Immune escape of Omicron lineages BA.1, BA.2, BA.5.1, BQ.1, XBB.1.5, EG.5.1 and JN.1.1 after vaccination, infection and hybrid immunity

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Abstract

Since their emergence in late 2021, SARS-CoV-2 Omicron replaced earlier variants of concern and marked a new phase in the SARS-CoV-2 pandemic. Until the end of 2023, Omicron lineages continue to circulate and continue to evolve, with new lineages causing infection waves throughout 2022 and 2023. In the population, this leads to a complex immunological exposure background, characterized by immunity derived through vaccination, in the 5th year of the pandemic in the majority of individuals followed by at least one or even multiple infections or only natural infection in individuals that did not receive a vaccine.

In this study, we use eight authentic SARS-CoV-2 isolates (ancestral lineage B.1 and the seven Omicron lineages BA.1, BA.2, BA.5.1, BQ.1, XBB.1.5, EG.5.1 and JN.1.1) in a live virus neutralization assay to study immune escape in 97 human sera or plasma of different immunological backgrounds (vaccination, hybrid immunity due to one or two natural infections and natural infection without vaccination in children and adults).

We showed a gradually increasing immune escape after vaccination and hybrid immunity in from B.1 to BA.1/BA.2 to BA.5.1 to BQ.1 to XBB.1.5 to EG.5.1, but remarkably, no more enhanced immune escape of JN.1.1 compared to EG.5.1, with the latter two showing almost identical neutralization titers in individuals with hybrid immunity due to one or more infections. In vaccinated but never infected individuals, neutralization was markedly reduced or completely lost for XBB.1.5., EG.5.1 and JN.1.1, while in those with hybrid immunity, titers were reduced but almost all sera still showed some degree of neutralization. After a single infection without vaccination, reduced or complete loss of neutralization occurred for BQ.1, XBB.1.5, EG.5.1 and JN.1.1 compared to BA.1/BA.2. Furthermore, we observed that, although absolute titers differed between groups, the pattern of immune escape between the variants remains comparable across groups, with strongest loss of neutralization for BQ.1, XBB.1.5, EG.5.1 and JN.1.1 was observed across the different immunological backgrounds.

Our results show gradually increasing antibody escape of evolving Omicron lineages over the last two years of Omicron circulation until variant EG.5.1, but not anymore for the currently dominant lineages JN.1.1, suggesting other mechanisms than immune escape to be behind the rapid global emergence of JN.1.

Introduction

The emergence of the SARS-CoV-2 in late 2019 has been followed by a number of virus variants.[1] Two years later, the emergence of the Omicron variant of concern (VOC) marked a significant shift, enhancing immune evasion due to extensive mutations in its Spike region. This has led to widespread infections by overcoming immunity from vaccines and prior natural infection. Omicron's distinct genetic profile, particularly in the Spike region, positions it as a potential new serotype of SARS-CoV-2.[2,3]

Global observations have documented successive waves of infections since the initial emergence of Omicron, with a huge number of evolving Omicron lineages. Consequently, a complex immunological landscape now exists in the population, where immunity is derived from vaccines, one or multiple infections due to pre-Omicron or Omicron-variants, or a combination therefore, known as hybrid immunity. In most individuals, the immunological background of SARS-CoV-2 today consists of multiple, antigenically different exposures to SARS-CoV-2. On the other hand, some individuals have never received a vaccine and were only infected after the circulation of Omicron, in particular younger children, for which there is not vaccine recommendation on many countries. This leads to immune responses in the population at both extremes of the exposure spectrum.[2-9] Despite population immunity, SARS-CoV-2 continues to circulate. Multiple new variants have arisen within the Omicron clade, with XBB1.5, XBB.1.16, EG.5, BA.2.86 and JN.1 being the latest variants of interest (VOIs) declared by WHO. BA.2.86, occurring first in July 2023, has a remarkable number of mutations compared to earlier Omicron variants known to allow antibody evasion.[10] Its decedent, JN.1 has acquired an additional mutation S:L455S in the Spike. This mutation was shown to be associated with significantly enhanced immune evasion capabilities but also increased transmissibility.[5,11-15] In early 2024, JN.1 and its descending lineages showed a string increase globally, outcompeting earlier variants.

Methods

Setting

The University Hospitals of Geneva (HUG) is a tertiary center that ran an outpatient testing Centre for SARS-CoV-2 from 2020-2022 and is conducting all SARS-CoV-2 testing for the routine diagnostic of the adjacent hospitals. This centre is also leading the national genomic surveillance of SARS-CoV-2 and continues to performs full genome sequencing of SARS-CoV-2 specimens obtained through the diagnostic for regular reports on the circulation of

SARS-CoV-2 variants in Switzerland.[16,17] Left-over material of sequenced specimens of viral transport medium is stored at -70°C to generate viral isolates of specimens from lineages of interest or concern. Furthermore, serum and plasma from convalescent individuals, post-vaccination specimens, and samples from individuals with hybrid immunity (vaccination and infection) are collected through multiple ongoing studies.

Viruses and cells

Vero-E6 (ATCC CRL-1586) and Vero-E6-TMPRSS (Vero-E6 overexpressing TMPRSS2 protease, provided by National Institute for Biological Standards and Controls, NIBSC, Cat. Nr. 100978) cells were cultured in complete DMEM GlutaMax I medium supplemented with 10% fetal bovine serum, 1x non-essential amino acids, and 1% antibiotics, Penicillin/Streptomycin (all reagents from Gibco, USA).

All SARS-CoV-2 viruses used in this study were isolated from residual nasopharyngeal swabs collected, under an approval that allows the usage of anonymized left-over materials for virus culture. Both, the initial clinical specimen, and the obtained virus isolates were fully sequenced (**Table S1**). For this study, the following virus isolates were used (according to Pango lineages designation[18]: B.1 (ancestral virus), Omicron BQ.1 and BA.4.6, isolated and propagated on Vero-E6; Omicron BA.1 and BA.5.1, isolated on Vero-TMPRSS, then propagated to Vero-E6 for generation of virus stocks; Omicron BA.2, Omicron XBB.1.5, Omicron EG.5.1 and Omicron JN.1.1, isolated and propagated on Vero-TMPRSS. All virus stocks were titrated on the same cell line on which the virus stock was produced (either Vero-E6 or Vero-TMPRSS). All experiments with live infectious SARS-CoV-2 were approved and followed the standard operating procedures of our BSL-3 facility.

Individual samples

Immunocompetent and healthy individual samples consisted of serum or plasma samples collected after vaccination, infection or a combination of both (hybrid immunity). Plasma samples from vaccinated healthy individuals, vaccinated with two doses of BNT162b2 (Pfizer/BioNTech) or mRNA-1273 (Moderna) were available from a prospective observational study (n=14) (Ethics approval number: CCER 2021-00430). Serum samples were collected from boosted healthy individuals, with three doses of BNT162b2 or mRNA-1273 vaccine (n=19) (Ethics approval number: CCER 2020-02323). Asymptomatic or undetected infections of the vaccinated-only group were excluded in those samples by testing all specimens for antibodies against SARS-CoV-2 nucleocapsid (Roche Elecsys anti-SARS-CoV-2 N assay), and only specimens with negative result were used. Specimens of individuals with hybrid immunity were collected from adults vaccinated with BNT162b2 or mRNA-1273 vaccine and

with one or more documented infections. Serums of breakthrough infection samples were collected from individuals with either 2x mRNA vaccine followed by an Omicron BA.1 (n=11) breakthrough infection or 3x mRNA vaccine followed by an Omicron BA.2 (n=11) breakthrough infection (Ethics approval number: CCER 2020-02323).

For individuals with infections with two different VOCs (n=18) (e.g. Alpha and Omicron (n=9) or Delta and Omicron (n=9), Ethics approval number: CCER 2020-02323), the infecting variant of each episode was either determined by sequencing of the diagnostic samples or extrapolated by the time of infection, taking the knowledge on variant circulation generated by the Swiss national genomic surveillance program into account.[19]

Convalescent sera from unvaccinated adults and children with confirmed SARS-CoV-2 infection in early 2022 were collected in the context of the prospective observational study "SEROCoV-WORK+/Specchio-COVID19" at the Geneva University Hospitals (HUG) (Ethics approval number: CCER 2020-00881).

For these individuals, infection history was assessed by a questionnaire and was indicated by the individuals to be either diagnosed by RT-PCR or Ag-RDT, but no respiratory specimens of the acute infection episode were available and therefore sequencing of the infecting variant was not possible. In these cases, infection information (RT-PCR or Ag-RDT -confirmed diagnosis) was self-reported by the participants and/or by the parent of the participant (for children) at the time of blood drawing. Based on the data from our Swiss national genomic surveillance, the variants circulating at that time were to the vast majority Omicron BA.1 and Omicron BA.2, with only few Delta sequences remaining in January 2022[20]. Data on collection time of specimens after vaccination and/or infection are displayed in **Tables 1-4**. Only one serum per individual of a single collection time point was used in this study.

A written informed consent was obtained from all adult participants, and from the legally appointed representatives (parents) of all minor participants. All approvals were obtained from the Cantonal Ethical board of the Canton of Geneva, Switzerland (Commission Cantonal d'Ethique de la Recherche). Since no differences are to be expected in neutralizing capacity between plasma or serum, both sample types were used in parallel.

Focus reduction neutralization test (FRNT)

FRNT was used to determine the infectious titer after neutralization. Vero-TMPRSS cells were seeded at a density of 4×10^5 cells/mL in 96-well cell culture plates. All sera/plasma were heat-inactivated at 56 °C for 30 min and serially diluted in Opti-Pro serum-free medium starting from 1:10 until up to 1:20,480 if necessary. Sera/plasma were mixed with 50 PFU or FFU of the respective SARS-CoV-2 isolate (B.1, Omicron BA.1, Omicron BA.2, Omicron BA.5.1, Omicron BQ.1, Omicron XBB.1.5, Omicron EG.5.1 and Omicron JN.1.1) and incubated at 37 °C for 1 h.

All samples were run in duplicate, and for each neutralization experiment, an infection control (no serum/plasma) and a reference serum were used to ensure reproducibility between different experiments. Vero-TMPRSS cells were washed 1× with PBS and inoculated with the virus serum/plasma mixture for 1 h. Afterward, the inoculum was removed and 100 µL of the pre-warmed overlay medium mixed with 2.4% Avicel (DuPont) at a 1:1 ratio was added. After incubation for 16-24 hours at 37 °C, 5% CO_2, the overlay medium was removed, and cells were fixed in 6% formaldehyde solution for at least 1 h at room temperature. Cells were permeabilized with 0.1% Triton X-100 and blocked with 1% BSA (Sigma-Aldrich). Plates were incubated with a primary monoclonal antibody targeting SARS-CoV-2 nucleocapsid protein (purchased from Geneva Antibody Facility, JS02, diluted to 0.3 µg ml^{-1}) for 1 hour at room temperature and then with peroxidase-conjugated secondary antibody (Jackson ImmunoResearch, 109-036-09, diluted to 1:2,000) for 30 minutes at room temperature. Foci were visualized using True Blue HRP substrate (Avantor) and imaged on an ELISPOT reader (CTL). We defined a cluster of adjacent cells expressing viral antigen as a focus. Foci were counted in wells inoculated with virus-serum/plasma mixtures and compared to foci counts in infection control wells. The 90% reduction endpoint titers ($FRNT_{90}$) were calculated by fitting a 4-parameter logistics curve with variable slope to the foci counts of each serum/plasma using GraphPad Prism version 9.1.0. For samples that did not reach 90% reduction at a 1:10 dilution, we extrapolated the titer until a dilution of 0.5. If the extrapolation reached a titer below 0.5, the sample was given a value of 0.5. All samples with a titer below 1, i.e. undiluted sample are considered negative.

Statistical analysis

Data collection was done using Excel 2019. Geometric means with 95% CI were used for the comparison of $FRNT_{90}$ titers. Statistical analyses for $FRNT_{90}$ were conducted using GraphPad Prism version 9.1.0 software and performed using repeated measures one-way ANOVA with Dunnett's multiple comparisons test with log10 transformed $FRNT_{90}$ titers.

Results

In our study, we assessed immune escape from existing antibody responses from multiple immunological backgrounds to 8 authentic live virus isolates, consisting of ancestral SARS-CoV-2 B.1 and Omicron lineages BA.1, BA.2, BA.5.1, BQ.1, XBB.1.5, EG.5.1 and JN.1.1.

1. Neutralization capacity of sera or plasma after infection, vaccination, and hybrid immunity to Omicron lineages

A panel of sera/plasma was used from (i) double vaccinated BNT162b2 or mRNA-1273 individuals (n=14) or monovalent boosted (3 doses of BNT162b2 or mRNA-1273, n=19) individuals without prior or subsequent infection, (ii) individuals with hybrid immunity after receiving two or three doses of BNT162b2 or mRNA-1273 followed by a break-through infection with either Omicron BA.1 (n = 11) or Omicron BA.2 (n = 11), respectively, (iii) individuals with hybrid immunity, receiving one, two or three doses of the BNT162b2 or mRNA-1273 vaccine and two documented infections with two different VOCs (infected with Alpha, followed by infection with Omicron, n= 9, or infected with Delta, followed by infection with Omicron, n=9) and (iv) a panel of convalescent sera from unvaccinated individuals, adults (n=12) and children (n=12) infected between January and March 2022, a period that was characterized by high circulation of Omicron BA.1 and BA.2. (**Table 1-4**).

1.1. *Neutralizing capacity in vaccinated but never infected individuals against Omicron lineages*

We investigated a total of 33 individuals' specimens, either double-vaccinated (n = 14) or monovalent boosted individuals with either BNT162b2 or mRNA-1273 that had never been infected with SARS-CoV-2 (*n=19*) for neutralization against ancestral SARS-CoV-2 lineage B.1 as well as SARS-CoV-2 Omicron lineages BA.1, BA.2, BA.5.1, BQ.1, XBB.1.5, EG.5.1 and JN.1.1. For double vaccinated individuals, the highest neutralizing capacity was observed against the ancestral SARS-CoV-2 virus B.1 with geometric mean $FRNT_{90}$ titers of 251.7 (95%CI: 158.3-400.1) but much reduced titers were observed against all Omicron lineages with $FRNT_{90}$ titers of 5.7 (95%CI: 2.8-11.5) for BA.1, 10.4 (95%CI: 6.6-16.3) for BA.2, 2.9 (95%CI: 1.5-5.5) for BA.5.1, 1.5 (95%CI: 0.8-3.0) for BQ.1, 1.0 (95%CI: 0.6-1.4) for XBB.1.5 and 0.6 (95%CI: 0.5-0.8) for JN.1.1. None of the samples neutralized EG.5.1. Compared to B.1, this results in a fold-change reduction of 44.2 for Omicron BA.1, 24.2 for Omicron BA.2, 87.0 for Omicron BA.5.1, 163.0 for Omicron BQ.1, 261.7 for Omicron XBB.1.5 and 408.5 for Omicron JN.1.1. Although titers were much reduced compared to B.1, none of the samples failed to neutralize Omicron BA.2. An increasing number of samples with complete failure to neutralize was observed for Omicron BA.1, Omicron BA.5.1, Omicron BQ.1, Omicron XBB.1.5,Omicron EG.5.1 and Omicron JN.1.1 with 2/14 (14.3%), 4/14 (28.6%), 7/14 (50%), 7/14 (50%), 14/14 (100%) and 12/14 (85.7%), respectively (**Figure 1A**).

For boosted individuals, overall geometric mean $FRNT_{90}$ titers were higher against all viruses. Geometric mean $FRNT_{90}$ titers were 357.5 (95%CI: 255.3-500.6) against B.1, 68.8 (95%CI: 39.7-119.2) against Omicron BA.1, 27.6 (95%CI: 15.5-49.1) against Omicron BA.2, 13.7 (95%CI: 10.7-17.4) against Omicron BA.5.1, 6.2 (95%CI: 3.1-12.3) against Omicron BQ.1, 2.1 (95%CI: 1.0-4.1) against Omicron XBB.1.5, 0.8 (95%CI: 0.5-1.3) against EG.5.1 and 1.0

(95%CI: 0.6-1.6) against Omicron JN.1.1. Compared to B.1, this results in a fold-change reduction of 5.2 for Omicron BA.1, 12.9 for Omicron BA.2, 26.2 for Omicron BA.5.1, 57.9 for Omicron BQ.1, 174.1 for Omicron XBB.1.5, 440.1 for Omicron EG.5.1 and 356.4 for Omicron JN.1.1. No complete loss of neutralization in this group was observed for variants B.1, Omicron BA.1, Omicron BA.2, and Omicron BA.5.1, while 3/19 samples were not neutralized for Omicron BQ.1 (16%), 9/19 (47.4%) for Omicron XBB.1.5, 16/19 (84.2%) for Omicron EG.5.1 and 12/19 (63.2%) for Omicron JN.1.1 (**Figure 1B**).

1.2. Neutralizing capacity of vaccinated individuals with breakthrough infection (hybrid immunity)

Geometric mean $FRNT_{90}$ titers in the hybrid immunity group were higher than for vaccinated individuals. They were 865.4 (95%CI: 450.9-1661.0) against B.1, 416.5 (95%CI: 175.6-987.8) against Omicron BA.1, 56.7 (95%CI: 31.8-100.9) against Omicron BA.2, 65.4 (95%CI: 30.3-141.4) against Omicron BA.5.1, 17.4 (95%CI: 7.6-39.9) against Omicron BQ.1, 11.3 (95%CI: 5.1-24.9) against Omicron XBB.1.5, 8.4 (95%CI: 3.5-20.3) for Omicron EG.5.1 and 7.1 (95%CI: 3.6-14.0) for Omicron JN.1.1. Fold reduction in neutralization was 2.1 for Omicron BA.1, 15.3 for Omicron BA.2, 13.2 for Omicron BA.5.1, 49.8 for Omicron BQ.1, 76.5 for Omicron XBB.1.5, 102.9 for Omicron EG.5.1 and 122.5 for Omicron JN.1.1. Complete loss of neutralization was observed only for 1 sample each for Omicron XBB.1.5, Omicron EG.5.1 and Omicron JN.1.1 (9.1%) (**Figure 1C, 4**).

For boosted individuals with Omicron BA.2 breakthrough infection, geometric mean $FRNT_{90}$ titers were 818.7 (95%CI: 541.5-1238.0) for B.1, 266.2 (95%CI: 134.2-528.0) for Omicron BA.1; 415.8 (95%CI: 250.5-690.1) for Omicron BA.2, 85.1 (95%CI: 44.7-161.9) for Omicron BA.5.1, 50.2 (95%CI: 24.2-104.0) for Omicron BQ.1, 33.6 (95%CI: 16.7-67.4) for Omicron XBB.1.5, 7.4 (95%CI: 2.7-20.7) for Omicron EG.5.1 and 6.2 (95%CI: 2.8-13.5) for Omicron JN.1.1. This equals a fold-change loss compared to B.1 of 3.1 for Omicron BA.1, 2.0 for Omicron BA.2, 9.6 for Omicron BA.5.1, 16.3 for Omicron BQ.1, 24.4 for Omicron XBB.1.5, 110.3 for Omicron EG.5.1 and 133.0 for Omicron JN.1.1. No complete loss of neutralization in this group was observed for variants B.1, Omicron BA.1, Omicron BA.2, Omicron BA.5.1, Omicron BQ.1 and Omicron XBB.1.5, while 2/11 samples were not neutralized for Omicron EG.5.1 (18.2%) and 1/11 (9.1%) for Omicron JN.1.1 (**Figure 1D, 4**).

Although titers for B.1 were highest in both groups, the second highest neutralization titers were found for infecting virus, e.g. neutralization for BA.1. was higher in the BA.1-infected group and neutralization for BA.2 was higher in the BA.2.-infected group. No difference was seen between the groups in the neutralization titers for EG.5.1. and JN.1.1 which were both comparably low independent of the infecting virus.

1.3. Neutralizing capacity in vaccinated individuals infected with breakthrough infection from two antigenically different VOCs (multi-variant hybrid immunity) towards Omicron lineages

We have investigated vaccinated individuals (n=18) who subsequently have been exposed to at least two antigenically different variants through two independent infection episodes that included a pre-Omicron VOC (Alpha, n=9 or Delta, n=9) and another infection episode with an Omicron lineage. The geometric mean $FRNT_{90}$ titers were 226.2 (95%CI: 153.8-332.8) against B.1, 80.33 (95%CI: 57.3-112.6) against Omicron BA.1, 32.3 (95%CI: 20.5-50.7) against Omicron BA.2, 22.4 (95%CI: 17.7-28.4) against Omicron BA.5.1, 7.6 (95%CI: 3.6-16.1) against Omicron BQ.1, 8.1 (95%CI: 4.3-15.3) against Omicron XBB.1.5, 2.4 (95%CI: 1.0-5.4) against Omicron EG.5.1 and 2.5 (95%CI: 1.2-4.8) against Omicron JN.1.1. Compared to B.1, this results in a fold-change reduction of 2.8 for Omicron BA.1, 7.0 for Omicron BA.2, 10.1 for Omicron BA.5.1, 29.8 for Omicron BQ.1, 27.8 for Omicron XBB.1.5, 95.4 for Omicron EG.5.1 and 92.2 for Omicron JN.1.1. Loss of neutralization was observed for Omicron BQ.1, Omicron XBB.1.5, Omicron EG.5.1 and Omicron JN.1.1 in 2, 1, 7 and 6 samples (11.1%, 5.6%, 38.9% and 33.3%), respectively (**Figure 2, 4**).

1.4. Neutralizing capacity from unvaccinated adults and children infected in early 2022

We also studies neutralization of Omicron variants in 24 sera (adults, n=12; children, n=12) of unvaccinated individuals with a single infection between January and March 2022 (most likely exposed to Omicron BA.1 or BA.2). Due to the limited volume of serum available for this group, we have only assessed neutralization towards Omicron variants BA.1, BQ.1, XBB.1.5, EG.5.1 and JN.1.1 in this cohort.

Geometric mean $FRNT_{90}$ titers in this group for adult individuals were 29.1 (95%CI: 13.0-65.1) against Omicron BA.1, 1.3 (95%CI: 0.6-2.6) against Omicron BQ.1, which equals a 23.1-fold reduction of neutralization to Omicron BA.1; 0.8 (95%CI: 0.5-1.4) against Omicron XBB.1.5, which equals a 35.1-fold reduction of neutralization to Omicron BA.1 and none of the samples neutralized Omicron EG.5.1 and Omicron JN.1.1. Complete loss of neutralization was observed for 7/12 (58.3%) samples for Omicron BQ.1, 8/12 (66.7%) samples for Omicron XBB.1.5 and all samples for EG.5.1 (12/12, 100%) and JN.1.1 (12/12, 100%) (**Figure 3A, 4**).

For children, geometric mean $FRNT_{90}$ titers were 43.3 (95%CI: 18.0-103.7) against Omicron BA.1, 2.3 (95%CI: 0.9-5.8) against Omicron BQ.1, which equals a 19.1-fold loss of neutralization to Omicron BA.1 and 1.1 (95%CI: 0.5-2.4) against Omicron XBB.1.5, which equals a 38.5-fold reduction of neutralization compared to Omicron BA.1, 1.2 (95%CI: 0.6-2.5) against Omicron EG.5.1, which equals a 34.8-fold reduction compared to Omicron BA.1 and 0.6 (95%CI: 0.4-0.8) against Omicron JN.1.1, which equals a 74.0-fold reduction compared to

Omicron BA.1. Of note, complete loss of neutralization was observed for 5/12 (41.7%) samples for Omicron BQ.1, 8/12 (66.7%) samples for Omicron XBB.1.5, 6/12 (50%) samples for Omicron EG.5.1 and 11/12 (91.7%) for Omicron JN.1.1 (**Figure 3B, 4**).

1.5. Heatmap of neutralization data across different immunological backgrounds

To summarize the findings across the cohorts, we have displayed the fold change of geometric mean $FRNT_{90}$ titers in comparison to the ancestral virus B.1 for all cohorts (**Figure 4**). Across cohorts, a consecutive loss in neutralization was observed from B.1 to BA.1/BA.2. to BA.5.1 to BQ.1 to XBB.1.5. and to EG.5.1/JN.1. The effect was the strongest for sera from individuals that were only vaccinated but never infected, and the least pronounced for individuals exposed to more than one natural infection with different variants. The differences between EG.5.1 and JN.1. were only subtle across groups, and JN.1.1 did not show an enhanced immune escape compared to EG.5.1. In vaccinated but never infected individuals, there was even a tendency for better neutralization of JN.1.1 compared to EG.5.1.

Discussion

With the emergence of Omicron in late 2021, the COVID-19 pandemic has entered a new phase. It has been previously shown that Omicron, compared to earlier VOCs, could overcome immunity from various exposures, including prior infections and/or vaccinations, and showed a distinct phenotype in *ex-vivo* infections compared to previous variants[2]. In the continuous emergence of new Omicron lineages, intrinsic transmissibility and immune pressure are considered as the main drivers of viral evolution[21].

A range of studies have shown the increasing escape from prior vaccination, infection and/or hybrid immunity for Omicron lineages, in particular those that are currently classified as VOIs such as XBB.1.5, XBB.1.6 and EG.5.

Omicron BA.2.86 with its highly mutated spike with over 30 mutations compared to other Omicron lineages and a genetic distance that is comparable to that of the first Omicron lineages BA.1 to that of Delta, was initially suspected of potential enhanced immune escape properties.[22] Multiple experimental data with pseudotyped viruses and live viruses neutralization, however, showed escape from immunity that was similar to or only slightly diminished compared to Omicron XBB variants such as XBB.1.5 and EG.5.[10,14,23-30] Despite its first detection in mid-2023, number of BA.2.86 sequences remained low and did not show signs of rapid increase over many months, although the virus was continuing to circulate globally.[1] One possible explanation was presumed lower viral fitness, as studies in cell culture have shown that the growth rate of BA.2.86 is equal or lower to that of EG.5.1.[14,24,31] BA.2.86

was also found to be less pathogenic in the animal model compared with EG.5.1, BA.2 or BA.2.75.[31,32]

In comparison with the parent lineage BA.2.86, JN.1 has an additional L455S substitution in the spike protein that was described to be associated with increased escape from humoral immunity as well as transmissibility.[5,11-15] However in contrast to its parental lineage BA.2.86, JN.1 showed a rapid increase in numbers of sequences in late 2023 and was then designated as a VOI.[22] Indeed, after a prolonged period of continuous co-circulation of multiple Omicron lineages for most of 2022 and 2023, JN.1 has largely outcompeted earlier variants and became dominant. At the same time, it was shown to be associated with a wave of infections worldwide.[11,15]

While multiple studies have assessed neutralization of BA.2.86 using both pseudovirus and live virus, limited data on the immune escape assessment of JN.1 are available. Jeworowski et al have provided a summary of currently existing studies on BA.2.86 and JN.1 both from pseudovirus and live virus data, and they could show in 39 sera upon live virus neutralization that JN.1 yielded lower geometric mean titers and lower fold change values compared pseudotyped virus.[33,15]

The present study presents an assessment of emerging SARS-CoV-2 variants in an authentic virus neutralization assay against panel of human sera and plasma. To add to the complexity of the underlying immunity, we have here used cohorts with immunity at both ends of the exposure spectrum, which reflects the complex situation in the population in the fifth year after the beginning of the pandemic. Here we show that recently emerged SARS-CoV-2 Omicron variants namely BQ.1, XBB.1.5, EG.5.1 and JN.1.1, display pronounced immune evasion to earlier Omicron variants, but that JN.1.1, a descendant from the now dominant JN.1, does not show an additional immune escape compared to EG.5.1. We also showed that earlier findings on hybrid immunity remain valid, that is that hybrid immunity continued to offer better protection compared to monovalent vaccination or natural infection, which suggest that the natural infection, in addition to the vaccines, can effectively boost the immune response.

The use of authentic live virus isolates and $FRNT_{90}$ to assess the neutralization titers of a large number of serum/plasma samples with a heterogeneous immunological background of the population adds strength to our findings. Indeed, according to the reported data, results may be different when using a pseudovirus instead of a live virus. This underscores once again the importance of having data with authentic live viruses.

It should be noted that our study has some limitations. First, we had a low number of sera that were available for the individual groups, especially for those that were exposed to more than

one variant. Most of sera tested here were collected in 2022 or earlier, not covering the exposures to more recent Omicron variants (experiments with immune escape of BQ.1, XBB.1.5, EG.5.1. and JN.1.1 in more recent samples from individuals infected with an XBB-lineage are still ongoing). We also did not include studies on viral fitness and replicative capacity in polarized human airway cells or the induction of innate immune responses of authentic JN.1.1 isolate in comparison to the other Omicron variants (BA.1, BA.2, BA.5.1, BQ.1, XBB.1.5 and EG.5.1), as these experiments are currently ongoing in our laboratory.

In summary, our data show that continuous assessment of newly evolving SARS-CoV-2 VOIs, taking the different groups within the population into account, remains crucial to understand viral strategies to overcome existing immunity. In the case of JN.1 that showed a rapid global increase but no enhanced immune escape, other factors than immune escape seem to be the driving force behind this variant success.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Authorship contributions

M.Bek., and M.E.L performed the experiments and conducted the analysis; K.A., C.A., P.S.R, D.D. and M.Bel helped to carry out some experiments; M.Bek, K.H.F, C.S.E., M.E.Z, S.S., I.G., O.P., M.Bel., and L.K. conducted the clinical studies and/or helped with clinical sample collection; I.E., M.Bek designed and supervised the study; M.Bek., M.E.L and I.E wrote the main manuscript. All authors have contributed to the final version of the manuscript.

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Table 1. Characteristic of vaccinated individuals' samples.

Vaccine	Number of individuals	Sample type	Gender *(M/F)*	Age *mean*	WPLV *Mean weeks (range)*	Date of last vaccination
2x mRNA vaccine	14	Plasma	2/12	51 (36-62)	4 (4-5)	March-May 2021
3x mRNA vaccine	19	Serum	9/10	43 (26-63)	13 (3-22)	November 2021-January 2022

WPLV weeks post last dose of vaccine.

Table 2. Characteristic of hybrid immunity (breakthrough with BA.1 or BA.2) individuals' samples.

Vaccination/infection status	Number of individuals	Sample type	Gender *(M/F)*	Age *mean*	WPLV *Mean weeks (range)*	WPP *Mean weeks (range)*	Interval vaccination – infection Mean weeks (range)	Variant identification*
2x mRNA vaccine & BA.1 breakthrough	11	Serum	5/6	39 (25-55)	34 (12-52)	15 (2-15)	27 (8-41)	Sequencing (n=11)

3x mRNA vaccine & BA.2 breakthrough	11	Serum	5/6	39 (25-62)	22 (15-35)	7 (3-10)	15 (5-32)	Sequencing (n=11)

WPLV weeks post last dose of vaccine; *WPP* weeks post positive RT-PCR; * the infecting variant of each episode was determined by sequencing of the diagnostic samples.

Table 3. Characteristic of multi-VOC infected individuals' samples.

Vaccination/infection status	**Number of individuals**	**Sample type**	**Gender**	**Age**	**WPLV**	**WPLP**	**Interval vaccination – last infection**	**Variant identification****	
			(M/F)	***mean***	***Mean weeks (range)***	***Mean weeks (range)***	**Mean weeks (range)**	**Alpha or Delta**	**Omicron**
Vaccination* + Alpha & Omicron breakthrough	9	Serum	5/4	41 (25-50)	42 (30-64)	17 (10-29)	25 (12-44)	Sequencing (n=3)	Sequencing (n=5)
Vaccination* + Delta & Omicron breakthrough	9	Serum	3/6	40 (29-51)	53 (27-87)	21 (4-41)	31 (18-55)	Sequencing (n=6)	Sequencing (n=1)

*Vaccination consisted of either 1 (n=6), 2 (n=10) or 3 (n=2) doses of BNT162b2 or mRNA-1273 vaccine. *WPLV* weeks post last dose of vaccine; *WPLP* weeks post last positive RT-PCR; ** the infecting variant of each episode was either determined by sequencing of the diagnostic samples or extrapolated according to the dominance of the variant at that time based on the data from our Swiss national genomic surveillance (Figure S1).

Table 4. Characteristic of convalescent children and adults' individuals' samples.

Infecting virus	Number of individuals	Sample type	Gender *(M/F)*	Age *mean*	WPD Mean days (range)	Infection period	Variant identification*
Omicron in adults	12	Serum	2/10	40 (28-46)	15 (9-21)	January-March 2022	Extrapolated (n=12)
Omicron in children	12	Serum	6/6	5 (2-7)	17 (12-21)	January-March 2022	Extrapolated (n=12)

WPD weeks post Diagnosis; *The infecting variant of each episode was extrapolated according to the dominance of the variant at that time based on the data from our Swiss national genomic surveillance (Figure S1). Individuals were infected between January and March 2022 when the predominant circulation of Omicron BA.1 and BA.2 were taking place (<90%).

Figures

Figure 1. Neutralization in vaccine and hybrid immunity-derived blood specimens against eight authentic isolates of SARS-CoV-2 variants (B.1 and Omicron lineages including BA.1, BA.2, BA.5.1, BQ.1, XBB.1.5, EG.5.1 and JN.1.1). Bars represent geometric mean titers (GMT) of 90% reduction endpoint titers ($FRNT_{90}$) with 95% confidence interval. **A**–**D** Cohorts of individuals with **A)** double-dose mRNA vaccination (n= 14), **B)** boosted mRNA vaccination (n= 19), **C)** Omicron BA.1 breakthrough infection following double mRNA vaccination (n= 11) and **D)** Omicron BA.2 breakthrough infection following 3 mRNA vaccination (n= 11). Colored numbers above bars refer to fold change reduction of GMT versus the B.1 (pre-VOC) variant. Colored numbers below each bar represent the number of specimens with complete loss of neutralization ($FRNT_{90}$ titer < 1). Repeated measures one-way ANOVA with Dunnett's multiple comparisons test using log10 transformed $FRNT_{90}$ titers was performed to analyze the statistical significance.

Figure 2. Neutralization in hybrid immunity-derived blood specimens against eight authentic isolates of SARS-CoV-2 variants (B.1 and Omicron lineages including BA.1, BA.2, BA.5.1, BQ.1, XBB.1.5, EG.5.1 and JN.1.1). Bars represent geometric mean titers (GMT) of 90% reduction endpoint titers ($FRNT_{90}$) with 95% confidence interval. Cohort of vaccinated individuals with dual SARS-CoV-2 infections (e.g. Alpha and Omicron (n=9) or Delta and Omicron (n=9)) (n= 18). Colored numbers above bars refer to fold change reduction of GMT versus the B.1 (pre-VOC) variant. Colored numbers below each bar represent the number of specimens with complete loss of neutralization ($FRNT_{90}$ titer < 1). Repeated measures one-way ANOVA with Dunnett's multiple comparisons test using log10 transformed $FRNT_{90}$ titers was performed to analyze the statistical significance.

Figure 3. Neutralization in infection-derived blood specimens against five authentic isolates of SARS-CoV-2 variants (omicron sublineages including BA.1, BQ.1, XBB.1.5, EG.5.1 and JN.1.1). Bars represent geometric mean titers (GMT) of 90% reduction endpoint titers ($FRNT_{90}$) with 95% confidence interval. **A-B** cohorts of convalescent specimens that are derived from **A** unvaccinated adult individuals (n= 12) and **B** unvaccinated children individuals (n= 12) with confirmed SARS-CoV-2 infection in early 2022 (thus, probably Omicron BA.1 or BA.2). Colored numbers above bars refer to fold change reduction of GMT versus the Omicron BA.1 variant. Colored numbers below each bar represent the number of specimens with complete loss of neutralization ($FRNT_{90}$ titer < 1). Repeated measures one-way ANOVA with Dunnett's multiple comparisons test using log10 transformed $FRNT_{90}$ titers was performed to analyze the statistical significance.

Figure 4. Heatmap of fold-reduction in neutralization based on $FRNT_{90}$ data. Values of fold-reduction in neutralization ($FRNT_{90}$) of B.1 and Omicron sublineages including BA.1, BA.2, BA.5.1, BQ.1, XBB.1.5, EG.5.1 and JN.1.1 are presented as heat maps with lighter colors implying greater changes. The immune sera/plasma were organized into cohorts of individuals with double-dose mRNA vaccination (n = 14), boosted individuals with three doses of mRNA vaccine (n= 19), Omicron BA.1 breakthrough infection of double-vaccinated individuals (n= 11), Omicron BA.2 breakthrough infection individuals following 3 doses of mRNA vaccine (n= 11) and vaccinated Individuals with dual SARS-CoV-2 Infections (n= 18).

Figure S1. Trend of SARS-CoV-2 variants in Switzerland over time. From December 2020 until September 2023: from left to right, Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617), Omicron BA.1, Omicron BA.2, Omicron BA.5, Omicron BQ.1 and Omicron XBB.1.5 SARS-CoV-2 variants (https://cov-spectrum.org/explore/Switzerland/AllSamples/Past6M).

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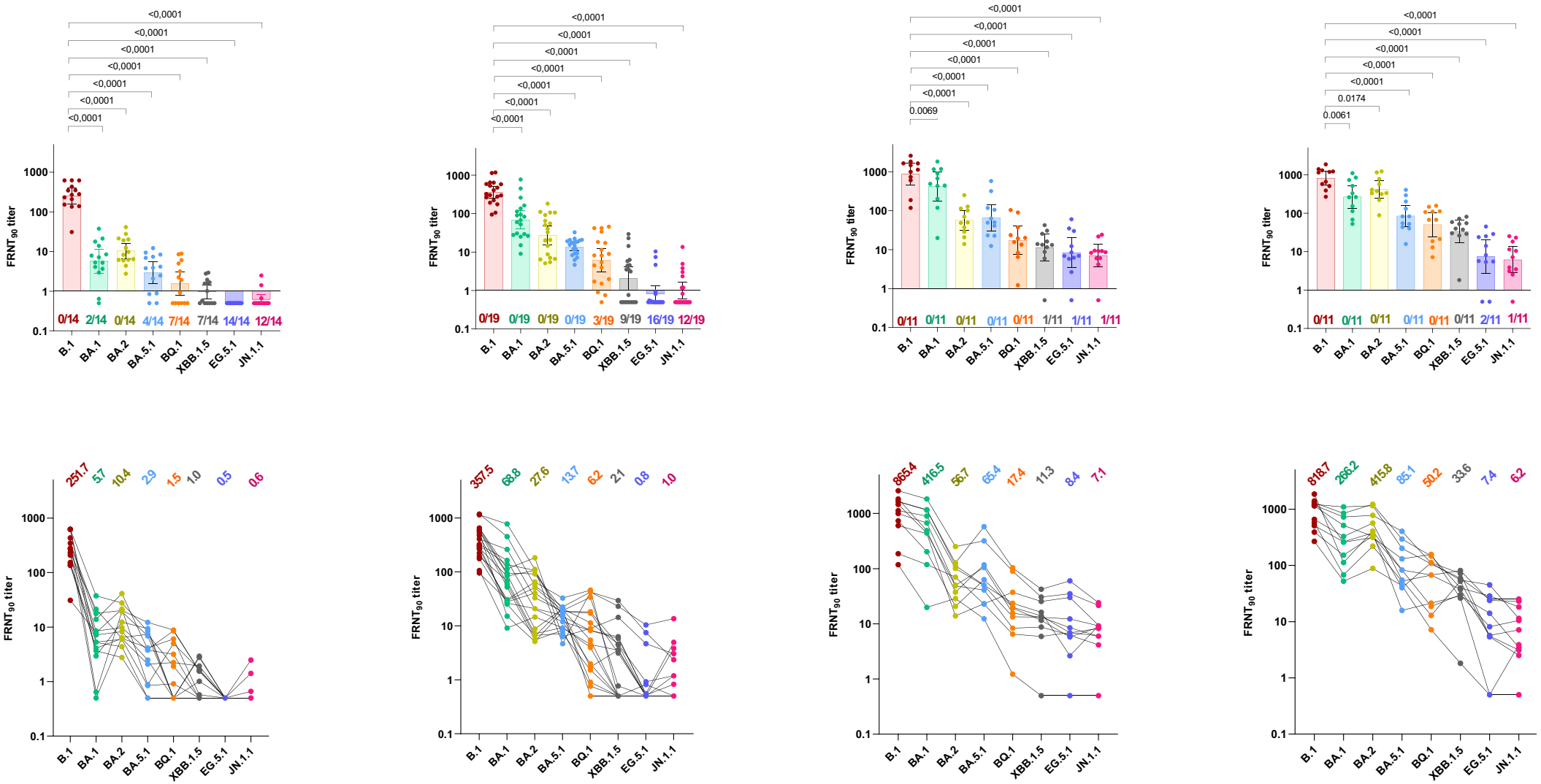
Figure 1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818.7 266.2 415.8 85.1 50.2 33.6 7.4 6.2
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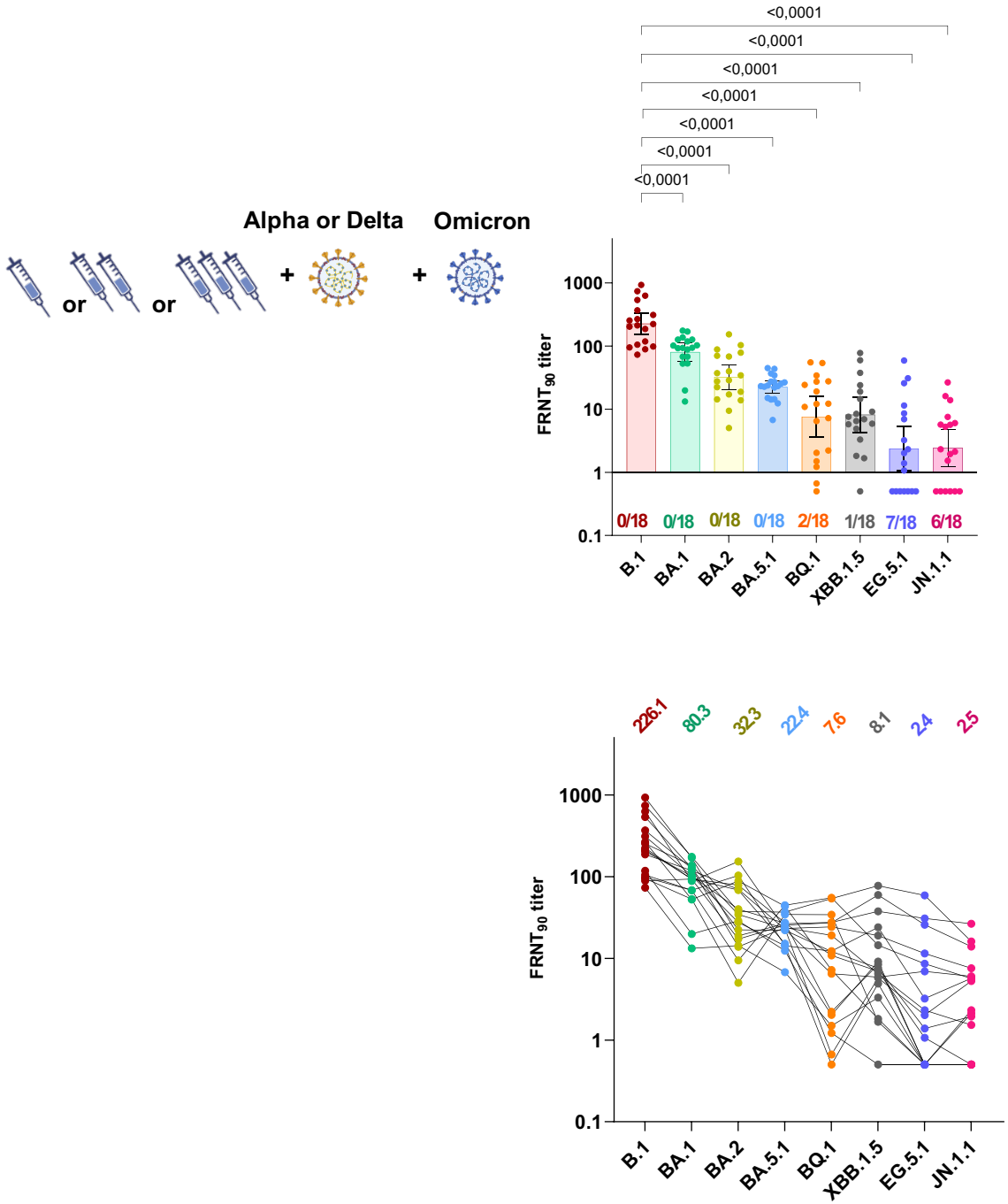
BQ.1
XBB.1.5
EG.5.1
JN.1.1

Figure 2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BA.5.1
BQ.1
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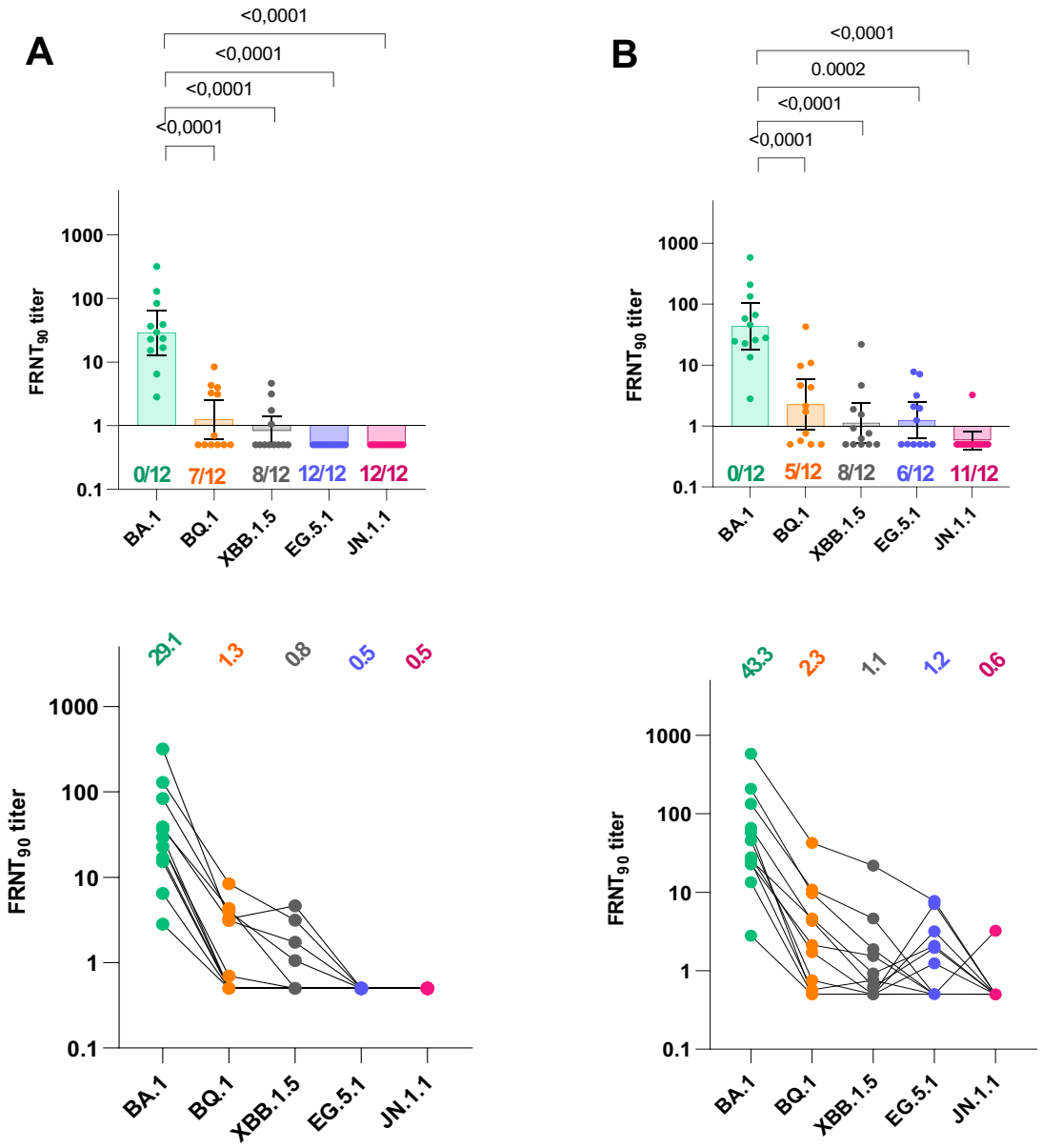
8.1
24
25

Figure 3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BQ.1
XBB.1.5
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JN.1.1
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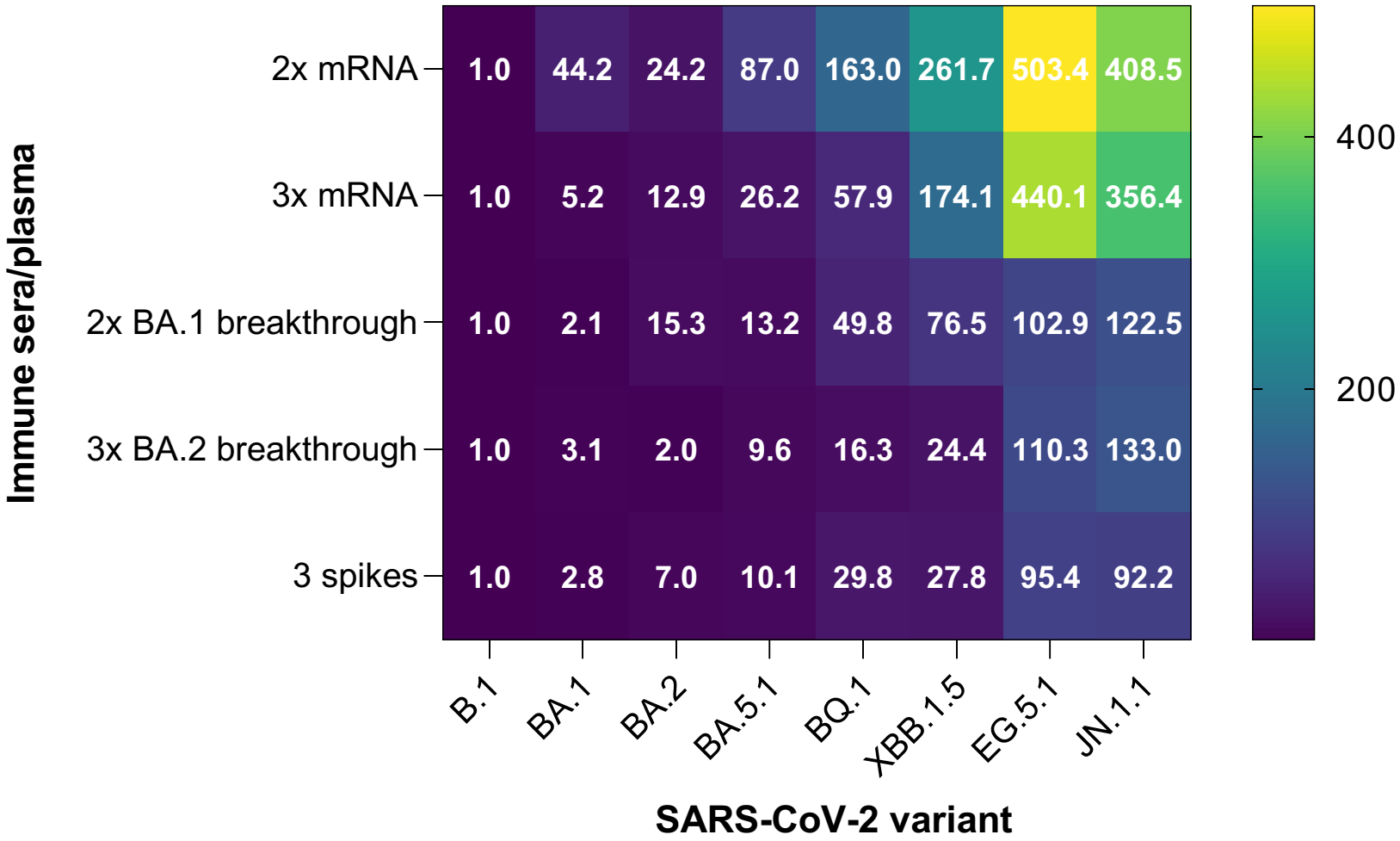
Figure 4


Immune sera/plasma
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3x mRNA
2x BA.1 breakthrough
3x BA.2 breakthrough
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1.0 5.2 12.9 26.2 57.9 174.1 440.1 356.4
1.0 2.1 15.3 13.2 49.8 76.5 102.9 122.5
1.0 3.1 2.0 9.6 16.3 24.4 110.3 133.0
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B.1
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BA.2
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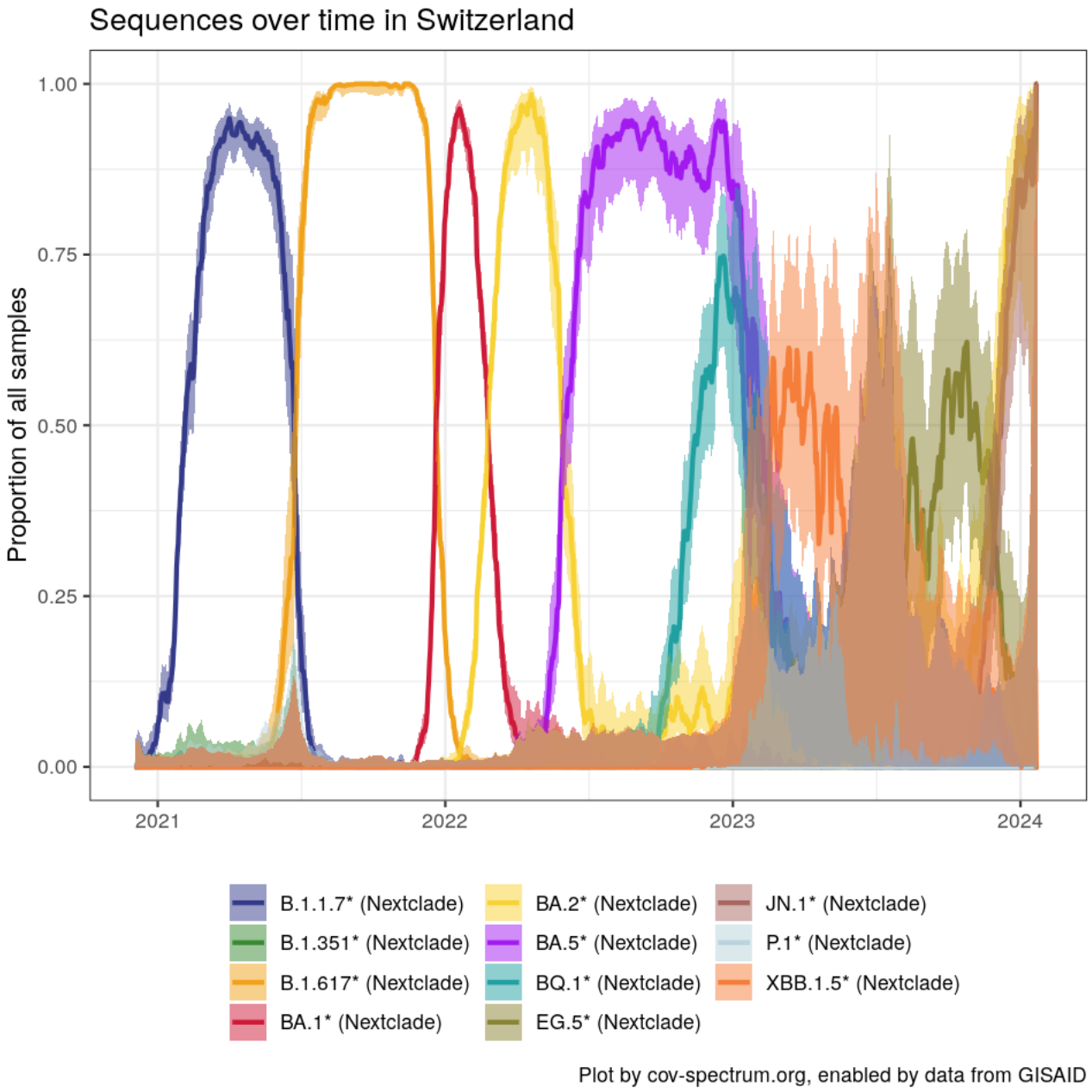
JN.1.1
SARS-CoV-2 variant
400
200

Figure S1.


Sequences over time in Switzerland
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2021
2022
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B.1.351* (Nextclade)
B.1.617* (Nextclade)
BA.1* (Nextclade)
BA.2* (Nextclade)
BA.5* (Nextclade)
BQ.1* (Nextclade)
EG.5* (Nextclade)
JN.1* (Nextclade)
P.1* (Nextclade)
XBB.1.5* (Nextclade)
Plot by cov-spectrum.org, enabled by data from GISAID