9 RoA) or negative (total Ig<0.9 RoA) results were defined according to manufacturer's instructions. For anti-SARS-CoV-2 S1 IgA values $\geq$ 1.1 RoA, 1.1>IgA $\geq$ 0.8 RoA and IgA<0.8 RoA were defined as positive, borderline and negative results respectively. The QuantiVac ELISA IgG allows converting the relative units (RU) per ml to binding antibody unit per ml (BAU $\cdot$ ml $^{-1}$). In order to obtain qualitative results RU values recalculated to BAU $\cdot$ ml $^{-1}$ according to manufacturer's instructions; IgG $\geq$ 35.2 BAU $\cdot$ ml $^{-1}$ was considered as positive, 35.2>IgG $\geq$ 25.6 BAU $\cdot$ ml $^{-1}$ as borderline and IgG<25.6 BAU $\cdot$ ml $^{-1}$ as negative anti-SARS-CoV-2 S1 IgG result.

Neutralization Plaque Assay

VeroE6/TMPRSS2 cells (1.2×10^5) were seeded in a 48-well plate with culture medium (DMEM high glucose medium supplemented with 10% FCS, 1% L-Glutamine, 1% Penicillin/Streptomycin; all reagents were obtained from Sigma Aldrich, Missouri, USA) and incubated overnight at 37 °C and 5% CO $_2$. On the following day, whole serum or plasma samples were serial-diluted from 1:8 to 1:1024 and incubated with SARS-CoV-2 wild type or variant strains (4×10^2 PFU $\cdot$ ml $^{-1}$) for 1 h at 37 °C. After incubation, VeroE6/TMPRSS2 cells were inoculated with antibody-opsonized SARS-CoV-2 for 1h at 37 °C and 5% CO $_2$. After incubation, inoculate was replaced with culture medium containing 1.5% carboxymethylcellulose (Sigma Aldrich, Missouri, USA). Cells were incubated for 3 days at 37 °C and 5% CO $_2$ before plaque visualization and counting. For this, cells were washed and fixed with 10% neutral buffered formalin (Sigma Aldrich, Missouri, USA) for 1h at RT. Fixation was followed by staining using 0.5% (w/v) Crystal violet solution (Sigma Aldrich, Missouri, USA) for 15 min at RT. To determine the neutralizing capacity 50% and 90% neutralizing titer values (NT50 and NT90 values) from neutralization curves were calculated using four-parameter nonlinear regression in GraphPad Prism v.9. In order to obtain qualitative results NT50 $\geq$ 1:32, 1:32>NT50 $\geq$ 1:16 and NT50<1:16 were set as positive, borderline or negative result. For NT90 areas were defined for NT90 $\geq$ 1:16 as positive, 1:16>NT90 $\geq$ 1:8 as borderline and NT90<1:8 as negative result.

Statistical analysis

Statistical analysis was performed using GraphPad Prism v.9. Statistical significance of SARS-CoV-2-specific antibody ratio as well as of NT50 and NT90 levels were determined using Mann-Whitney-U test for nonparametric distribution (GraphPad Prism).

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RESULTS

High SARS-CoV-2-specific antibody titers in vaccinated vs. convalescent individuals

In this study 83 fully vaccinated individuals immunized with either the vector-based vaccine ChAdOx1 (n=33, Table S1) or the two mRNA-based vaccines BNT162b2 (n=31, Table S2) and mRNA-1237 (n=19, Table S3) as well as COVID-19 convalescent patients (n=24, Table S4) were included. The average sampling day of vaccinated persons after their second dose was day 41 (day 21 – 104) and the average sampling day for COVID-19 convalescent patients after positive PCR test was 137 days (22 – 206 days). To characterize differences in the antibody titers induced by the three studied vaccines and in COVID-19 convalescent individuals, we first performed three SARS-CoV-2-specific antibody tests. Using ELISA based test methods we investigated the presence of SARS-

CoV-2-specific IgG (Fig. 1A, above) and IgA (Fig. 1B, above) antibodies against the S1 region of the SARS-CoV-2 spike protein in serum samples. In addition, total SARS-CoV-2-specific Igs (Fig. 1C, above) against the receptor binding domain (RBD) of the viral spike protein were determined. These analyses revealed that 100% of individuals vaccinated with mRNA vaccines BNT162b2 and mRNA-1273 were tested positive for IgGs against S1 region (Fig. 1A, below). In contrast 97% of vector-based vaccine ChAdOx1 and only 62.5% patients of the convalescent group were positive for IgGs (Fig. 1A, below, ChAdOx1 and convalescent). Similar to IgGs, also 100% BNT162b2 vaccinated participants were positive for serum IgA. 84.2%, 50% and 16.7% tested positive for serum IgA in the mRNA-1273, ChAdOx1 and convalescent group, respectively (Fig. 1B, below). Further analyses showed that median antibody titers of SARS-CoV-2-specific IgG and IgA were significantly higher in individuals vaccinated with mRNA-based vaccines such as BNT162b2 (IgG: 679.0; 95% confidence interval (CI) 626.1 – 733.7; IgA: 5.3; 95% CI 3.9 – 7.1) and mRNA-1273 (IgG: 618.6; 95% CI 492.4 – 672.9; IgA: 3.9; 95% CI 0.9 – 6.0) compared to vector-based vaccine ChAdOx1 (IgG: 259.5; 95% CI 181.3 – 337.9; IgA: 0.7; 95% CI 0.6 – 1.4) or detected in convalescent patients (IgG: 41.8; 95% CI 17.6 – 77.6; IgA: 0.6; 95% CI 0.4 – 1.0) (Fig. 1A+B, above; Tab. S5). Significant differences were also found between the mRNA-based vaccines in induction of SARS-CoV-2-specific IgA, but not IgG levels against the S1 region (Fig. 1A+B, above; BNT162b2 vs. mRNA-1273). Analyses of total SARS-CoV-2-specific Igs against the RBD region of the spike protein demonstrated that 100% of vaccinated and 91.7% of convalescent COVID-19 patients were tested positive (Fig 1C, below). No significant differences were detected here between the three vaccinated groups (ChAdOx1: 18.4; 95% CI 17.9 – 18.7; BNT162b2: 18.0; 95% CI 17.5 – 18.7; mRNA-1273: 18.5; 95% CI 18.1 – 18.7), but total Igs levels were significantly lower in convalescence (15.5; 95% CI 6.4 – 17.0) compared to vaccinated individuals (Fig. 1C, above; Tab. S5). Furthermore, we investigated sex-specific differences for SARS-CoV-2-specific IgG, IgA and total Igs induced in vaccinated and convalescent individuals, but no significant differences were found (Fig. S1).

ChAdOx1 induced neutralization against SARS-CoV-2 and circulating variants

Subsequently, we aimed to determine the neutralizing activity of individuals vaccinated with the vector-based vaccine ChAdOx1. In this regard, serum samples were incubated in various concentrations with the original viral strain and circulating variants that emerged

since the end of 2020. Among these variants were SARS-CoV-2 Alpha-, Beta-, Alpha-E484K- and Delta variant.

We calculated half maximal neutralization titers (NT50) and found that 96.2%, 96.2%, 88.5%, 88.5% and 69.2% of ChAdOx1 vaccinated individuals could neutralize SARS-CoV-2 WT strain, Alpha-, Alpha-E484K-, Beta- and Delta virus variant respectively (Fig. 2A). NT50 values were calculated from neutralization curves using four-parameter nonlinear regression and a median neutralization curve of each virus is shown in Fig. 2B. Analyses of individual NT50 values demonstrated that the median neutralization capacity induced by the ChAdOx1 vaccine are significantly lower against the Alpha-E484K-, Beta- and Delta variants (Alpha-E484K: 107.3; 95% CI 53.1 – 224.1; $p < 0.0001$; Beta: 179.6; 95% CI 137.7 – 224.0; $p = 0.0004$; Delta: 64.7; 95% CI 34.0 – 200.8; $p < 0.0001$) compared to SARS-CoV-2 WT strain (322.7; 95% CI 260.6 – 606.4) (Fig. 2C; Tab. S6). However, no significantly higher median neutralization titer was detected against the Alpha virus variant (460.9; 95% CI 291.8 – 640.0) (Fig. 2C; Tab. S6). Calculating relative neutralization titers of each SARS-CoV-2 variant against the SARS-CoV-2 WT strain revealed a 70%, 47% and 82% decrease of neutralizing capacity against Alpha-E484K-, Beta- and Delta virus variant, respectively (Fig. 2D, orange). In fact, median NT50 values were only elevated (13%) against Alpha variant in the ChAdOx1 vaccinated individuals (Fig 2D, blue). In addition, NT90 values were also calculated and confirmed that among the circulating variants only the Alpha variant could show elevated neutralization titers compared to SARS-CoV-2 wild type strain (Fig. S2A-C; Tab. S6).

mRNA-based vaccines demonstrate strong neutralization against circulating variants

For mRNA-based vaccine BNT162b2 we found that 95.8%, 95.8%, 79.2%, 95.8% and 87.5% of study participants tested positive for neutralization against SARS-CoV-2 WT strain or Alpha-, Alpha-E484K, Beta- or Delta virus variant (Fig. 3A). These already high numbers were even elevated in the mRNA-1273 group, since in this group positive neutralization was determined in 94.7% against SARS-CoV-2 WT strain, 100.0% against Alpha variant, 94.7% in Alpha-E484K variant, 94.7% in Beta variant and 94.7% against Delta variant (Fig 4A). NT50 values of individuals vaccinated with BNT162b2 (Fig. 3B) or mRNA-1273 (Fig. 4B) were calculated from neutralization curves using four-parameter nonlinear regression and median neutralization curve of each virus is depicted.

Comparison of individual NT50 values demonstrated that median neutralization capacity in the BNT162b2 vaccinated group were significantly lower against Alpha-E484K- and Beta variant (Alpha-E484K: 72.8; 95% CI 53.2 – 348.8; $p=0.0053$; Beta: 129.2; 95% CI 64.6 – 251.0; $p=0.0303$) compared to SARS-CoV-2 wild type (217.5; 95% CI 128.0 – 854.1) (Fig. 3C, Tab. S6). No significant difference in the median NT50 values could be observed between the Delta variant (214.2; 95% CI 105.1 – 300.1) and the wild type strain (Fig. 3C; Tab. S6). Interestingly, only NT50 values between the Beta variant (Beta: 405.7; 95% CI 83.4 – 642.9) and SARS-CoV-2 wild type strain (541.9; 95% CI 232.1 – 1291.0) were significantly lower ($p=0.0456$), whereas no significant difference between the wild type strain and the circulating virus variants (Alpha-E484K: 270.4; 95% CI 228.3 – 596.1; Delta: 466.8 95% CI 102.1 – 835.4) were detected for individuals vaccinated with mRNA-1273 (Fig. 4C; Tab. S6). However, median NT50 values against the Alpha variant for both mRNA-based vaccine groups (BNT162b2: 315.2; 95% CI 164.5 – 838.2; mRNA-1273: 996.5; 95% CI 564.6 – 1407.0) were slightly increased compared to median NT50 value against wild type virus variants (Fig. 3C, 4C; Tab. S6). Analyses of relative neutralization titers of each SARS-CoV-2 variant against the SARS-CoV-2 wild type strain in BNT162b2 group displayed a 67%, 41% and 2% decrease of neutralizing capacity against Alpha-E484K-, Beta- and Delta virus variant respectively (Fig. 3D, orange). Calculation of the relative virus neutralization of the mRNA-1273 group showed a 50%, 25% and 14% reduced neutralization against Alpha-E484K-, Beta- and Delta virus variant respectively (Fig. 4D, orange). Individuals vaccinated with both mRNA vaccines acquired elevated neutralization capacity against SARS-CoV-2 Alpha variant up to 82% compared to SARS-CoV-2 wild type strain (Fig. 3D and Fig. 4D, blue). In addition, NT90 values were calculated for the BNT162b2 and mRNA-1273 group (Fig. S3, S4, Tab. S6, right). These data confirmed, that for the mRNA-1273 group elevated neutralization titers compared to SARS-CoV-2 WT strain were only detected against the Alpha variant (Fig., S4A-C, Tab. S6). In contrast, the BNT162b2 group NT90 values showed a reduction of relative neutralization capacity for the SARS-CoV-2 Alpha variant (Fig. S3A-C; Tab. S6).

Neutralization capacity of COVID-19 convalescent patients

Serum samples from recovered and proven COVID-19 patients were analyzed and half maximal neutralization titers (NT50) were analyzed. In this patient group we found that 79.0%, 89.4%, 47.4%, 79.0% and 36.9% of convalescent individuals could neutralize

SARS-CoV-2 wild type strain or Alpha-, Alpha-E484K-, Beta- and Delta virus variant respectively (Fig. 5A). NT50 values were calculated from neutralization curves using four-parameter nonlinear regression and a median neutralization curve of each SARS-CoV-2 wild type and circulating variant is depicted in Fig. 5B. Individual NT50 values within the convalescent group showed that the neutralization capacity against SARS-CoV-2 Alpha variant (420.0; 95% CI 208.3 – 769.8.0) was higher compared to the wild type strain (241.9; 95% CI 109.1 - 353.8) (Fig. 5C; Tab. S6). Furthermore, median NT50 values were lower for the Beta variant (161.7; 95% CI 92.4 – 308.5) and significantly decreased in convalescent patients against Alpha-E484K- and Delta variant (Alpha-E484K: 56.9; 95% CI 22.4 – 129.8; $p=0.0055$; Delta: 92.0; 95% CI 3.4 – 221.3; $p=0.0013$) (Fig. 5C; Tab. S6). In this group highest median NT50 values were detected against SARS-CoV-2 Alpha variant, while median neutralization titers for Alpha-E484K and Delta variant were the lowest (Fig. 5C, Tab. S6). Calculating relative neutralization titers of each SARS-CoV-2 variant against the SARS-CoV-2 wild type strain revealed a 93%, 16% and 95% decrease of neutralizing capacity against Alpha-E484K-, Beta- and Delta virus variant, respectively (Fig. 5D, orange). In comparison, median NT50 values were elevated 25% against the Alpha variant (Fig 5D, blue). Analyses of NT90 values confirmed that among the circulating variants only the Alpha variant could show elevated neutralization titers compared to SARS-CoV-2 WT strain (Fig. S5A-C; Tab. S6).

Positive Correlation between IgA and IgG antibody titers and NT50 values against SARS-CoV-2 wild type virus

Results from antibody titers and neutralization assays (NT50 values) observed in COVID-19 vaccinated or convalescents individuals were statistically analyzed to identify a correlation between higher amounts of IgA or IgG antibodies and enhanced neutralization of SARS-CoV-2 WT strain. Therefore, we next performed correlation analyzes between antibody titers and corresponding NT50 values from each study participants using two-tailed nonparametric Spearman correlation. For ChAdOx1 vaccinated individuals we found a non-significant IgA/NT50 and IgG/NT50 correlation of $r=0.3091$; $p=0.3869$ and $r=0.1678$; $p=0.4331$ respectively (Fig. 6A). Furthermore, significant positive relation for BNT162b2- ($r=0.5249$; $p=0.0084$) and a positive correlation for mRNA-1273 ($r=0.4719$; $p=0.0774$) immunized, but not for convalescent ($r=0.8$; $p=0.333$) individuals (Fig. 6B-D, upper panel) were found for IgA/NT50 correlation. Similar

results were obtained for calculation of IgG/NT50 correlations. Here, we found a significant, positive relation for BNT162b2- ($r=0.6149$; $p=0.0014$), mRNA-1273 ($r=0.73459$; $p=0.0011$) immunized and also for convalescent ($r=0.67749$; $p=0.0069$) individuals (Fig. 6B-D, lower panel). Correlation between total SARS-CoV-2-RBD-specific Igs and NT50 values were not calculated for vaccinated individuals, since all antibody titers were detected in the saturated range of the ELISA test. However, a significant positive relation between total RBD-specific antibodies and NT50 values was found for convalescent patients (data not shown).

Comparison of NT50 values of COVID-19 vaccinated individuals and convalescent patients

Finally, we compared the efficacy of SARS-CoV-2 neutralization by sera from individuals immunized with mRNA- or vector-based vaccines and convalescent patients for SARS-CoV-2 and circulating variants. For SARS-CoV-2 wild type strain we found that 79.0% of recovered patients showed sufficient neutralization, while more than 94% of vaccinated individuals could neutralize the wild type strain (Fig. 7A, left). Analyses of the individual data revealed significant differences between convalescent patients and mRNA-1273 vaccinees ($r=0.0228$) as well as between persons immunized with ChAdOx1 and mRNA-1273 vaccinees ($r=0.0454$) (Fig. 7A, right). Individuals vaccinated with BNT162b2 showed similar half-maximum neutralization results to the COVID-19 recovered group (Fig. 7A, right). Ample neutralization against the SARS-CoV-2 Alpha variant was demonstrated in convalescent patients (89.4%) as well as in BNT162b2 (95.8%) or ChAdOx1 (96.2%) immunized individuals (Fig. 7B, left). All mRNA-1273 vaccinated study participants were able to neutralize SARS-CoV-2 Alpha variant (Fig. 7B, left) and analyses of the individual data showed significant higher neutralization titers for mRNA-1273 compared to convalescent patients ($p=0.0248$) or people immunized with ChAdOx1 ($p=0.0009$) or BNT162b2 ($p=0.0038$) (Fig. 7B, right). Neutralization assays using the Beta virus variant demonstrated, that 79.0% of recovered- and 88.5% ChAdOx1 vaccinated individuals tested positive, while more than 94% of participants immunized with mRNA-based vaccines could efficiently neutralize the virus (Fig. 7D, left). No significant differences were detected between the BNT162b2-, mRNA1273 or convalescent groups, while mRNA-1273 vaccinated people showed significantly higher NT50 values compared to the ChAdOx1 group ($p=0.0388$) (Fig. 7D, right). For the SARS-CoV-2 Alpha-E484K variant

NT50 values for recovered patients or mRNA-1273-, BNT162b2 and ChAdOx1 vaccinated individuals were 47.4%, 94.7, 79.2% and 88.5%, respectively (Fig. 7C, left). Further analyses revealed that mRNA-1273 demonstrated significantly higher neutralization titers compared to ChAdOx1 ($p=0.0015$) or BNT162b2 ($p=0.0194$) immunized or recovered participants ($p=0.0001$) (Fig. 7C, right). Significant lower NT50 values were also found between convalescent patients and the ChAdOx1- ($p=0.0162$) or the BNT162.2 group ($p=0.0080$) (Fig 7C, right). This already impaired neutralization capacity against the Alpha-E484k variant is even reduced when examining the Delta virus variant. Indeed, only 50.0% of convalescent and 69.2% of ChAdOx1 vaccinated individuals could efficiently neutralize this SARS-CoV-2 variant (Fig. 7E, left). Best results were achieved by the mRNA-1273 (94.7%) followed by BNT162b2 (87.5%) vaccinated participants (Fig. 7E, left). In addition, here median NT50 values were significantly higher of mRNA-1273 immunized people, compared to ChAdOx1 ($p=0.0009$) vaccinated or convalescent individuals ($p<0.0001$) (Fig. 7E, right). Furthermore, the BNT162b2 group also showed a significant higher median NT50 value than ChAdOx1 vaccinees ($p=0.0130$) and COVID-19 recovered ($p=0.0005$) (Fig 7E, right). Significant lower NT50 values were found between convalescent patients and the ChAdOx1 group ($p=0.0282$) (Fig 7E, right). Analyses of NT90 values confirmed that among the tested groups, individuals immunized with the mRNA-based vaccines showed elevated neutralization titers compared to ChAdOx1 vaccinated or recovered participants (Fig. S6A-E).

DISCUSSION

In this study we compared humoral immune responses and neutralization titers in individuals immunized with three different COVID-19 vaccines and in convalescent patients. Most of the studies on humoral immune responses in COVID-19 vaccinated or convalescent patients investigated serum IgG levels, but there is compelling evidence that secretory and circulating IgA play an important role in immunity to COVID-19 (22). For that reason, we here investigated IgG and IgA levels in serum samples of vaccinated and convalescent individuals. We observed a robust IgG response to viral spike protein and its RBD in all vaccinated participants, however the highest median antibody titers were detected in both mRNA-based vaccines. This is in accordance with other published data, which showed that two vaccine doses achieved high antibody titers across all ages using

either ChAdOx1, BNT162b2 or mRNA1273 (23, 24). At the same time, we found that antibody levels in convalescent patients have a high titer variation, which has been previously reported and correlated with the duration and severity of clinical symptoms, but not with patient age (25).

In case of SARS-CoV-2-specific serum IgA responses we could confirm highest titers in mRNA-based vaccines compared to the vector-based vaccine or convalescent patients. IgA antibodies are a heterogeneous group of Igs and occur in secretory, polymeric and monomeric forms (26). Although recent studies demonstrated that there is only a weak correlation between mucosal IgA and serum IgA antibodies, since they are mostly generated locally in the salivary glands, some studies described that mucosal IgA were even detectable in seronegative IgA convalescent patients (27). Therefore, IgA levels determined here in vaccinated people might not reflect the situation in the mucosa. In fact, it is possible that the number of IgA positives individuals was indeed higher. A study by Sterlin and colleagues also found that specific IgA concentrations in the serum decreased notably one month after onset of symptoms, whereas IgA levels remained detectable in saliva for a longer time (28). Furthermore, anti-SARS-CoV-2 RBD IgA were also detected in mRNA-based vaccine recipients and salivary IgAs in both groups displayed detectable neutralizing abilities (29, 30). Whether a strong vaccine-induced mucosal immunity conducted by IgG and IgA levels in mucus and saliva, may contribute to protection of infection and reduced person-to-person transmission of SARS-CoV-2 remains to be investigated. A recent study investigating the relationship of Selective IgA deficiency (SIgAD) and severe COVID-19 infection found a 7.7-fold higher risk of severe COVID-19 in patients with SIgAD (31). Our data revealed a significant, positive relation between Igs (IgA and IgG) and NT50 values for immunized and convalescent individuals, suggesting that the observed humoral responses were protective. A correlation between neutralization titers after COVID-19 or SARS-CoV-2 vaccination and protection against SARS-CoV-2 infection has been demonstrated by several studies (32, 33). Accordingly, the strength of the humoral response after illness or vaccination might be clinically relevant (24). Of note, all of these studies used SARS-CoV-2 wild type virus or pseudotyped viruses for determining neutralization abilities, but novel SARS-CoV-2 variants with the potential of higher transmission and more severe infection have emerged (21, 34, 35). Due to mutations in the RBD region of the viral spike protein, these VOCs or VOIs have

the potential to escape antibody binding and neutralization efficacy, which we analyzed here using sera from vaccinated and convalescent individuals. We found that all three investigated vaccines could neutralize Alpha-, Alpha-E484K, Beta- and Delta variant in addition to SARS-CoV-2 wild type virus, but in some individuals only low or no neutralization was detected. In our cohort neutralization against Alpha-E484K and Delta variant was strongly reduced, especially in individuals immunized with vector-based vaccine ChAdOx1. Other studies support our findings for Delta variant and observed an efficacy of 88% for BNT162b2 and 67% for ChAdOx1 (36). Interestingly, we found an increased effectiveness for all vaccines and convalescent patients for Alpha variant, which is contradictory to current literature showing also reduced protection for Alpha variant (16, 36). Here we also studied the performance of a second mRNA-based vaccine and found that mRNA-1273 had the highest neutralization compared to BNT162b2- and ChAdOx1 vaccinees or convalescent patients. At the moment, only few articles on mRNA-1273 are available showing also that mRNA vaccines are highly-effective with a slightly higher efficacy for mRNA-1273 recipients (37, 38). In addition, Steensels et al. observed higher total Ig titers against RBD of SARS-CoV-2 in participants vaccinated with 2 doses of mRNA-1273 compared with those vaccinated with BNT162b2. A possible explanation for this might be the higher mRNA content in mRNA-1273 compared with BNT162b2 and the longer interval between priming and boosting for mRNA-1273 (4 weeks vs 3 weeks for BNT162b2). (24). In comparison, here we did not find differences of total Igs against RBD between mRNA-1273 and BNT162b2 and detected higher IgG and IgA for BNT162b2. Limitations of this study include the small number of study participants and the lack of data on cellular immunity, which we previously investigated in COVID-19 patients with mild, severe or critical disease progression (39). The impact of cellular immunity in protection against infection and prevention of virus transmission has been studied and is still subject of ongoing investigations (40, 41). This is of importance since T cells might limit disease progression in case of low neutralizing antibody levels and that generation of T cell responses differ between mRNA- and vector-based vaccines (42, 43). Also, cellular immunity in COVID-19 convalescent patients has to be determined in more detail, since our data also showed, that antibody titers and neutralization ability ranged widely between individuals of this group. Due to these heterogeneous results within the COVID-19 convalescent group, it is still very difficult to assess how and if protection of recovered

individuals is facilitated. Novel COVID-19 vaccine formulations using various platforms and new vaccine technologies are developed at the moment to deal with new challenges against the current pandemic (44). New formulations also include nasal vaccine application in an attempt to enhance innate and adaptive mucosal immunity (45). Identifying whether novel vaccine candidates can also increase efficacy against emerging SARS-CoV-2 virus variants and reduce breakthrough infections is a priority for future investigations.

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Figure legends

Fig. 1: SARS-CoV-2 antibody titer analysis using sera from fully vaccinated (ChAdOx1, BNT162b2 or mRNA-1273) or convalescent participants. (A) Individual IgG antibody titers against SARS-CoV-2 S1 domain for individuals fully vaccinated with ChAdOx1 (n=33), BNT162b2 (n=31), mRNA-1273 (n=23) and of convalescent patients (n=29) were performed with the Anti-SARS-CoV-2-QuantiVac-ELISA (IgG) kit are shown above. Results are presented in binding antibody unit per ml serum (BAU·ml⁻¹). Corresponding percentages of participants and patients with positive, borderline or negative IgG antibodies against SARS-CoV-2 S1 are visualized in the graph below. (B) Individual IgA antibody titers against SARS-CoV-2 S1 domain for fully vaccinated and convalescent participants were performed with the Anti-SARS-CoV-2-ELISA (IgA) kit. Results are presented above in ratio of absorbance (RoA). Corresponding percentages of participants with positive, borderline or negative IgA antibodies against SARS-CoV-2 S1 are visualized in the graph below. (C) Individual total Ig antibody titers against SARS-CoV-2 RBD for participants fully vaccinated and convalescent individuals were performed with the WANTAI SARS-CRV-2 Ab ELISA kit. Results are presented above in ratio of absorbance (RoA). Corresponding percentages of participants with positive, borderline or negative total Igs against SARS-CoV-2 S1 are visualized in the graph below. Statistical significance between the four groups was determined by Mann-Whitney-U test for nonparametric distribution (*: p<0.05; **: p<0.01; ***: p<0.001; ****: p<0.0001). Medians are visualized as red lines together with the interquartile range as error bar. Cut-off values are illustrated by grey dashed line.

Fig. 2: SARS-CoV-2 neutralization titer (NT50) analysis using serum samples from fully vaccinated ChAdOx1 (n=25) participants against SARS-CoV-2 WT, Alpha, Alpha E484K, Beta and Delta variant. (A) Percentages of vaccinees tested positive, borderline or negative for half-maximum neutralization against SARS-CoV-2 WT and variants are shown. (B) Neutralization curves of ChAdOx1 immunized individuals including highlighted median neutralization curves for WT and each variant. (C) Individual NT50 serum dilutions for all tested SARS-CoV-2 viruses. Statistical significance between WT and variants was determined by Mann-Whitney-U test for nonparametric distribution (****: p<0.0001). Medians are visualized as red lines together with the interquartile range

as error bars. The cut-off value is illustrated by grey dashed line. **(D)** Determination of NT50 fold changes of SARS-CoV-2 variants relative to WT.

Fig. 3: SARS-CoV-2 neutralization titer (NT50) analysis using serum samples from fully vaccinated BNT162b2 (n=24) individuals against SARS-CoV-2 WT, Alpha, Alpha E484K, Beta and Delta variant. **(A)** Percentages of vaccinees tested positive, borderline or negative for half-maximum neutralization against SARS-CoV-2 WT and variants are presented. **(B)** Neutralization curves of BNT162b2 immunized participants including highlighted median neutralization curves for WT and each variant. **(C)** Individual NT50 serum dilutions for all tested SARS-CoV-2 viruses. Statistical significance between WT and variants was determined by Mann-Whitney-U test for nonparametric distribution (*: $p < 0.05$; **: $p < 0.01$). Medians are visualized as red lines together with the interquartile range as error bars. The cut-off value is illustrated by grey dashed line. **(D)** Determination of NT50 fold changes of SARS-CoV-2 variants relative to WT.

Fig. 4: SARS-CoV-2 neutralization titer (NT50) analysis using serum samples from fully vaccinated mRNA1273 (n=23) individuals against SARS-CoV-2 WT, Alpha, Alpha E484K, Beta and Delta variant. **(A)** Percentages of vaccinees tested positive, borderline or negative for half-maximum neutralization against SARS-CoV-2 WT and variants are presented. **(B)** Neutralization curves of mRNA1273 immunized participants including highlighted median neutralization curves for WT and each variant. **(C)** Individual NT50 serum dilutions for all tested SARS-CoV-2 viruses. Statistical significance between WT and variants was determined by Mann-Whitney-U test for nonparametric distribution (*: $p < 0.05$; **: $p < 0.01$). Medians are visualized as red lines together with the interquartile range as error bars. The cut-off value is illustrated by grey dashed line. **(D)** Determination of NT50 fold changes of SARS-CoV-2 variants relative to WT.

Fig. 5: SARS-CoV-2 neutralization titer (NT50) analysis using sera from convalescent patients (n=24) against SARS-CoV-2 WT, Alpha, Alpha E484K, Beta, and Delta variant. **(A)** Percentages of COVID-19 patients tested positive, borderline or negative for half-maximum neutralization against SARS-CoV-2 WT and variants are shown. **(B)** Neutralization curves of patients including highlighted median neutralization

curves for WT and each variant. **(C)** Individual NT50 serum dilutions for all tested SARS-CoV-2 viruses. Statistical significance between WT and variants was determined by Mann-Whitney-U test for nonparametric distribution (*: $p < 0.05$; **: $p < 0.01$). Medians are visualized as red lines together with the interquartile range as error bars. The cut-off value is illustrated by grey dashed line. **(D)** Determination of NT50 fold changes of SARS-CoV-2 variants relative to WT.

Fig. 6: Correlation between SARS-CoV-2-specific antibody titers and corresponding NT50 values against SARS-CoV-2 WT. Dependence between SARS-CoV-2-specific IgA (upper panel) and IgG (lower panel) and NT50 values from SARS-CoV-2 WT virus was calculated for **(A)** ChAdOx1, **(B)** BNT162b2, **(C)** mRNA1273 vaccinated and **(D)** convalescent participants by nonparametric Spearman correlation analyses. Correlation of Ig/NT50. To improve visualization of the trend a linear regression with 95% confidence interval (CI) was plotted. IgA titers are presented in Ratio of Absorbance (RoA), IgG titers in binding antibody unit per ml serum ($\text{BAU} \cdot \text{ml}^{-1}$) and NT50 values as dilution factor for serum (1:x).

Fig. 7: Comparison of neutralization titers (NT50 values) from individuals fully vaccinated with ChAdOx1, BNT162b2, mRNA-1273 and convalescent patients. Percentages (left) and individual NT50 serum dilutions (right) of vaccinated or convalescent participants tested positive, borderline and negative against **(A)** WT, **(B)** Alpha, **(C)** Alpha-E484K, **(D)** Beta and **(E)** Delta variant are shown. Statistical significance between the four cohorts was determined by Mann-Whitney-U test for nonparametric distribution (*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$). Medians are visualized as red lines together with the interquartile range as error bar. Cut-off values are illustrated by grey dashed line.

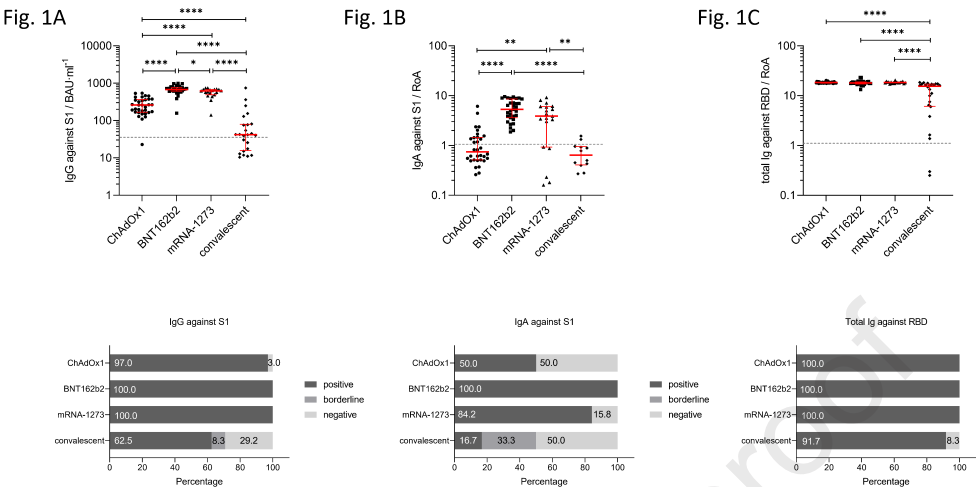


Fig. 2A

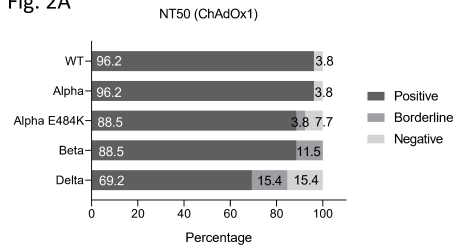


Fig. 2C

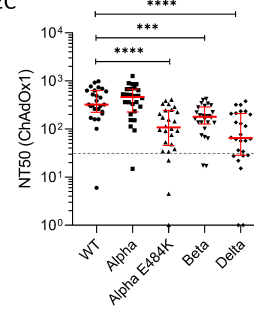


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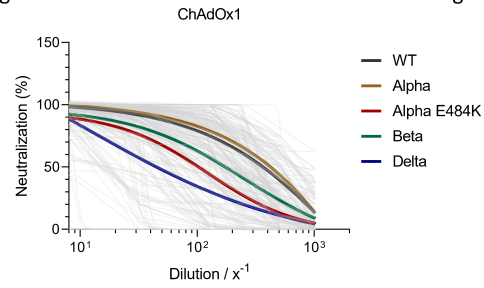


Fig. 2D

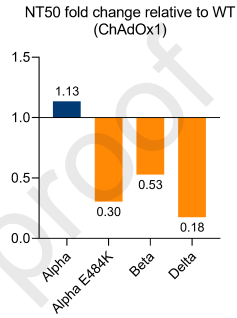


Fig. 3A

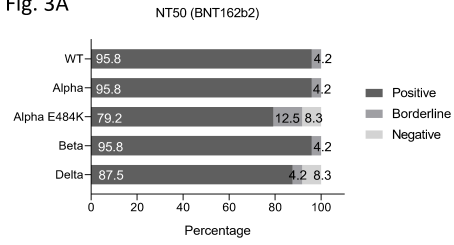


Fig. 3C

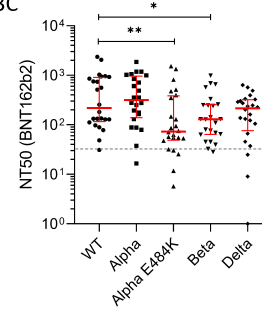


Fig. 3B

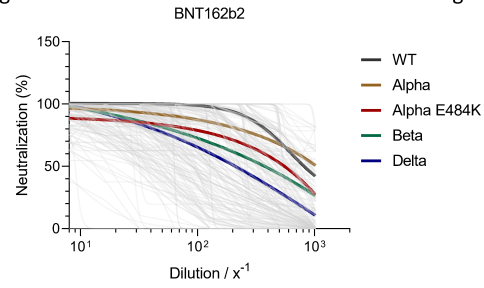


Fig. 3D

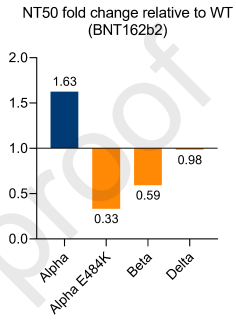


Fig. 4A

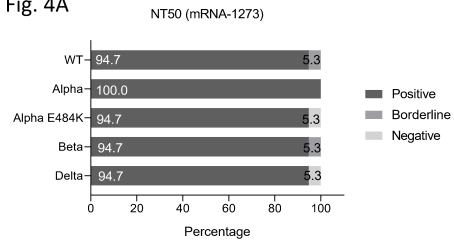


Fig. 4C

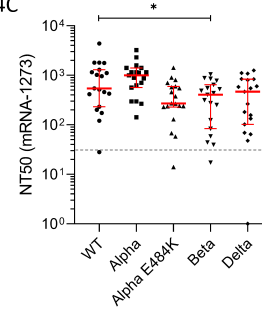


Fig. 4B

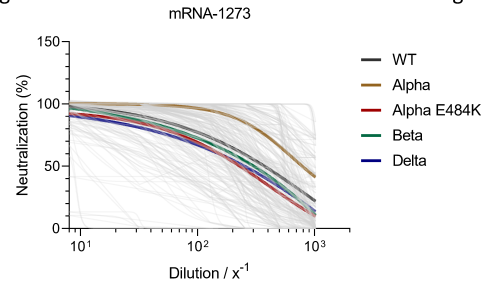


Fig. 4D

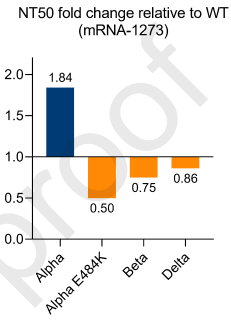


Fig. 5A

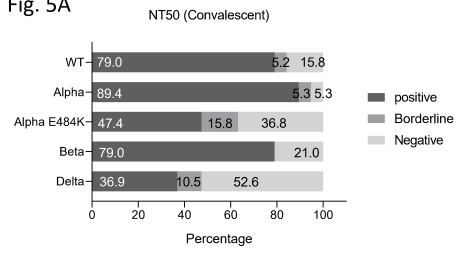


Fig. 5C

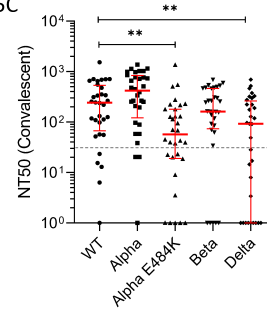


Fig. 5B

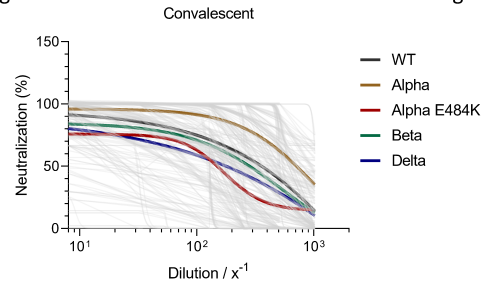


Fig. 5D

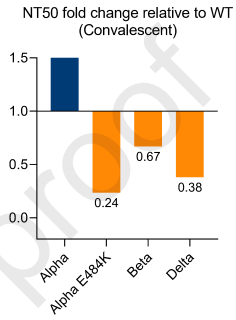


Fig. 6A ChAdOx1

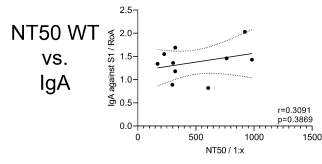


Fig. 6B BNT162b2

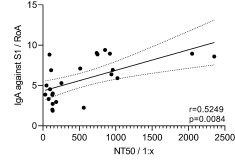


Fig. 6C mRNA-1273

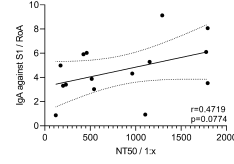
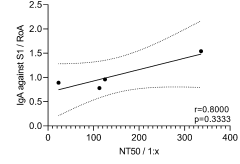
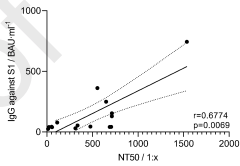
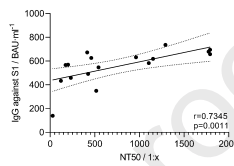
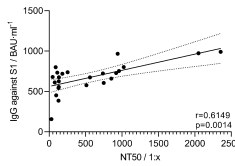
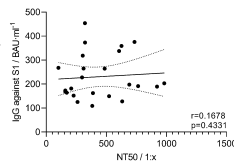


Fig. 6D Convalescent



NT50 WT vs. IgG



Online Repository

Fig. S1: SARS-CoV-2 serum antibody titer comparison of female (f) and male (m) participants. Fully vaccinated individuals using ChAdOx1 (upper row), BNT162b2 (middle row) and mRNA-1273 (lower row). IgG antibody titer against SARS-CoV-2 S1 domain for immunized participants using ChAdOx1 (f=19; m=14), BNT162b2 (f=14; m=17) and mRNA-1273 (f=14; m=9) were performed with the Anti-SARS-CoV-2-QuantiVac-ELISA (IgG) kit. Results for IgG are presented in binding antibody unit per ml serum (BAU·ml⁻¹). IgA antibody titers against SARS-CoV-2 S1 domain for vaccines were performed with the Anti-SARS-CoV-2-ELISA (IgA) kit. Results for IgA are presented in ratio of absorbance (RoA). Total Ig antibody titer against SARS-CoV-2 RBD immunized participant were performed with the WANTAI SARS-CoV-2 Ab ELISA kit. Results for total Igs are presented in ratio of absorbance (RoA). Statistical significance was determined by Mann-Whitney-U test for nonparametric distribution.

Fig. S2: SARS-CoV-2 neutralization titer (NT90) analysis with serum samples from fully vaccinated ChAdOx1 participants (n=25) against SARS-CoV-2 WT, Alpha, Alpha E484K, Beta and Delta variant. (A) Percentages of vaccinees tested positive (NT90≥1:16), borderline (1:16>NT90≥1:8) or negative (NT90<1:8) for NT90 neutralization against SARS-CoV-2 WT and variants. **(B)** Individual NT90 serum dilutions against SARS-CoV-2 WT and variants. Statistical significance between WT and variants was determined by Mann-Whitney-U test for nonparametric distribution (**: p<0.01; ***: p<0.001; ****: p<0.0001). Medians are visualized as red lines together with the interquartile range as error bars. The cut-off value is illustrated by grey dashed line. **(C)** Determination of NT90 fold changes of SARS-CoV-2 variants relative to WT.

Fig. S3: SARS-CoV-2 neutralization titer (NT90) analysis with serum samples from fully immunized BNT162b2 participants (n=24) against SARS-CoV-2 WT, Alpha, Alpha E484K, Beta and Delta variant. (A) Percentages of vaccinees tested positive (NT90≥1:16), borderline (1:16>NT90≥1:8) or negative (NT90<1:8) for NT90 neutralization against SARS-CoV-2 WT and variants. **(B)** Individual NT90 serum dilutions against SARS-CoV-2 WT and variants. Statistical significance between WT and variants was determined by Mann-Whitney-U test for nonparametric distribution (**: p<0.01;

: $p < 0.001$; *: $p < 0.0001$). Medians are visualized as red lines together with the interquartile range as error bars. The cut-off value is illustrated by grey dashed line. **(C)** Determination of NT90 fold changes of SARS-CoV-2 variants relative to WT.

Fig. S4: SARS-CoV-2 neutralization titer (NT90) analysis with serum samples from fully vaccinated mRNA1273 participants (n=23) against SARS-CoV-2 WT, Alpha, Alpha E484K, Beta and Delta variant. **(A)** Percentages of vaccinees tested positive ($NT90 \geq 1:16$), borderline ($1:16 > NT90 \geq 1:8$) or negative ($NT90 < 1:8$) for NT90 neutralization against SARS-CoV-2 WT and variants. **(B)** Individual NT90 serum dilutions against SARS-CoV-2 WT and variants. Statistical significance between WT and variants was determined by Mann-Whitney-U test for nonparametric distribution (**: $p < 0.01$; ***: $p < 0.001$; ****: $p < 0.0001$). Medians are visualized as red lines together with the interquartile range as error bars. The cut-off value is illustrated by grey dashed line. **(C)** Determination of NT90 fold changes of SARS-CoV-2 variants relative to WT.

Fig. S5: SARS-CoV-2 neutralization titer (NT90) analysis with serum samples from recovered COVID-19 patients (n=24) against SARS-CoV-2 WT, Alpha, Alpha E484K, Beta and Delta variant. **(A)** Percentages of vaccinees tested positive ($NT90 \geq 1:16$), borderline ($1:16 > NT90 \geq 1:8$) or negative ($NT90 < 1:8$) for NT90 neutralization against SARS-CoV-2 WT and variants. **(B)** Individual NT90 serum dilutions against SARS-CoV-2 WT and variants. Statistical significance between WT and variants was determined by Mann-Whitney-U test for nonparametric distribution (*: $p < 0.05$). Medians are visualized as red lines together with the interquartile range as error bars. The cut-off value is illustrated by grey dashed line. **(C)** Determination of NT90 fold changes of SARS-CoV-2 variants relative to WT.

Fig. S6: Comparison of neutralization titers (NT90 values) from individuals fully vaccinated with ChAdOx1, BNT162b2, mRNA-1273 and convalescent patients. Percentages (left) and individual NT90 values (right) of vaccinated or convalescent participants tested positive ($NT90 \geq 1:16$), borderline ($1:16 > NT90 \geq 1:8$) and negative ($NT90 < 1:8$) for 90% neutralization positive, borderline and negative against **(A)** WT, **(B)** Alpha, **(C)** Alpha-E484K, **(D)** Beta and **(E)** Delta variant are shown. Statistical significance

between the four cohorts was determined by Mann-Whitney-U test for nonparametric distribution (*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; ****: $p < 0.0001$). Medians are visualized as red lines together with the interquartile range as error bar. Cut-off values are illustrated by grey dashed line.

Tab. S1: Characteristics from individuals fully vaccinated with ChAdOx1 included in the study (n=33). Age, sex, sampling day after second vaccine dose as well as results from antibody testing are presented. Results for total Ig against SARS-CoV-2 RBD and for IgA against SARS-CoV-2 domain S1 are shown in ratio of absorbance (RoA). For IgG against SARS-CoV-2 domain S1 results are presented in binding antibody units per ml serum (BAU·ml⁻¹). Serum samples used for the neutralization experiments are labeled in column 'NT analysis'. The average age of the participants was 43 years, the percentage of women was 58%. All samples of ChAdOx1 vaccinees were taken in between 29 and 36 days after the second dose.

Tab. S2: Characteristics from individuals fully vaccinated with BNT162b2 included in the study (n=31). Age, sex, sampling day after second vaccine dose as well as results from antibody testing are presented. Results for total Ig against SARS-CoV-2 RBD and for IgA against SARS-CoV-2 domain S1 are shown in ratio of absorbance (RoA). For IgG against SARS-CoV-2 domain S1 results are presented in binding antibody units per ml serum (BAU·ml⁻¹). Serum samples used for the neutralization experiments are labeled in column 'NT analysis'. The average age of the participants was 41 years, the percentage of women was 45%. All samples of BNT162b2 vaccinees were taken in between 21 and 78 days after the second dose.

Tab. S3: Characteristics from individuals fully vaccinated with mRNA-1273 included in the study (n=23). Age, sex, sampling day after second vaccine dose as well as results from antibody testing are presented. Results for total Ig against SARS-CoV-2 RBD and for IgA against SARS-CoV-2 domain S1 are shown in ratio of absorbance (RoA). For IgG against SARS-CoV-2 domain S1 results are presented in binding antibody units per ml serum (BAU·ml⁻¹). Serum samples used for the neutralization experiments are labeled in column 'NT analysis'. The average age of the participants was 54 years, the percentage

of women was 61%. All samples of mRNA-1273 vaccinees were taken in between 63 and 104 days after the second dose.

Tab. S4: Characteristics from SARS-CoV-2 convalescent patients included in the study (n=29). Age, sex, sampling day after second vaccine dose as well as results from antibody testing are presented. Results for total Ig against SARS-CoV-2 RBD and for IgA against SARS-CoV-2 domain S1 are shown in ratio of absorbance (RoA). For IgG against SARS-CoV-2 domain S1 results are presented in binding antibody units per ml serum (BAU·ml⁻¹). Serum samples used for the neutralization experiments are labeled in column 'NT analysis'. The average age of the participants was 49 years, the percentage of women was 48%. All samples of convalescent patients were taken in between 22 and 306 days after the second dose.

Tab. S5: List of medians with corresponding 95% confidence interval (CI) for antibody titers. Medians including lower and upper confidence limit (CL) of anti-SARS-CoV-2-S1 IgG, anti-SARS-CoV-2-S1 IgA and Anti-SARS-CoV-2 RBD total Ig are shown for each participant group are shown.

Tab. S6: List of medians with corresponding 95% confidence interval (CI) for neutralization titers. Medians including lower and upper confidence limit (CL) of NT50 and NT90 values for all SARS-CoV-2 viruses and participant groups are shown.

Total Ig against RBD

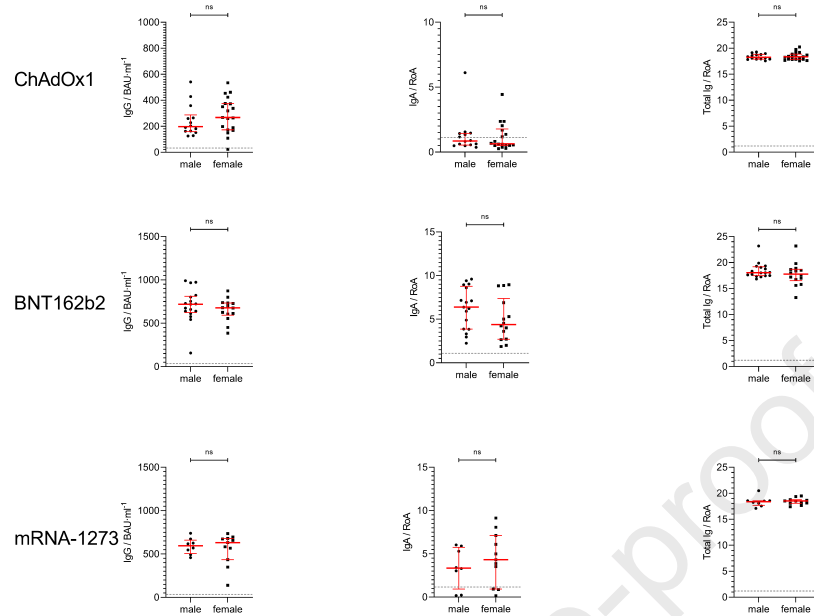


Fig. S2A

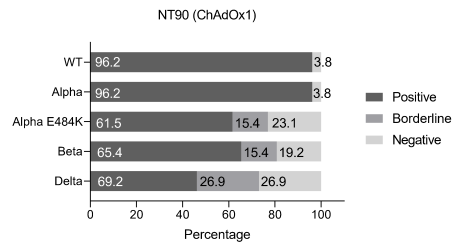


Fig. S2B

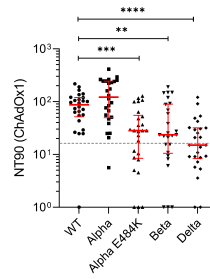


Fig. S2C

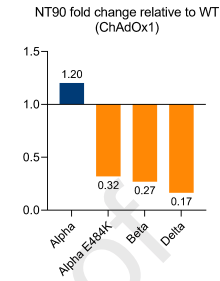


Fig. S3A

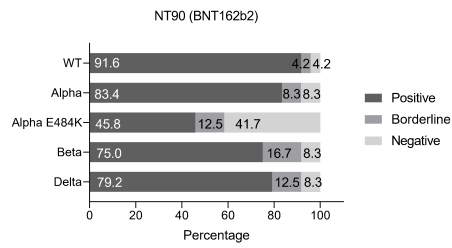


Fig. S3B

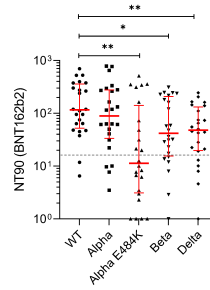


Fig. S3C

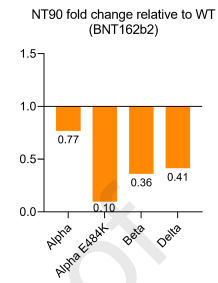


Fig. S4A

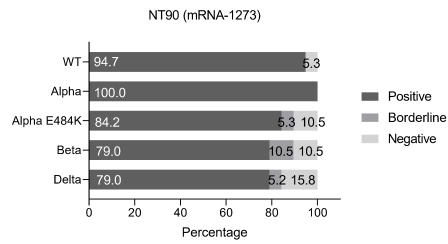


Fig. S4B

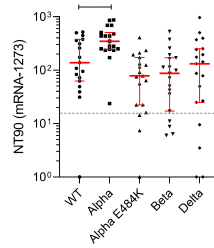


Fig. S4C

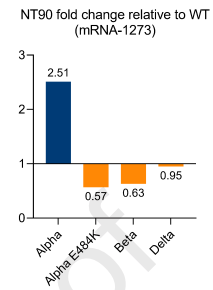


Fig. S5A

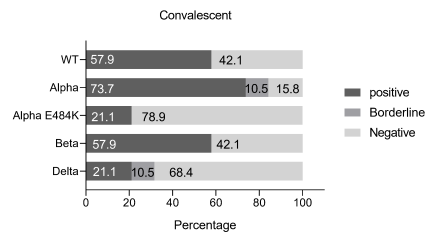


Fig. S5B

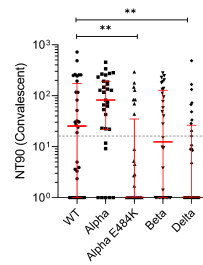


Fig. S5C

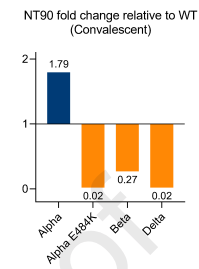


Fig. S6A

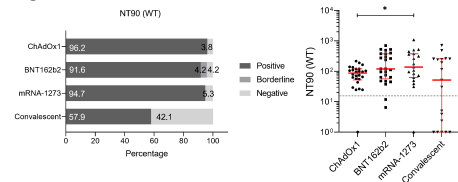


Fig. S6B

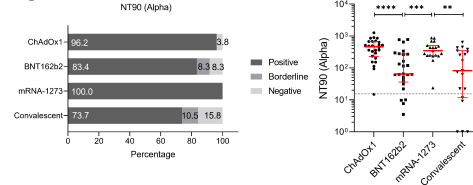


Fig. S6C

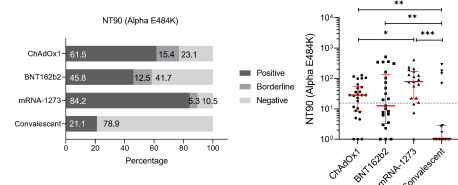


Fig. S6D

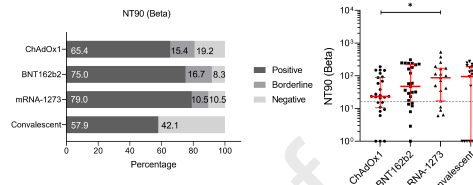


Fig. S6E

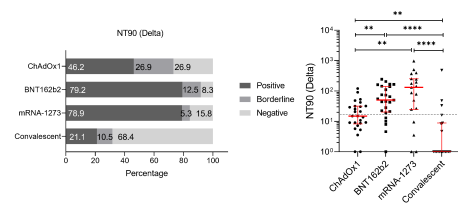


Fig. 7A

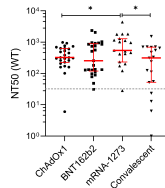
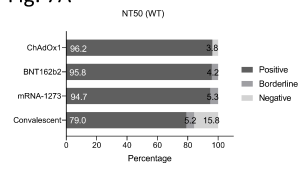


Fig. 7B

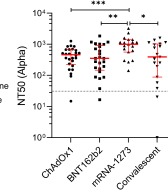
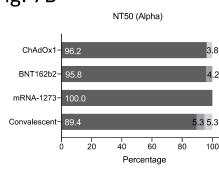


Fig. 7C

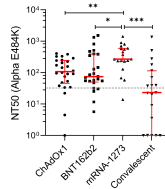
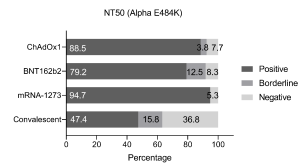


Fig. 7D

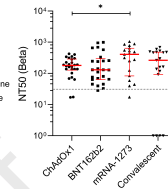
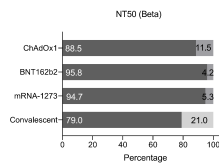
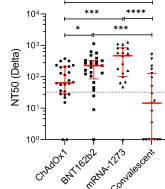
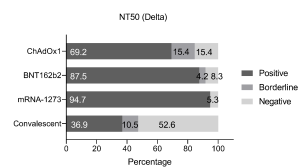


Fig. 7E



Tab. S1: ChAdOx vaccinated individuals

[illegible]

Tab. S2: BNT162b2 vaccinated individuals

[illegible]

Tab. S3: mRNA-1273 vaccinated individuals

[illegible]

Tab. S4: COVID-19 convalescent patients

ID	Age	Gender	days after diagnosis	NT analysis	Total anti-RBD Ig (Wantai)		Anti-S1 IgG (Euroimmun)		Anti-S1 IgA (Euroimmun)	
					Results	Ratio / RoA	Results	Concentration / BAU·ml ⁻¹	Results	Ratio / RoA
C1	22	F	107	yes	positive	16.57	positive	54.15	positive	1.54
C2	23	F	107	yes	positive	16.44	borderline	30.29	negative	0.27
C3	27	M	22	yes	positive	6.00	positive	77.58	borderline	0.78
C4	30	F	113	yes	positive	6.43	positive	39.30	negative	0.45
C5	33	F	205	yes	positive	7.54	negative	12.83	N/A	N/A
C6	38	M	205	yes	positive	16.02	positive	41.39	N/A	N/A
C7	39	F	122	yes	positive	16.99	positive	40.38	borderline	0.89
C8	40	F	111	yes	negative	0.30	negative	11.74	N/A	N/A
C9	44	F	122	yes	positive	16.12	positive	42.58	negative	0.50
C10	45	F	206	yes	positive	17.12	positive	129.27	N/A	N/A
C11	48	F	137	yes	positive	1.63	negative	11.10	negative	0.28
C12	48	F	205	yes	positive	17.34	positive	249.19	N/A	N/A
C13	50	F	95	yes	positive	11.15	negative	17.64	borderline	0.96
C14	51	F	205	yes	positive	17.87	positive	154.11	N/A	N/A
C15	54	M	120	yes	positive	1.38	borderline	25.59	negative	0.43
C16	58	M	205	yes	positive	18.29	positive	362.28	N/A	N/A
C17	59	M	205	yes	positive	9.97	positive	44.92	N/A	N/A
C18	60	F	205	yes	positive	17.33	positive	42.17	N/A	N/A
C19	66	M	48	yes	positive	18.43	positive	743.44	N/A	N/A
C20	50	M	111	no	negative	0.25	negative	10.40	N/A	N/A
C21	35	M	96	no	positive	3.84	negative	11.90	negative	0.40
C22	31	M	151	no	positive	13.40	negative	15.12	N/A	N/A
C23	50	M	97	no	positive	15.03	positive	75.47	positive	1.32
C24	23	M	99	no	positive	16.31	positive	80.86	borderline	0.92
Average age / years			43							
n (female) / %			54							
min days after diagnosis			22							
max days after diagnosis			206							

Tab. S5 List of medians for antibody titers

participant group and antibody test	Median antibody titer (lower CL-upper CL at 95%)
ChAdOx1 IgG	259.5 (95% CI 181.3-337.9)
BNT162b2 IgG	679.0 (95% CI 626.1-733.7)
mRNA-1273 IgG	618.6 (95% CI 492.4-672.9)
convalescent IgG	41.8 (95% CI 17.6-77.6)
ChAdOx1 IgA	0.7 (95% CI 0.6-1.4)
BNT162b2 IgA	5.3 (95% CI 3.9-7.1)
mRNA-1273 IgA	3.9 (95% CI 0.9-6.0)
convalescent IgA	0.6 (95% CI 0.4-1.0)
ChAdOx1 total Ig	18.4 (95% CI 17.9-18.7)
BNT162b2 total Ig	18.0 (95% CI 17.5-18.7)
mRNA-1273 total Ig	18.5 (95% CI 18.1-18.7)
convalescent total Ig	15.5 (95% CI 6.4-17.0)

Tab. S6 List of medians for neutralization titers

Participant group and virus	Median NT50 (lower CL-upper CL at 95%)	Median NT90 (lower CL-upper CL at 95%)
ChAdOx1 WT	322.7 (95% CI 260.6-606.4)	86.8 (95% CI 56.0-109.5)
ChAdOx1 Alpha	460.9 (95% CI 291.8-640.0)	121.4 (95% CI 55.6-240.1)
ChAdOx1 Alpha E484K	107.3 (95% CI 53.1-224.1)	28.2 (95% CI 10.4-47.8)
ChAdOx1 Beta	179.6 (95% CI 137.7-224.0)	23.5 (95% CI 15.4-68.4)
ChAdOx1 Delta	64.7 (95% CI 34.0-200.8)	15.0 (95% CI 9.1-30.6)
BNT162b2 WT	217.5 (95% CI 128.0-854.1)	115.7 (95% CI 63.6-301.6)
BNT162b2 Alpha	315.2 (95% CI 164.5-838.2)	89.0 (95% CI 40.8-271.1)
BNT162b2 Alpha E484K	72.8 (95% CI 53.2-348.8)	11.4 (95% CI 3.5-73.2)
BNT162b2 Beta	129.2 (95% CI 64.6-251.0)	41.9 (95% CI 17.4-181.0)
BNT162b2 Delta	214.2 (95% CI 105.1-300.1)	47.9 (95% CI 21.1-110.3)
m-RNA1273 WT	541.9 (95% CI 232.1-1291.0)	137.8 (95% CI 62.5-376.7)
m-RNA1273 Alpha	996.5 (95% CI 564.6-1407.0)	345.5 (95% CI 245.4-504.6)
m-RNA1273 Alpha E484K	270.4 (95% CI 228.3-596.1)	78.3 (95% CI 22.3-172.0)
m-RNA1273 Beta	405.7 (95% CI 83.4-642.9)	86.8 (95% CI 17.1-170.5)
m-RNA1273 Delta	466.8 (95% CI 102.1-835.4)	131.1 (95% CI 24.9-251.8)
Convalescent WT	241.9 (95% CI 109.1-353.8)	45.7 (95% CI 18.7-193.1)
Convalescent Alpha	420.0 (95% CI 208.5-769.8)	82.0 (95% CI 23.0-168.0)
Convalescent Alpha E484K	56.9 (95% CI 22.4-129.8)	1.0 (95% CI 1.0-5.2)
Convalescent Beta	161.7 (95% CI 92.4-308.5)	12.4 (95% CI 1.0-94.9)
Convalescent Delta	92.0 (95% CI 3.4-221.3)	1.0 (95% CI 1.0-16.2)