The Journal of Infectious Diseases

BRIEF REPORT

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Serum Neutralization Against SARS-CoV-2 Variants Is Heterogenic and Depends on Vaccination Regimen

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Omicron variants are still the dominant SARS-CoV-2 viruses worldwide, therefore determination of the level of protection from infection and severe disease is essential. Here, we investigated humoral and cellular immunity of individuals immunized by ChAdOx1, BNT162b2, and mRNA-1273 and our results show that IgG and neutralization titers wane over time. However, strongest neutralization against Omicron BA.1 and T-cell responses were detected in ChAdOx1 vaccinees 6 months after the second dose, while no long-lasting neutralization was shown against BA.2 in any cohort. Crucially, our investigation revealed that immunity against variants of concern is heterogenic and dependent on the immunization status.

Keywords. COVID-19 vaccines; neutralizing antibodies; omicron BA1 and BA2; SARS-CoV-2; T-cell responses; virus neutralization.

Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, numerous variants of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have emerged. Modification of the viral spike (S) protein elicited by mutations in the genome can have severe implications for transmissibility, infectivity, or immune evasion. These so-called escape mutations of SARS-CoV-2 were classified by the World Health Organization as variants of concern (VOCs). At the end of 2021 the Delta (B.1.617.2) variant was the most dominant VOC, which was replaced by the Omicron BA.1 (B.1.1.529.1) and subsequently by another VOC called Omicron BA.2. The emergence of both Omicron variants raised awareness due to their higher transmissibility and spread [1]. Alongside higher transmission, relative hospitalization rates were remarkably lower than during the Delta wave. The altered pathogenesis was linked to mutational changes of the virus and to existing immunity from previous infections or vaccinations [2]. In the context of vaccinations, data show that booster vaccines were required for individuals fully immunized with mRNA-based vaccines for effective neutralization against Omicron BA.1 [3]. However, for Omicron BA.2 (B.1.1.529.2) it might be a different situation. Although 21 common mutations were identified, they differ in 28 positions (18 only in BA.1 and 10 only in BA.2), which may again affect transmissibility and infectivity [4].

Despite the promising possibility of increased immunity against BA.1 by booster vaccination, in August 2022 only 30% of people worldwide (43% in Europe, 39% in North America, and 3% in Africa) had received a third vaccines dose. More specifically, 62% of the world's population (66% in Europe, 64% in North America, and 22% in Africa) were fully immunized in August 2022, which required only 2 vaccine doses [5]. Until May 2022, Omicron BA.1 was the dominant VOC in South America, while Omicron BA.2 is still circulating in parts of Asia [6]. The immune response induced by vaccination to protect against Omicron BA.1 or BA.2 still raises questions.

To evaluate the effectiveness of 3 major vaccines, ChAdOx1, BNT162b2, and mRNA-1273, we here analyzed SARS-CoV-2 spike-specific antibody binding titers of 109 individuals. In addition, neutralization against SARS-CoV-2 wild-type (WT), Delta, and Omicron BA.1 and BA.2 was investigated 1 and 6 months after the second vaccine dose. Furthermore, we examined induction of cellular immunity by analyzing SARS-CoV-2 S-specific T-cell responses in all cohorts.

METHODS

Ethics Statement

Written informed consent was obtained from all donors of leftover nasopharyngeal/oropharyngeal specimens, EDTA-whole blood, and serum samples by the participating clinics. The Ethics Committee of the Medical University of Innsbruck approved the use of anonymized leftover specimens of SARS-CoV-2 vaccinated individuals (ECS1166/2018) for scientific purposes.

Human Samples

In this study serum samples and peripheral blood mononuclear cells (PBMCs) from 109 healthy persons twice vaccinated with

Received 30 August 2022; editorial decision 25 October 2022; accepted 28 October 2022; published online 1 November 2022

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The Journal of Infectious Diseases®   2023;227:528–32

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https://doi.org/10.1093/infdis/jiac432

ChAdOx1 (n = 53; Supplementary Table 1), BNT162b2 (n = 28; Supplementary Table 2), or mRNA-1237 (n = 28; Supplementary Table 2) were collected from individuals 1 month and 6 months after immunization. The geometric mean age of all participants was 42.8 years and the percentages of female and male participants included in the study were 57.8% and 42.2%, respectively. Correlation between the participant's age and the analyzed parameters is shown in Supplementary Figure 3. The geometric mean sampling times of vaccinees were 31 and 185 days (2× ChAdOx1), 56 and 149 days (2× BNT162b2), and 53 and 173 days (2× mRNA-1237) after the second vaccine dose.

Viruses

Clinical specimens for SARS-CoV-2 (Delta, Omicron BA.1, and Omicron BA.2) from COVID-19–positive swabs (ethics statement, ECS1166/2020), and SARS-CoV-2 virus (WT) from repositories (BEI Resources; Centre for AIDS Reagents/National Institute for Biological Standards and Control; No. 52281) were propagated as previously described [7, 8].

Antibody-Binding Determination Against Receptor-Binding Domain of SARS-CoV-2 Spike Protein

Serum samples from vaccinated participants were analyzed by SARS-CoV-2 IgG II Quant assay (Abbott). The chemiluminescent microparticle immunoassay SARS-CoV-2 IgG II Quant assay was performed to assess anti–SARS-CoV-2 immunoglobulin G (IgG) against receptor-binding domain (RBD). Determined results in AU/mL were recalculated to binding antibody unit (BAU)/mL according to manufacturer instructions to obtain a cutoff value of 7.1 BAU/mL for positive results.

Neutralization Plaque Assay

VeroE6/TMPRSS2 cells (1.2×10^5) were seeded in a 48-well plate with culture medium (Dulbecco's Modified Eagle's high-glucose medium supplemented with 10% fetal calf serum [FCS], 1% L-glutamine, and 1% penicillin/streptomycin; all reagents were obtained from Sigma Aldrich) and incubated overnight at 37°C and 5% CO_2 as previously described [7]. On the following day, whole-serum samples were serial diluted from 1:8 to 1:1024 and incubated with SARS-CoV-2 WT or variant strains (4×10^2 plaque-forming units/mL) for 1 hour at 37°C. After incubation, VeroE6/TMPRSS2 cells were inoculated for 1 hour at 37°C and subsequently cultured with medium containing 1.5% carboxymethylcellulose (Sigma Aldrich) for 3 days at 37°C followed by plaque visualization and counting. For this, cells were washed and fixed with 10% neutral buffered formalin (Sigma Aldrich) for 1 hour at room temperature. Fixed cells were stained using 0.5% (w/v) crystal violet solution (Sigma Aldrich) for 15 minutes at room temperature. To determine the neutralizing capacity half-maximum neutralizing titers (NT_{50}) from neutralization curves were calculated using 4-parameter nonlinear regression in GraphPad Prism version 9. A cutoff NT_{50} value of 1:32 was set for a positive result.

SARS-CoV-2–Specific T-Cell Response

Interferon-γ (IFN-γ) production of activated PBMCs was assessed by enzyme-linked immunospot (ELISpot) assay [7, 8]. Briefly, ELISpot MultiScreen HTS 96-well filter plates (Millipore) were activated using 35% ethanol, washed and coated overnight with anti-human IFN-γ monoclonal antibody 1-D1K (2 µg/mL; Mabtech). Then, 5×10^5 PBMCs/well were counted and seeded in Roswell Park Memorial Institute medium supplemented with 5% heat-inactivated human AB serum and 1% L-glutamine (all obtained from Sigma Aldrich). Cells were stimulated with 0.6 nM PepTivator SARS-CoV-2 Peptide Pools (Miltenyi Biotec) of SARS-CoV-2 spike glycoprotein (S/S1) in duplicates. As positive controls, cells were stimulated with a mixture of Cytomegalovirus/Epstein-Barr Virus/Influenza Virus peptide pools (2 µg/mL; Mabtech) or cell activation cocktail (1:500; Biolegend). To determine the background level for each donor, PBMCs were seeded with culture medium only. Following overnight incubation, IFN-γ production was detected using biotinylated anti-human IFN-γ monoclonal antibody 7-B6-1 (1 µg/mL in Dulbecco's Buffered Saline [D-PBS] containing 0.5% FCS; Mabtech) for 2 hours at room temperature, followed by incubation with streptavidin-alkaline phosphatase (1:1000 in D-PBS containing 0.5% FCS; Sigma Aldrich), and finally treatment with 50 µL ready-to-use 5-bromo-4-chloro-3-indolyl phosphate/nitro blue tetrazolium (BCIP/NBT) liquid substrate (Sigma Aldrich). Emerged spots were counted using ImmunoSpot Analyzer (Cellular Technology) and spot quality was checked using the ImmunoSpot Software version 5.0.9.15.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism version 9. Statistical significance of SARS-CoV-2–specific antibody ratio, of IFN-γ T-cell response, as well as of NT_{50} levels were determined using either Mann-Whitney *U* test or Kruskall-Wallis test with Dunn multiple correction (GraphPad Prism). Correlations between SARS-CoV-2 RBD-specific antibody titer, IFN-γ T-cell response, or NT_{50} levels and participant's age were calculated using nonparametric Spearman correlation analysis (GraphPad Prism).

RESULTS

Anti-SARS-CoV-2 RBD-specific IgG were detected in all cohorts 1 month after the second dose, with the highest values for mRNA-based vaccines, mRNA1273 and BNT162b2 (Figure 1*A* and Table 1). Lowest antibody levels were found for ChAdOx1 vaccinees 6 months after the second dose, while mRNA-based vaccine cohorts remained up to 5-times higher

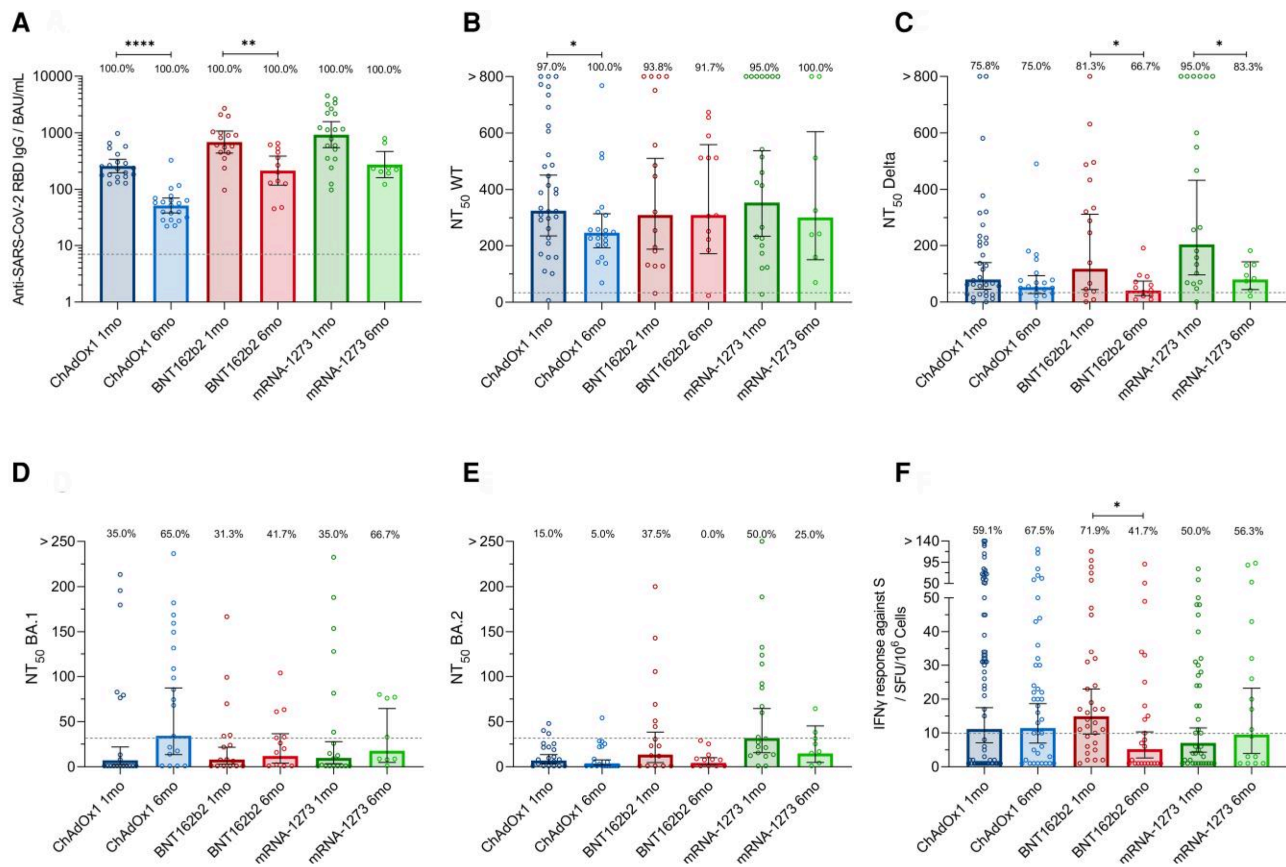

Figure 1. SARS-CoV-2 RBD-specific IgGs, neutralization of SARS-CoV-2, and induction of spike-specific T cells of vaccinated (ChAdOx1, BNT162b2, or mRNA-1273) participants 1 and 6 months after full immunization. *A*, Geometric means of anti–SARS-CoV-2 RBD IgG are presented in BAU/mL for twice-vaccinated participants 1 and 6 months after immunization. *B–E*, Geometric means of NT_{50} serum dilutions of ChAdOx1-, BNT162b2-, and mRNA1273-vaccinated participants against (*B*) WT, (*C*) Delta, (*D*) BA.1, and (*E*) BA.2 variants 1 and 6 months after the second vaccine dose. *F*, Geometric means of the IFN-γ T-cell response against SARS-CoV-2 S are shown in SFU per 10^6 cells for twice-vaccinated participants 1 and 6 months after immunization. Numbers above each column show percentages with (*A*) positive antibody-binding titer (IgG above 7.1 BAU/mL); (*B–E*) positive neutralization titers (NT_{50} above 1:32); or (*F*) positive T-cell responses (above 10 SFU per 10^6 cells). Error bars indicate 95% confidence interval. Cutoff values are indicated by dashed lines. Statistical significance between the groups was determined by Kruskall-Wallis test with Dunn multiple correction (* $P < .05$; ** $P < .01$; **** $P < .0001$). Abbreviations: BAU, binding antibody unit; IFN-γ, interferon-γ; IgG, immunoglobulin G; NT_{50}, half-maximum neutralizing titer; RBD, receptor-binding domain; S, spike glycoprotein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SFU, spot forming units; WT, wild type.

(Figure 1*A*, Supplementary Figure 1*A*, and Table 1). Neutralization titers were calculated for all serum samples in plaque assays using replication-competent SARS-CoV-2 viruses as described earlier [8]. In general, high neutralization capacity against SARS-CoV-2 WT was found in all tested groups 1 month after the second dose. In the 3 vaccine groups, neutralization against WT remained elevated 6 months after the second vaccine (Figure 1*B* and Table 1). Positive neutralization against Delta was found for BNT162b2- and mRNA1273-vaccinated individuals and to a lesser extend also for CHAdOx1 vaccinees (Figure 1*C* and Table 1). After 6 months, the best neutralizing abilities against Delta were demonstrated for mRNA1273-vaccinated individuals (Figure 1*C* and Table 1). In contrast, neutralization above cutoff for Omicron BA.1 6 months after the second vaccine was only detected for ChAdOx1 vaccinees with a NT_{50} value of 34.4 (Figure 1*D*). To exclude the possibility that the overall positive naturalization after 6 months was due to natural infection between the 2 sampling time points, we tested the ChAdOx1 group for SARS-CoV-2 nucleocapsid (N)-specific IgGs (Supplementary Table 1). Geometric mean NT_{50} levels against BA.1 for BNT162b2- and mRNA1273-vaccinated people 6 months after the second dose reached 12 and 17.7, which was below cutoff. Overall, neutralization against Omicron BA.2 was even further impaired and effective neutralization was solely found in mRNA1273 vaccinees 1 month after the second vaccine dose (Figure 1*E*). No effective neutralization against BA.2 was found in any cohort 6 months after the second dose (Figure 1*E*). Decreased neutralization capacity observed for tested SARS-CoV-2 variants are additionally represented separately for each vaccine group in Supplementary Figure 1*B*–1*D*. The IgG antibody binding titers were significantly correlated with

Table 1. Antibody Response to Vaccination With 2 Doses of ChAdOx1, BNT162b2, or mRNA-1273 at 1 and 6 Months

Sample	Geometric Mean (95% CI)
Anti-SARS-CoV-2 RBD IgG, BAU/mL[a]	
ChAdOx1 1 mo	258.6 (197.1–339.3)
ChAdOx1 6 mo	51.7 (38.2–69.8)
BNT162b2 1 mo	685.9 (438.3–1073.0)
BNT162b2 6 mo	213.9 (118.8–385.3)
mRNA-1273 1 mo	925.9 (545.7–1571.0)
mRNA-1273 6 mo	274.1 (160.7–467.5)
NT_{50} against wild type[b]	
ChAdOx1 1 mo	325.4 (234.8–450.9)
ChAdOx1 6 mo	246.3 (192.7–314.6)
BNT162b2 1 mo	309.8 (188.0–510.5)
BNT162b2 6 mo	310.1 (171.9–559.2)
mRNA-1273 1 mo	354.2 (233.4–537.4)
mRNA-1273 6 mo	301.7 (150.4–604.9)
NT_{50} against Delta	
ChAdOx1 1 mo	79.9 (45.7–139.7)
ChAdOx1 6 mo	53.0 (30.0–93.5)
BNT162b2 1 mo	118.0 (44.6–312.3)
BNT162b2 6 mo	41.0 (22.7–74.1)
mRNA-1273 1 mo	204.2 (96.4–432.6)
mRNA-1273 6 mo	79.8 (44.5–142.9)
NT_{50} against Omicron BA.1	
ChAdOx1 1 mo	7.2 (2.4–22.0)
ChAdOx1 6 mo	34.4 (13.5–87.4)
BNT162b2 1 mo	8.0 (2.9–21.7)
BNT162b2 6 mo	12.0 (3.9–36.6)
mRNA-1273 1 mo	9.7 (3.4–27.8)
mRNA-1273 6 mo	17.7 (4.8–64.6)
NT_{50} against Omicron BA.2	
ChAdOx1 1 mo	6.9 (3.5–13.6)
ChAdOx1 6 mo	3.8 (1.8–7.6)
BNT162b2 1 mo	13.5 (4.7–38.4)
BNT162b2 6 mo	4.3 (1.8–10.2)
mRNA-1273 1 mo	31.8 (15.7–64.5)
mRNA-1273 6 mo	14.7 (4.8–45.3)
T-cell response against S, SFU per 10^6 cells[c]	
ChAdOx1 1 mo	11.1 (7.1–17.5)
ChAdOx1 6 mo	11.4 (7.0–18.6)
BNT162b2 1 mo	15.0 (9.7–23.0)
BNT162b2 6 mo	5.2 (2.6–10.3)
mRNA-1273 1 mo	7.1 (4.3–11.5)
mRNA-1273 6 mo	9.5 (3.9–23.2)

Abbreviations: BAU, binding antibody unit; CI, confidence interval; IgG, immunoglobulin G; NT_{50}, half-maximum neutralizing titer; RBD, receptor-binding domain; S, spike glycoprotein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SFU, spot-forming unit.

[a]Geometric mean of anti–SARS-CoV-2 RBD IgG titers with corresponding 95% CIs are shown in BAU/mL for each participant group.

[b]Geometric mean of NT_{50} values with corresponding 95% CIs for all SARS-CoV-2 virus subtypes and participant groups are shown.

[c]Geometric mean SFU per 10^6 cells with corresponding 95% CIs of interferon-γ T-cell response against SARS-CoV-2 S are shown for each participant group.

the neutralization ability against WT, Delta, and BA.2 (Supplementary Figure 2). To analyze SARS-CoV-2–specific induction of T cells, we performed IFN-γ ELISpot assays. We found that the strongest SARS-CoV-2 spike-specific T-cell responses were detected in BNT162b2-vaccinated followed by ChAdOx1-vaccinated individuals 1 month after the second dose (Figure 1*F* and Table 1). The T-cell responses were comparable 6 months after the second dose for ChAdOx1- and mRNA1273-vaccinated individuals, while a decreased T-cell response was detected for BNT162b2-vaccinated individuals 6 months after the second dose (Figure 1*F* and Supplementary Figure 1*E*). To exclude the possibility that differences between measured immune responses were age related, we performed Spearman correlation of antibody levels, neutralization titers, or T-cell responses and age of the vaccinees (Supplementary Figure 3). Here, no significant correlation was found (Supplementary Figure 3).

DISCUSSION

In summary, our studies confirm that antibodies wane over time and demonstrate that neutralization against VOCs, including Omicron BA.1 and BA.2, is heterogenic and dependent on the type of vaccine. Neutralization against Omicron BA.1 was observed in participants immunized with ChAdOx1, while BA.2 neutralization was found for recently immunized mRNA1273 individuals. Here, we demonstrated that all participants could induce IgG antibody responses 1 month after second immunization with ChAdOx1, BNT162b2, or mRNA1273 vaccination. However, antibody-binding titers declined after 6 months, but remained elevated in the BNT162b2 and mRNA1273 cohorts. These findings are in accordance with other published data, which also illustrated a superior induction of SARS-CoV-2–specific IgG for mRNA-based vaccines [9]. Omicron variants BA.1 and BA.2 bearing various mutations within the spike protein demonstrated higher transmission and infection rates compared to previous VOCs [10]. Thus, enhanced immune escape from neutralizing antibodies induced by vaccination and infection was observed [11, 12]. Our neutralization assays revealed that 2 vaccine doses showed effective neutralization against WT, and to a lower degree also against Delta, after 6 months. In contrast, using this 2-dose vaccine regimen, effective neutralization against Omicron BA.1 could only be observed in ChAdOx1 vaccinees, while no long-lasting neutralization ability could be shown for BA.2. Our findings with WT, Delta, and BA.1 are in line with published data investigating BNT162b2 or mRNA1273 vaccinees [3, 13]. In the present study, we provide a comprehensive comparison of immunity induced by 3 major COVID-19 vaccines used in most European countries, and in addition to BA.1 we also include data on BA.2. Most vaccinees presented the highest virus neutralization 1 month after the second dose, which declined over time. To our surprise, 6 months after the second dose, only the vector-based ChAdOx1 vaccine showed increased neutralization against BA.1, although the lowest antibody binding titers were measured for this cohort; however, this was not the case with Omicron BA.2. This increased neutralizing capacity of COVID-19 vaccines from 1 to 6 months

postvaccination might be explained by continued vaccine-induced somatic hypermutation of germinal center B cells [14]. Moreover, T-cell response stayed constant in ChAdOx1- and mRNA1273-vaccinated individuals, while it declined in BNT162b2 vaccinees 6 months after the second vaccination dose.

Due to weak protection from breakthrough infections and emergence of novel Omicron variants, and in the absence of a clear cutoff value for neutralizing antibody-binding titers, our data support the recommendation for booster doses worldwide.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Financial support. This work was supported by the Austrian Science Fund (grant numbers P34070-B to W. P. DOC 82 and P33510-B to D. W.); the Anniversary Fund of the Austrian National Bank (grant numbers P17614 to W. P. and P17633 to D. W.); and the State of Tyrol (grant number 70454 to W. P.). Funding to pay the Open Access publication charges for this article was provided by the Austrian Science Fund.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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