Human primary Omicron BA.1 and BA.2 infections result in sub-lineage-specific neutralization

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Abstract

The recently emerged Omicron variant is the most antigenically distinct SARS-CoV-2 variant of concern to date. As the heavily mutated spike protein enables escape from neutralizing antibodies, we studied the neutralizing activities of sera after Omicron BA.1 and BA.2 infections of naïve and vaccinated individuals. We show that primary BA.1 infections yielded reduced neutralizing antibody titers against wildtype (WT), Delta, and BA.2, while serum samples from individuals after BA.2 infection showed no cross-neutralization against the other variants. Fully vaccinated individuals were still able to neutralize both Omicron sub-lineages up to three months after vaccination, and Omicron-breakthrough infections showed equal cross-neutralizing activities against WT, Delta, BA.1, and BA.2. Our data demonstrate that Omicron variants are able to enhance cross-neutralizing antibodies in pre-immune individuals. Primary infections with one of the Omicron sub-lineages, however, induced variant-specific neutralizing antibodies. In particular, BA.2 infections generated a sub-lineage-specific response, emphasizing its antigenic distance.

Main

The SARS-CoV-2 Omicron (B.1.1.529) variant of concern is now prevalent in large parts of the world. It has been divided into three main sub-lineages BA.1, BA.2 and BA.3, which are characterized by a heavily mutated spike protein (Supplementary Fig. 1), leading to substantial escape from antibodies induced by previous infections and/or vaccinations [1,2]. Patients with primary BA.1 infections were shown to mount strongly reduced neutralizing antibody responses to strains circulating before Omicron [3–6], although vaccine-boosting regimens led to efficient cross-neutralization that may protect from disease [7–9]. The rapid increase in BA.2 infections, which is currently replacing BA.1 as the dominant variant [1], has raised the possibility that it may be more transmissible than BA.1 [10] and/or may escape antibody-mediated immunity, potentially including the protection gained from BA.1 infections [3].

Here, we report antibody neutralization data of Omicron BA.1, BA.2, and Delta variants in serum samples collected from individuals who had recovered from primary Omicron BA.1 or BA.2 infection or who had been vaccinated with or without previous infection. We analyzed the neutralizing capacity of serum samples obtained after primary wildtype (WT), Omicron BA.1 and BA.2 infections against a WT strain (isolated early in the pandemic with the D614G mutation) and the three variants of concern: Delta; Omicron BA.1; and Omicron BA.2. In addition, we tested samples from individuals who were infected with an Omicron variant following prior COVID-19 vaccination (breakthrough infection), and from individuals who had received three doses of a vaccine with and without prior infection. The characteristics of these cohorts are summarized in Table 1 and the Supplementary Tables 1 and 2.

Table 1
Cohorts and samples analyzed in this study.

		Median [IQR][a] NT titer			
	n	WT	Delta	Omicron BA.1	Omicron BA.2
Vaccinated (3 doses, mRNA vaccine)					
3–4 weeks	15	640 (480–1120)	320 (120–400)	160 (80–280)	160 (100–240)
3 months	15	160 (120–560)	120 (70–280)	40 (25–90)	60 (30–100)
Infected (WT + 3 doses mRNA vaccine)					
3–4 weeks	9	640 (480–1280)	480 (320–640)	120 (80–320)	240 (160–320)
Infected (WT)					
3–4 weeks	11	640 (400–640)	160 (80–280)	30 (25–40)	40 (35–70)
6 months	11	160 (100–280)	60 (40–100)	20 (15–25)	30 (20–35)
Infected (Omicron BA.1)					
3–4 weeks	18	≤ 10	≤ 10	60 (20–60)	20 (10–40)
Infected (Omicron BA.2)					
3–4 weeks	7	≤ 10	≤ 10	≤ 10	30 (12.5–40)
Omicron breakthroughs					
3–4 weeks	11	640 (480–960)	480 (320–640)	320 (280–800)	480 (240–800)

[a]IQR = interquartile range

Serum samples obtained from vaccinees three weeks and three months after the third dose of an mRNA vaccine (Table 1 and Supplementary Table 1) efficiently cross-neutralized Omicron variants. Neutralization titers were significantly lower than for WT (Fig. 1a; Table 1), but there was no significant difference between BA.1 and BA.2 (Mann-Whitney test, $p > 0.05$). We also detected Omicron cross-neutralization in individuals who had a WT infection before being vaccinated three times (Fig. 1b).

Samples obtained from primary infections with WT, Omicron BA.1, and Omicron BA.2 neutralized the heterologous strain to a much lesser extent than the homologous virus (Fig. 1c-e). Furthermore, Omicron NT titers were significantly reduced in samples obtained 3 weeks and 6 months after infection with the ancestral WT strain (Fig. 1c). Sera from Omicron BA.1 convalescents neutralized WT and Delta to a lesser extent, and even BA.2 neutralization was significantly lower (Fig. 1d). In contrast, samples from Omicron BA.2 convalescents did not cross-neutralize any other virus strain tested (Fig. 1e). However, all samples obtained from individuals after an Omicron infection who had been previously vaccinated (breakthrough

infection) were able to neutralize the two Omicron variants as efficiently as the WT and Delta viruses (Fig. 1f).

Consistent with the antigenic equidistance of BA.1 and BA.2 from the original SARS-CoV-2 strain [3], we show that neutralizing antibodies present in serum samples from primary Omicron patients are highly variant-specific. While samples from individuals after primary BA.1 infection exhibited some cross-neutralization of BA.2 (Fig. 1d), samples from primary BA.2-infected individuals showed no cross-neutralizing capabilities against any other variant (Fig. 1e). The two strains have 22 amino acid mutations in the spike protein in common, however there are considerable differences in the N-terminal domain (NTD), which is recognized by neutralizing antibodies [11] (Supplementary Fig. 1). Changes in the NTD might also affect its packing contacts with the receptor-binding domain (RBD)[12], the major target of neutralizing antibodies [13,14].

Multiple exposures to pre-Omicron-SARS-CoV-2, via three vaccinations (Fig. 1a) or mixed infection-vaccination scenarios (Fig. 1b), led to high titers with efficient neutralization of both Omicron variants. These data are in agreement with other studies that suggested an increase in the magnitude as well as the breath of neutralizing antibody responses by repeated exposure to the original antigen [3,4,7,8,15,16]. The Omicron NT titers, however, were lower in these cohorts than against pre-Omicron variants and a fast waning of neutralizing antibodies was observed (Fig. 1a).

Our data clearly show that primary infections with the currently circulating Omicron variants BA.1 and BA.2 result in sub-lineage-specific neutralization. With respect to the co-circulation as well as emergence of variants, our study additionally highlights the importance of booster vaccinations in immune protection.

Methods

Serum samples and ethical approval

The study was approved by the ethics committee of the Medical University of Vienna (EK 2156/2019, EK 1926/2020, EK 1291/2021) and performed in accordance with the Declaration of Helsinki. Since the samples had been acquired for virological diagnosis and had already been anonymized when they were integrated into the sample bank of the Center of Virology for research, the local ethics committee concluded that no written informed consent from the patients was required (EK 1035/2016, EK 1513/2016).

Virus strains and neutralization assay

All virus strains were isolated from nasopharyngeal swabs from COVID-19 patients using either Vero E6 cells, as described previously[17] (WT D614G and Delta), or VeroE6-TMPRSS2 cells, kindly provided by Anna Repic, Medical University of Vienna (both Omicron variants). The sequences of the strains were determined by next generation sequencing and uploaded to the GISAID database (D614G:

EPI_ISL_438123, Delta: EPI_ISL_4172121, Omicron BA.1: EPI_ISL_9110894, Omicron BA.2: EPI_ISL_11110193).

The live virus neutralization test (NT) was performed as described previously [17]. Two-fold serial dilutions of heat-inactivated serum samples were incubated with 50–100 $TCID_{50}$ SARS-CoV-2 for one hour at 37°C before the mixtures were added to Vero E6 (ECACC 85020206) cells. After three to five days at 37°C, NT titers were expressed as the reciprocal of the serum dilution required for prevention of virus-induced cytopathic effects. NT titers of serum samples ≥ 10 were considered positive.

Statistical analyses

Statistical analysis was performed with GraphPad Prism 9.3.1. The Mann-Whitney test was used for pairwise comparisons. The Kruskal-Wallis test followed by Dunn´s multiple comparison was used for analyzing four groups. P values < 0.05 were considered significant.

Declarations

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Author contributions

These authors contributed equally: Judith H. Aberle, Karin Stiasny

Contributions

Conceptualization, KS, JHA; investigation, KS, JHA, IM, JVC, SWA; formal analysis, KS, JHA, IM; resources, DS, MG, EH, MT, JD, OL, CB, EP, LW, AZ; writing - original draft, KS, JHA, IM; writing - review & editing, all authors; visualization, IM; supervision, KS

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Competing interests

None to declare with this project.

The Center for Virology received a research grant from Pfizer (2018-2021) on the epidemiology of tick-borne encephalitis in Austria, with KS as a principal investigator. KS is an inventor on a patent by the Medical University of Vienna on flavivirus IgM serodiagnosis.

Data availability

All data are included in the figure, table, and supplement of this manuscript.

Code availability

The GISAID accession numbers for the sequences of the different virus strains are listed in Methods.

Conflict of interest: The authors have declared that no conflict of interest exists.

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Figures

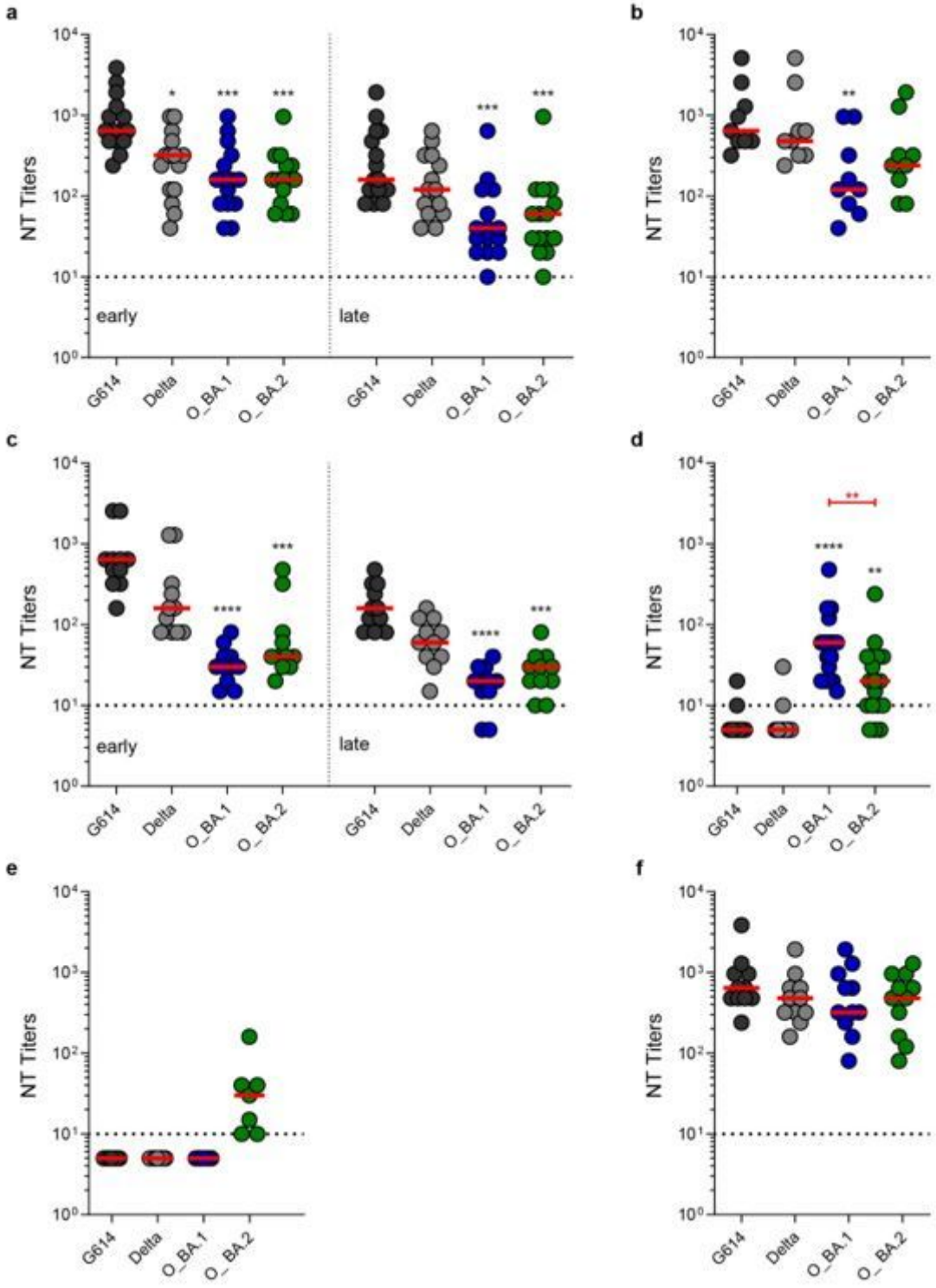

Figure 1

Neutralizing antibody titers against an ancestral wildtype (WT) strain (G614), and three variants of concern (Delta, Omicron BA.1, and Omicron BA.2) in post-vaccination and post-infection sera.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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