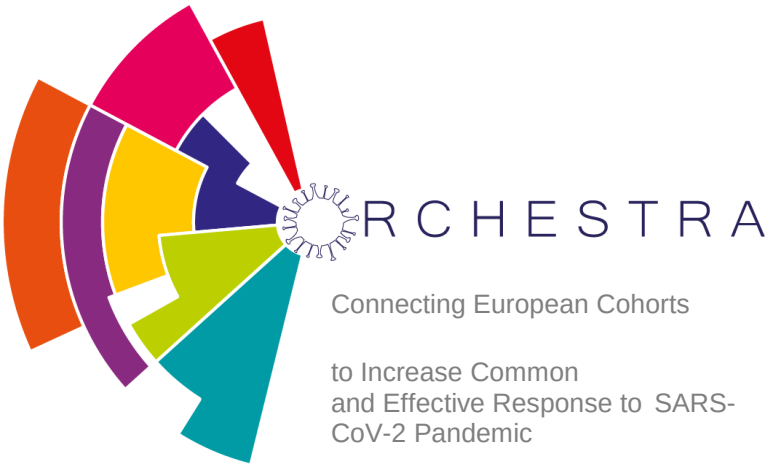

WP6 Deliverable 6.18

Report on viral genome sequences and serology in case of breakthrough infections

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1.0	23/03/2023	Matilda Berkell, Surbhi Malhotra-Kumar, Samir Kumar-Singh (Uantwerpen)

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Executive summary

WP and deliverable context

The present report is part of ORCHESTRA project, a three-year international research project aimed at tackling the coronavirus pandemic. ORCHESTRA provides an innovative approach to learn from the pandemic SARS-CoV-2 crisis, derive recommendations to further management of COVID-19 and be prepared for the possible future pandemic waves. The ORCHESTRA project aims at delivering sound scientific evidence for the prevention and treatment of the infections caused by SARS-CoV-2 assessing epidemiological, clinical, microbiological, and genotypic aspects of population, environment, and socio-economic features. The project builds upon existing, and new large scale population cohorts in Europe (France, Germany, Spain, Italy, Belgium, Romania, Netherlands, Luxemburg, and Slovakia) and non-European countries (India, Perú, Ecuador, Colombia, Venezuela, Argentina, Brazil, Democratic Republic of Congo, and Gabon) including SARS-CoV-2 infected and non-infected individuals of all ages and conditions. The primary aim of ORCHESTRA is the creation of a new pan-European cohort applying homogenous protocols for data collection, data sharing, sampling, and follow-up, which can rapidly advance the knowledge on the control and management of the COVID-19. Within ORCHESTRA project, Work Package 6 (WP6) aims at providing innovative laboratory capabilities combining serology, immunology, viral and human genomes, microbiota, and epigenetic analysis. It aims to describe markers and physiopathology of various COVID-19 outcomes including severe cases, long COVID and vaccine efficiency across various patient populations gathered within ORCHESTRA cohorts.

The objectives of WP6 are distributed in two parts: (1) a retrospective part on frozen samples obtained during 2020 and (2) a prospective part starting in 2021. The goal for the analyses of viral variants and serological markers is to allow description of circulating SARS-CoV-2 variants (both known variants and novel mutations) according to epidemics waves, stages of SARS-CoV-2 infection (mild vs severe) and setting (outpatients vs hospitalized), and to correlate it with serological data against SARS-CoV-2.

Content of the document

The present report describes serum anti-Spike (S), anti-Nucleocapsid (N), and anti-RBD (ribosomal binding domain) titres in patients with varying degrees of COVID-19 disease severity as well as the infecting SARS-CoV-2 clones and their viral loads in the context of the prospective studies within ORCHESTRA. Specifically, this report focuses on the different serological responses in patients with primary infection compared to those experiencing a breakthrough infection, defined by patients having received at least two doses of an anti-SARS-CoV-2 mRNA vaccine ≥ 14 days prior to COVID-19 diagnosis. Presently, the report is focused on the responses experienced shortly after diagnosis. It is also the objective of WP6 to study serological responses longitudinally and correlate with SARS-CoV-2 variants in patients within the two infection groups, however, presently only timepoints after the infection have been fully addressed. A final report on viral variants/serology for breakthrough, primary versus incidental SARS-CoV-2 infections will be provided at the end of the project.

Dissemination level: Public

Core content

Detailed description of the conducted tests

Sample collection

Patient cohorts in which samples were collected for this deliverable include patients with a microbiologically confirmed SARS-CoV-2 infection, including patients with mild, moderate, and severe COVID-19. Nasopharyngeal swab (NPS) and serum samples were collected in Verona (UNIVR, Italy), Bologna (UNIBO, Italy), and Seville (SAS, Spain) during the initial stages of COVID-19 infection. Additional serum samples were collected as 3 (M3), 6 (M6), 12 (M12), and 18 months after infection (M18). Collected samples were then transferred to Uantwerpen (Belgium) for analysis within WP6 of viral loads (RT-qPCR), strain typing (SARS-CoV-2 whole genome sequencing), and longitudinal assessment of humoral immune responses to infection for this deliverable.

RNA extraction, cDNA conversion, and SARS-CoV-2 whole genome sequencing

RNA was extracted using the MagMAX Viral/Pathogen II Nucleic acid kit on a KingFisher Flex Purification System (ThermoFisher). Each batch of samples taken forward for extraction was processed together with a Twist synthetic SARS-CoV-2 RNA positive Ctrl. 18 (Cat. No: 104338, Twist Bioscience). Extracted RNA was subjected to automated cDNA conversion and multiplexed library preparation using the Illumina COVIDSeq Test kit (Illumina Inc.) on a Zephyr G3 NGS system (PerkinElmer, MA, USA). DNA concentrations were quantified using the Qubit dsDNA HS Assay Kit (Invitrogen, Cat. No. Q33231) using a Qubit Fluorometer 3.0 (ThermoFisher). Pooled libraries were sequenced utilizing the High Output Kit v2 with a 1.4 nM PhiX Library positive control v3 using a 1% spike-in on a NextSeq 500/550 instrument (Illumina Inc.). All steps were performed according to manufacturer's instructions.

SARS-CoV-2 RT-qPCR

Real-Time RT-qPCR was performed using the TaqPath™ COVID-19 CE-IVD RT-PCR Kit (ThermoFisher) on a QuantStudio™ 5 Real Time PCR instrument (384-well block, 5 colors, ThermoFisher), which detects three genes in the SARS-CoV-2-viral genome: the S protein, N protein, and ORF1ab. MS2 (phage control) was added to each sample prior to RNA extraction to serve as internal control. RT-qPCR analysis was performed using FastFinder (UgenTec). Samples were considered positive if both the MS2 phage control (Ct < 32) and at least two gene targets were detected (Ct < 37).

SARS-CoV-2 variant detection

Raw sequencing data quality for each sample was assessed using FastQC (https://www.bioinformatics.babraham.ac.uk/projects/fastqc/) followed by quality trimming using a Phred score cut-off of 25 with TrimGalore v. 0.6.7 (https://github.com/FelixKrueger/TrimGalore). Read mapping was performed against the Wuhan-Hu-1 SARS-CoV-2 genome (GenBank: NC_045512.2) using the CLC Genomics Workbench v.9.5.3 (Qiagen) with a length and a similarity fraction of 0.5 and 0.8, respectively. Consensus sequences were extracted, and clade and lineage assignment performed using Nextstrain (https://clades.nextstrain.org/) and Pangolin (https://pangolin.cog-uk.io/), respectively.

Serology

IgG titres were measured in serum samples using V-PLEX SARS-CoV-2 Panels 2 and Panel 6 Kits (IgG) from Meso Scale Discovery (MSD, MD, USA) according to the manufacturer's instructions. Briefly, 96-well plates were blocked with MSD blocking buffer A for 30 minutes and washed three times with PBS-Tween (0.05%). Samples were diluted 1:10,000 or 1:25,000 in Diluent 100 (MSD), incubated for two hours in the prepared plates, and subsequently washed three times. Detection antibody with a sulfo-tag was added and after a one-hour incubation, plates were washed and read with MSD Gold Read Buffer B on the QuickPlex SQ 120 (MSD). Quantitative IgG results were measured in Antibody

Units (AU)/mL, converted to WHO Binding Antibody Units (BAU)/mL using a conversion factor provided by MSD.

Stratification of IgG responses

Antibody responses were stratified into the groups based on the quantitative IgG measurements as described in **Table 1**.

Table 1. Stratification of quantitative IgG results.

	Negative	Inconclusive	Low	Medium	High	Units
anti-Spike	<4.76	4.76 - <53	53 - <241	241 - <832	>832	BAU/mL
anti-RBD	<5.58	5.58 - <45	45 - <205	205 - <817	>817	BAU/mL
anti-N	<8.20	8.20 - <12	12 - <295	295 - <713	>713	BAU/mL

The upper limit for “Negative” was determined as the average plus one standard deviation of anti-Spike IgG measurements in 50 serum samples collected before 2019. The lower limits for “Low”, “Medium” and “High” were based on the BAU/mL concentrations of “Low” (NIBSC code 20/140), “Mid” (NIBSC code 20/148) and “High” (NIBSC code 20/150) WHO International Standards for anti-SARS-CoV-2 immunoglobulins.

Seroneutralization

ACE2 neutralization was measured in serum samples using V-PLEX SARS-CoV-2 Panel 6 or 13 Kits (ACE2) from Meso Scale Discovery (MSD, MD, USA) according to the manufacturer’s instructions.

Briefly, 96-well plates were blocked with MSD blocking buffer A for 30 minutes and washed three times with PBS-Tween (0.05%). All samples were diluted 1:100 or 1:250, loaded on the plates and incubated for one hour. ACE2 with a sulfo-tag was added and a one-hour incubation, plates were washed and read with MSD Gold Read Buffer B on the QuickPlex SQ 120 (MSD).

Additionally, for Wuhan, Alpha, Beta, Delta, Iota, and Gamma variants, a calibration curve was used to calculate neutralizing antibody concentrations in samples, by backfitting the measured signals for samples to the calibration curve. Neutralising antibody concentrations were measured in Units (U)/mL, which corresponds to neutralizing activity of 1 µg/mL monoclonal antibody to SARS CoV-2 Spike protein and was analysed as such.

Clinical data access and harmonisation

Data collected in this study was performed for patients with: (i) a serum or nasopharyngeal swab sample collected for analysis by WP6, (ii) clinical and patient characteristics data was available, and (iii) it was possible to link patient records to samples IDs received by WP6. Due to the involvement of many partners for collection of the required variables and a delay in reporting, data harmonization of patient-sample IDs and vaccination dates was particularly difficult in this project. Additionally, certain WP2 cohorts required agreements in addition to those implemented within the ORCHESTRA consortium to facilitate clinical data sharing within the project, further delaying access for WP6 analyses.

Key findings

Patient characteristics

Overall, 2566 patients with either a collected NPS or serum sample collected for analysis by WP6 with associated patient data were available for analysis for this deliverable. Patients where the date of COVID-19 diagnosis was unknown were excluded from further analysis (n = 117). As expected, the vast majority constituted primary infection cases in this study (78.6%), whereas 16.8% constituted breakthrough infections (**Table 2**).

Table 2. The number of patients available for analysis for each infection type. Patients without a recorded SARS-CoV-2 test date or vaccination date were grouped under "unclassified".

Type of infection	N (%)
Primary infection	2017 (78.6)
Breakthrough infection	432 (16.8)
Unclassified	117 (4.6)
Total	**2566**

Viral variants causing breakthrough infection

Of the total 2566 patients, SARS-CoV-2 whole genome sequencing was successfully performed, and the infecting viral variant could be identified for a total of 892 patients. As expected, most diagnosed cases (77.7%) cases constituted a primary infection compared to 22.3% constituting breakthrough infection cases (**Table 3**). Most of the recorded COVID-19 infections were with variants of concern (VOCs), where the rates of breakthrough infections increased over time. Patients infected by Alpha sub-lineages were primarily unvaccinated (98.3%), while patients infected with Delta and Omicron sub-lineages displayed higher frequencies of breakthrough cases (19.0%-33.3% and 36.1%-50.0%, respectively). These observations correlate well with the timeframe of the COVID-19 diagnoses and emergence of sub-lineages in relation to the rollout of the vaccination programs in Spain and Italy from where the samples were obtained.

When comparing viral loads in patients with primary and breakthrough infections, no significant differences were observed in Delta- and Omicron-infected patients (**Figure 1**). However, the viral loads were found to increase gradually over time with higher loads in Omicron-infected patients compared to those observed in Delta- and Alpha-infected patients (**Figure 2** and **Figure 3**).

Table 3. SARS-CoV-2 lineages split by infection type. Note that for certain clades (19A, 20A, 20B, 20C, 20D, 20E/EU1) additional samples have been processed and reported previously in D6.3 and D6.8.

SARS-CoV-2 lineage	Primary infection (%)	Breakthrough infection (%)	N
19A	3 (60.0)	2 (40.0)	5
20A	9 (69.2)	3 (23.1)	13
20B	5 (100.0)	0 (0.0)	5
20C	1 (50.0)	1 (50.0)	2
20D	1 (100.0)	0 (0.0)	1
20E/EU1	3 (100.0)	0 (0.0)	3
20I/Alpha	169 (98.3)	0 (0.0)	172
21A/Delta	4 (66.7)	2 (33.3)	6
21I/Delta	46 (79.3)	11 (19.0)	58
21J/Delta	325 (73.5)	108 (24.4)	442
21K/Omicron	108 (63.9)	61 (36.1)	169
21L/Omicron	5 (41.7)	6 (50.0)	12
21M/Omicron	2 (50.0)	2 (50.0)	4
Total	**681 (77.7)**	**196 (22.3)**	**877**

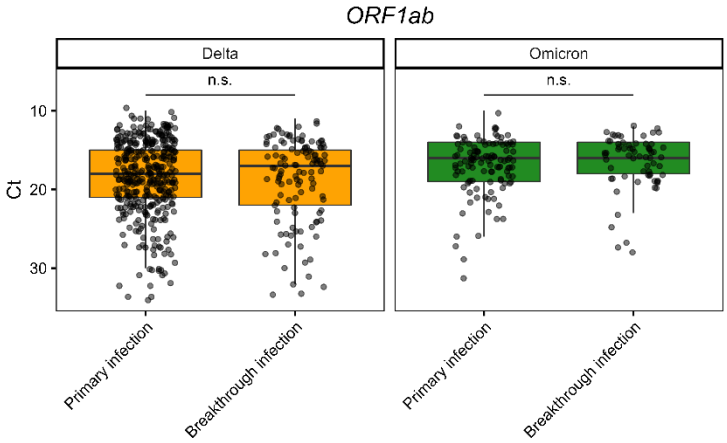


Figure 1. SARS-CoV-2 viral loads inferred by RT-qPCR detection of the ORF1ab gene in COVID-19 patients with primary and breakthrough infections caused by Delta and Omicron sub-lineages (N = 691). Box plots indicate median (middle line), 25th, 75th percentile (box), and 5th and 95th percentile (whiskers). All data points, including outliers, are displayed. **: p < 0.01. ***: p < 0.001. n.s.: non-significant.

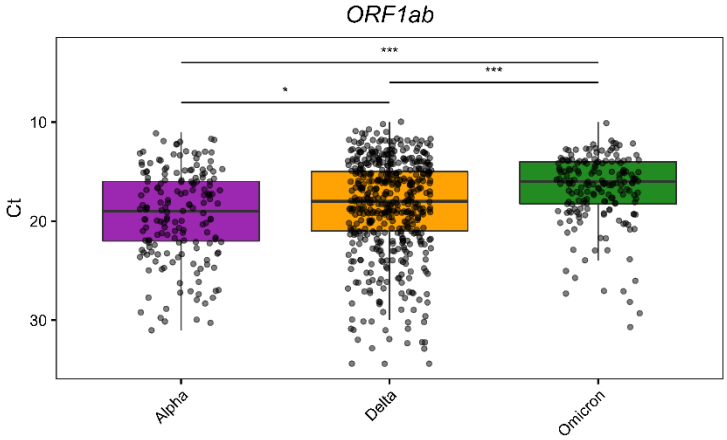


Figure 2. SARS-CoV-2 viral loads inferred by RT-qPCR detection of the ORF1ab gene in COVID-19 patients infected by variants of concern (VOCs, N = 840). Box plots indicate median (middle line), 25th, 75th percentile (box), and 5th and 95th percentile (whiskers). All data points, including outliers, are displayed. **: p < 0.01. ***: p < 0.001. n.s.: non-significant.

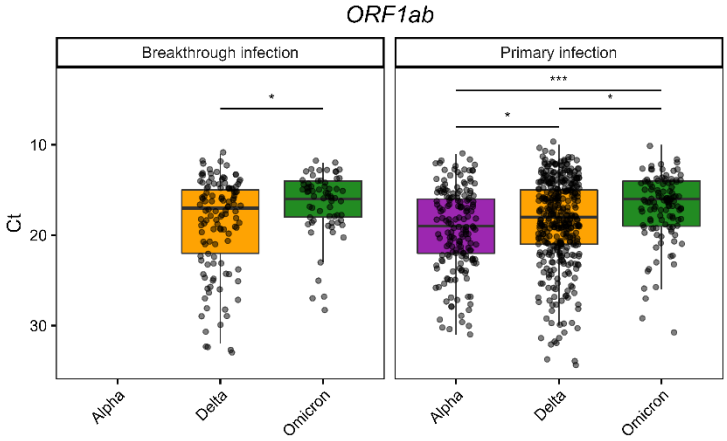


Figure 3. SARS-CoV-2 viral loads inferred by RT-qPCR detection of the ORF1ab gene in COVID-19 patients with primary and breakthrough infections caused by variants of concern (VOCs, N = 840). Box plots indicate median (middle line), 25th, 75th percentile (box), and 5th and 95th percentile (whiskers). All data points, including outliers, are displayed. **: p < 0.01. ***: p < 0.001. n.s.: non-significant.

Serology results

Of the available patients, 1160 provided serum samples during COVID-19 infection (T0) that were further analysed to assess anti-N, anti-S, and anti-RBD titres in response to primary and breakthrough infections (**Table 4**). Patients experiencing breakthrough infections displayed significantly higher anti-S and anti-RBD titres compared to primary infection patients, while anti-N titres were comparable between both patient groups (**Figure 4**). These data support the augmented humoral responses observed in patients with history of both vaccination and infection, when compared to patients without vaccination. Serum IgG was further studied in Delta- and Omicron-infected patients and showed similar trends in anti-S and anti-RBD titres, these differences were not sufficient to be significant (**Figure 5**).

Table 4. Overview of COVID-19 patients with primary and breakthrough infections providing serum samples during ongoing infection (T0), as well as after 3-month (M3), 6-month (M6), 12-month (M12), and 18-month (M18) follow-up. Patients without a recorded SARS-CoV-2 test date or vaccination date were grouped under “unclassified”.

Timepoint	Primary infection	Breakthrough infection	Unclassified	N
T0	834	294	32	1160
M3	150	13	15	178
M6	480	18	18	516
M12	615	2	24	641
M18	176	3	17	196
Total	2255	330	106	2691

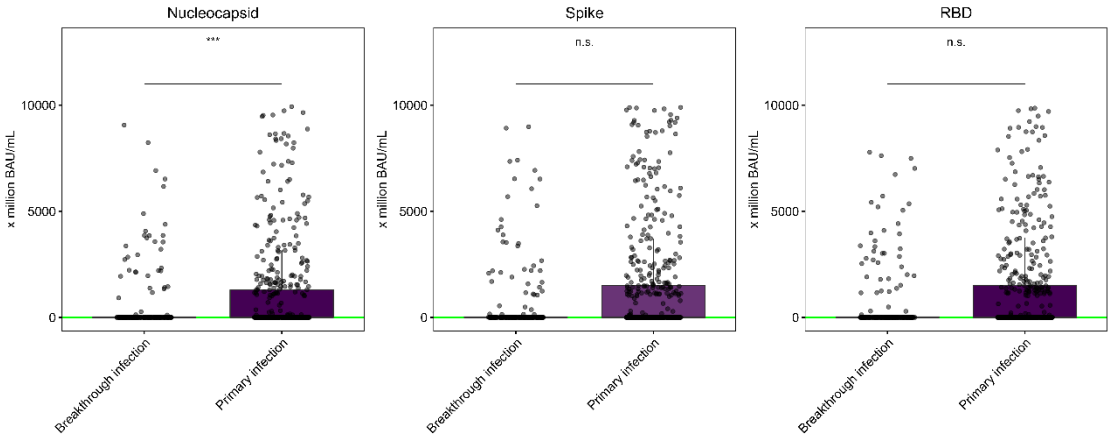


Figure 4. Anti-N, anti-S, and anti-RBD serology titers of COVID-19 patients during primary or breakthrough infection. Red, green, and blue lines indicate SARS-CoV-2 WHO reference standard values for low, medium, and high antibody titers, respectively. Box plots indicate median (middle line), 25th, 75th percentile (box), and 5th and 95th percentile (whiskers). All data points, including outliers, are displayed. **: $p < 0.01$. ***: $p < 0.001$. n.s.: non-significant. BAU: Binding antibody units.

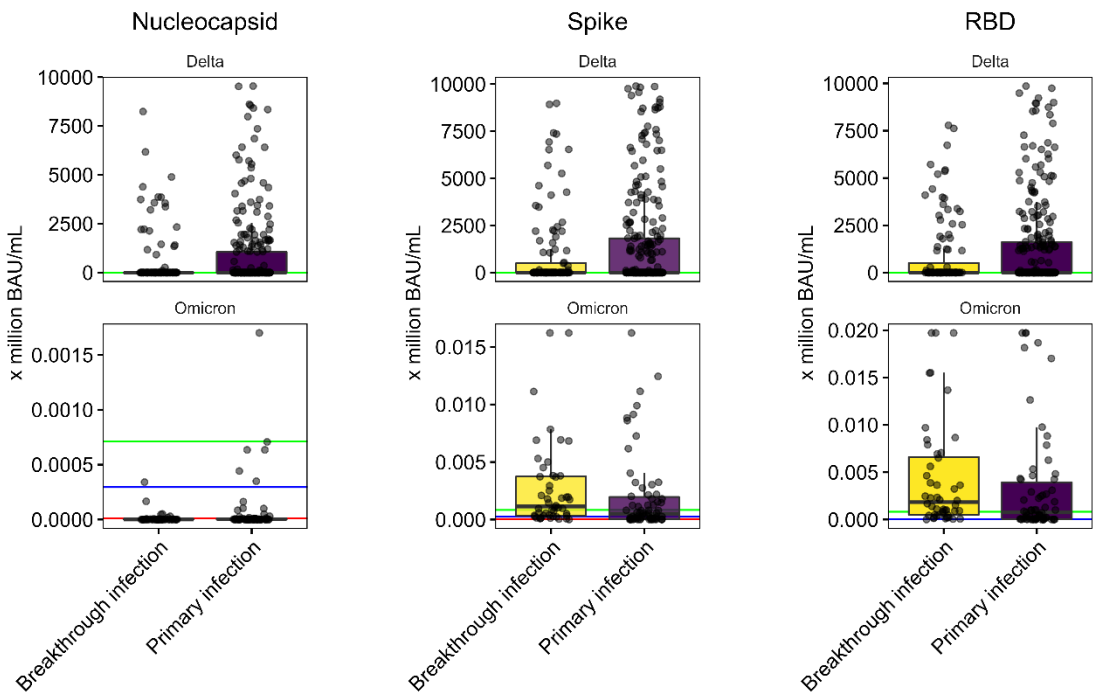
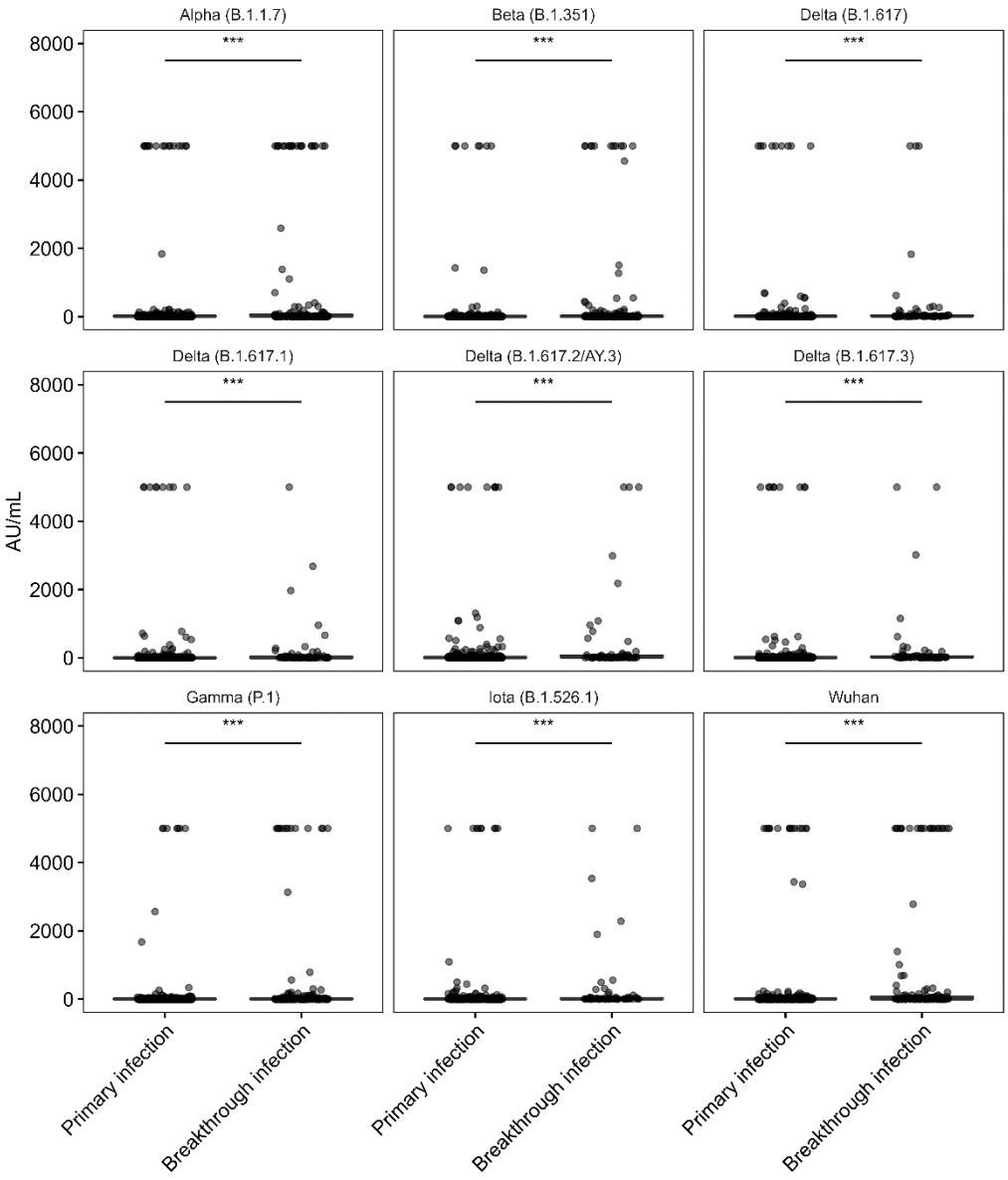


Figure 5. Anti-N, anti-S, and anti-RBD serology titers of COVID-19 patients infected by Delta or Omicron sub-lineages during primary or breakthrough infection. Red, green, and blue lines indicate SARS-CoV-2 WHO reference standard values for low, medium, and high antibody titers, respectively. Box plots indicate median (middle line), 25th, 75th percentile (box), and 5th and 95th percentile (whiskers). All data points, including outliers, are displayed. **: $p < 0.01$. ***: $p < 0.001$. BAU: Binding antibody units.

Seroneutralization

By looking at neutralization capacity of IgGs in serum in COVID-19 patients with primary and breakthrough infections, it was found that patients experiencing a breakthrough infection displayed higher neutralization capacity overall against the Wuhan strain as well as several VOCs, including Alpha, Beta, and Delta (**Figure 6**). When stratifying patients based on the infecting SARS-CoV-2 variant, a similar trend was observed for Delta-infected patients, but that these differences were not sufficient to be significant (**Figure 7** and **Figure 8**). Omicron-infected patients were not found to follow the same pattern (**Figure 9**), likely due to the limited number of patients with a primary COVID-19 infection in this dataset.

A



B

SARS-CoV-2 variant	N	Primary infection (AU/mL)	Breakthrough infection (AU/mL)	Kruskal-Wallis p-value
Wuhan	667	1.74 (1.74 - 14.55)	2.58 (2.58 - 72.82)	1.96e-05
Alpha (B.1.1.7)	667	2.81 (2.81 - 12.82)	3.39 (3.39 - 61.56)	2.288e-05
Beta (B.1.351)	667	0.13 (0.13 - 7.38)	1.31 (1.31 - 22.44)	8.4e-06
Delta (B.1.617)	431	2.67 (2.67 - 16.06)	11.36 (11.36 - 41.15)	6.695e-08
Delta (B.1.617.1)	431	0.13 (0.13 - 9.88)	4.36 (4.36 - 38.70)	0.0003911
Delta (B.1.617.2/AY.3)	431	0.13 (0.13 - 24.22)	13.61 (13.61 - 77.10)	1.645e-05
Delta (B.1.617.3)	431	2.05 (2.05 - 19.73)	13.82 (13.82 - 42.37)	4.601e-08
Gamma (P.1)	667	0.13 (0.13 - 6.10)	0.13 (0.13 - 22.33)	4.239e-05
Iota (B.1.526.1)	431	1.56 (1.56 - 11.75)	4.90 (4.90 - 37.85)	4.805e-05

Figure 6. Serum anti-S neutralization capacity measured against Wuhan, Alpha, Beta, Delta, Gamma, and Iota variants in COVID-19 patients with primary or breakthrough infections displayed as boxplots **(A)** and median serum titres (interquartile ranges) **(B)**. Box plots indicate median (middle line), 25th, 75th percentile (box), and 5th and 95th percentile (whiskers). All data points, including outliers, are displayed. Statistical significance was determined using Kruskal-Wallis. ***: $p < 0.001$. AU: antibody units.

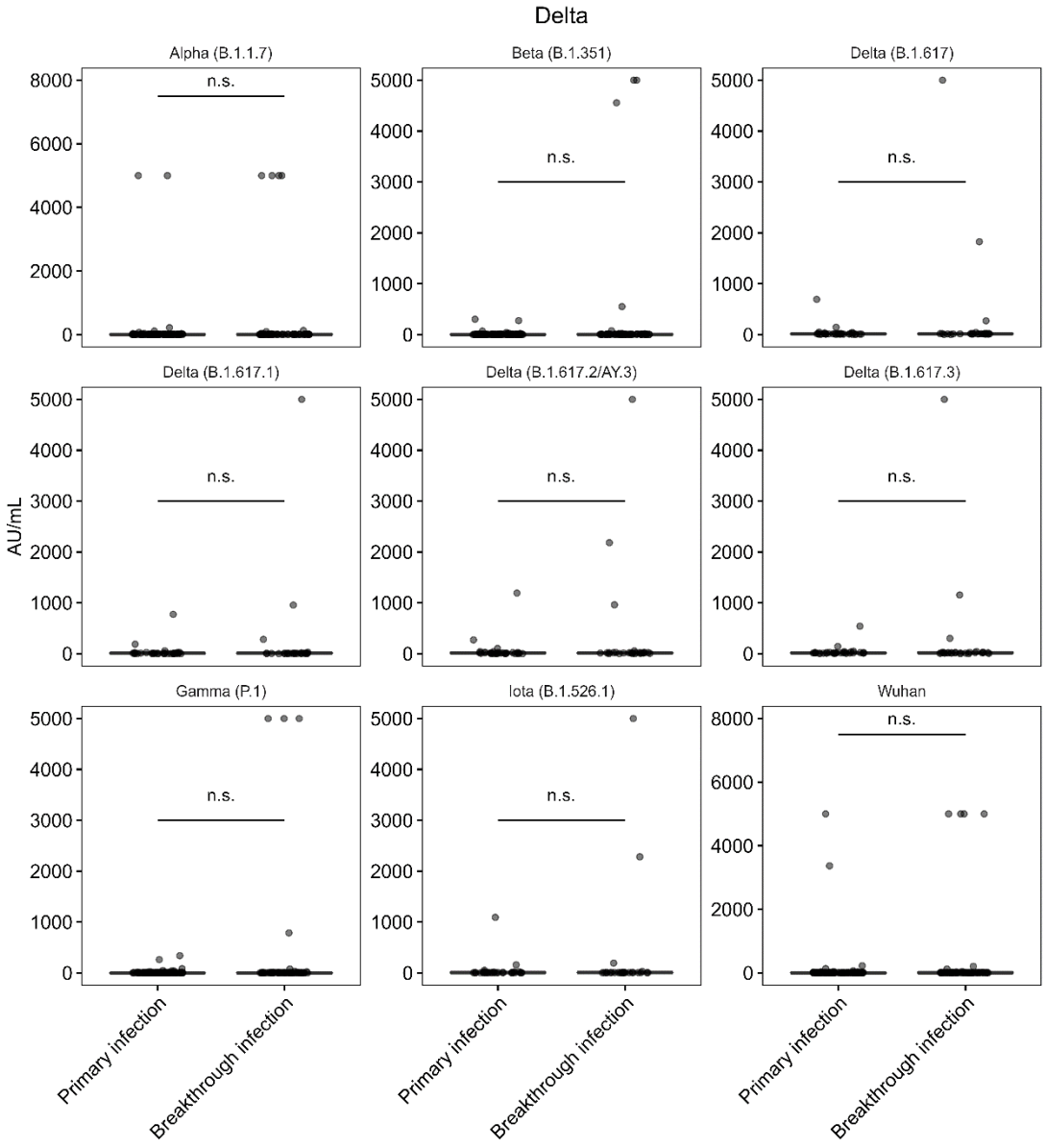
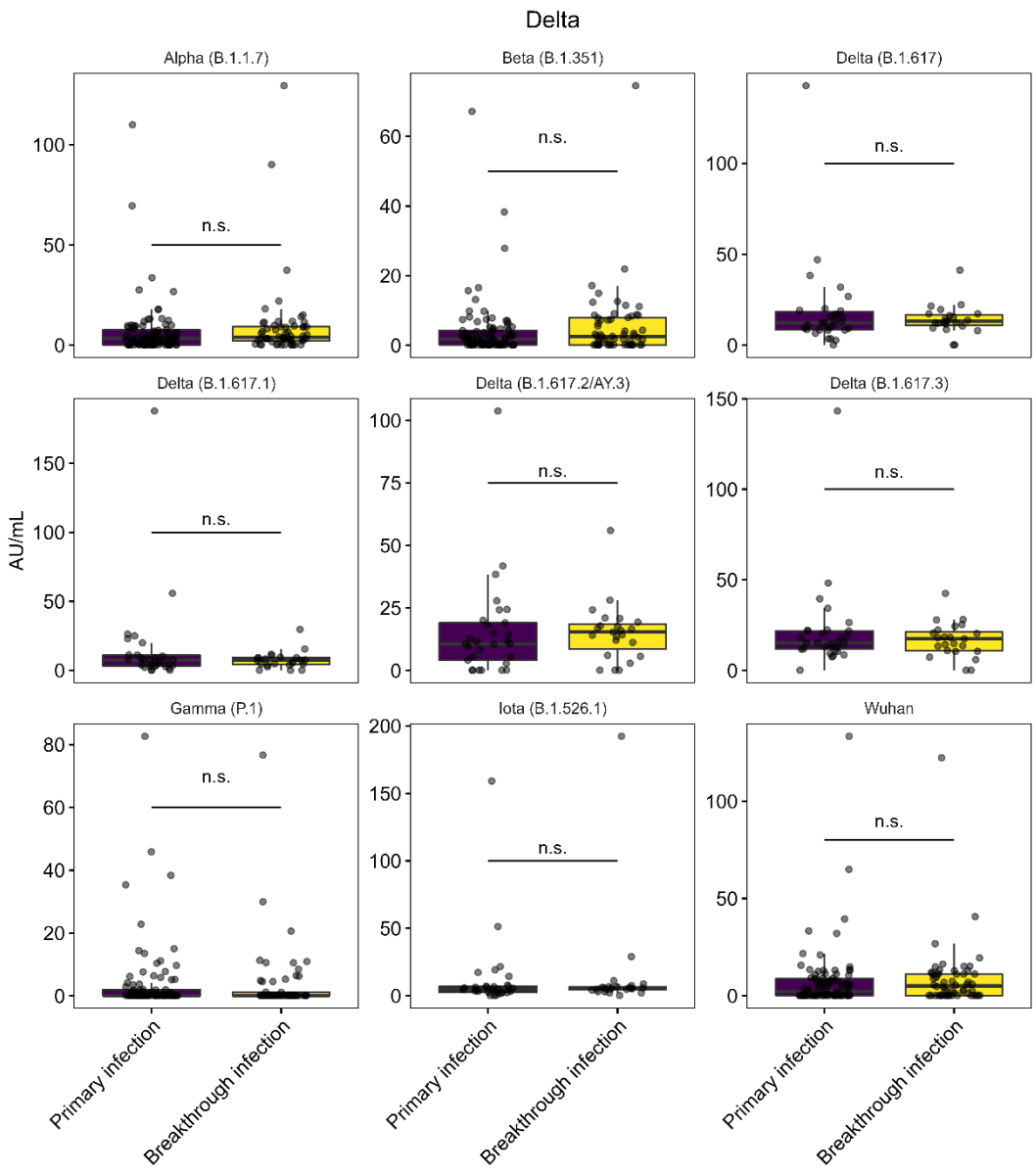


Figure 7. Serum anti-S neutralization capacity measured against Wuhan, Alpha, Beta, Delta, Gamma, and Iota variants in COVID-19 patients with primary or breakthrough infections caused by Delta sub-variants. Box plots indicate median (middle line), 25th, 75th percentile (box), and 5th and 95th percentile (whiskers). All data points, including outliers, are displayed. Statistical significance was determined using Kruskal-Wallis. Only patients for which a successfully sequenced SARS-CoV-2 genome was obtained are displayed in the plot. n.s.: non-significant. AU: antibody units.

A

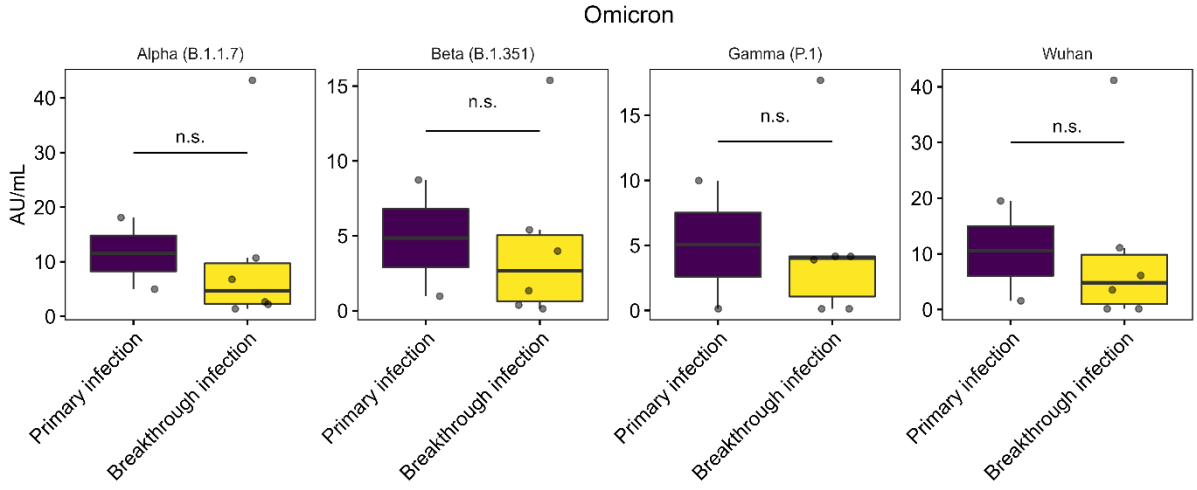


B

SARS-CoV-2 variant	N	Primary infection (AU/mL)	Breakthrough infection (AU/mL)	Kruskal-Wallis p-value
Wuhan	**156**	0.13 (0.13 - 9.06)	0.13 (0.13 - 12.89)	n.s.
Alpha (B.1.1.7)	**156**	0.13 (0.13 - 8.98)	2.37 (2.37 - 10.97)	n.s.
Beta (B.1.351)	**157**	0.13 (0.13 - 4.61)	0.13 (0.13 - 8.63)	n.s.
Delta (B.1.617)	**58**	8.46 (8.46 - 19.05)	11.70 (11.70 - 19.00)	n.s.
Delta (B.1.617.1)	**58**	3.28 (3.28 - 11.19)	4.64 (4.64 - 10.70)	n.s.
Delta (B.1.617.2/AY.3)	**58**	4.78 (4.78 - 22.16)	11.43 (11.43 - 20.96)	n.s.
Delta (B.1.617.3)	**58**	11.81 (11.81 - 21.97)	11.54 (11.54 - 25.09)	n.s.
Gamma (P.1)	**156**	0.13 (0.13 - 2.94)	0.13 (0.13 - 4.88)	n.s.
Iota (B.1.526.1)	**58**	2.46 (2.46 - 7.40)	4.75 (4.75 - 7.29)	n.s.

Figure 8. Serum anti-S neutralization capacity measured against Wuhan, Alpha, Beta, Delta, Gamma, and Iota variants in COVID-19 patients with primary or breakthrough infections caused by Delta sub-variants displayed as box plots **(A)** and median serum titres (interquartile ranges) **(B)**. Box plots indicate median (middle line), 25th, 75th percentile (box), and 5th and 95th percentile (whiskers). Patients with AU/mL > 200 are not displayed in (A). Statistical significance was determined using Kruskal-Wallis. Only patients for which a successfully sequenced SARS-CoV-2 genome was obtained are displayed in the plot. n.s.: non-significant. AU: antibody units.

A



B

SARS-CoV-2 variant	N	Primary infection (AU/mL)	Breakthrough infection (AU/mL)	Kruskal-Wallis p-value
Wuhan	8	6.05 (6.05 - 15.02)	0.98 (0.98 - 9.85)	n.s.
Alpha (B.1.1.7)	8	8.26 (8.26 - 14.81)	2.31 (2.31 - 9.71)	n.s.
Beta (B.1.351)	8	2.91 (2.91 - 6.79)	0.62 (0.62 - 5.04)	n.s.
Gamma (P.1)	8	2.59 (2.59 - 7.52)	1.07 (1.07 - 4.16)	n.s.

Figure 9. Serum anti-S neutralization capacity measured against Wuhan, Alpha, Beta, and Gamma variants in COVID-19 patients with primary or breakthrough infections caused by Omicron sub-variants displayed as boxplots **(A)** and median serum titres (interquartile ranges) **(B)**. Box plots indicate median (middle line), 25th, 75th percentile (box), and 5th and 95th percentile (whiskers). All data points, including outliers, are displayed. Statistical significance was determined using Kruskal-Wallis. Only patients for which a successfully sequenced SARS-CoV-2 genome was obtained are displayed in the plot.*: $p < 0.05$. **: $p < 0.01$. ***: $p < 0.001$. AU: antibody units.

Conclusions

Most of the recorded COVID-19 infections were with variants of concern (VOCs), where the rates of breakthrough infections increased over time. Patients infected by Alpha sub-lineages were primarily unvaccinated, while patients infected with Delta and Omicron sub-lineages displayed higher frequencies of breakthrough cases. No significant differences were observed in Delta- and Omicron-infected patients when comparing viral loads in primary and breakthrough infections. However, viral loads were found to increase gradually over time with higher loads in Omicron-infected patients compared to those observed in Delta- and Alpha-infected patients. Further, our analyses show that patients with breakthrough infections who have been fully vaccinated develop a stronger IgG response to SARS-CoV-2 Spike and Spike-RBD compared to primary infection cases, both overall as well as in the case of Delta and Omicron infections, while IgG responses to Nucleocapsid (reflective of natural infection responses) are comparable between infection types. Neutralization capacities of SARS-CoV-2 was also found to be higher among patients with breakthrough compared to primary infections, in line with serological response. As all data could not be reported as yet, we aim to further characterize viral variants and serological responses in patients with breakthrough infections in a separate deliverable, due at the end of the project, with data collected from additional sampling timepoints post infection as well as with data from additional cohorts participating in WP2 of ORCHESTRA.

References

NA

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