High rate of BA.1, BA.1.1 and BA.2 infection in triple vaccinated

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Abstract

Background: Booster vaccine doses offer protection against severe COVID-19 caused by omicron but are less effective against infection. Characteristics such as serological correlates of protection, viral abundance and clearance of omicron infections in triple vaccinated individuals are scarce.

Methods: We conducted a 4-week twice-weekly SARS-CoV-2 qPCR screening shortly after an mRNA vaccine booster in 375 healthcare workers. Anti-Spike IgG levels and neutralization titers were determined at study start. qPCR-positive participants were sampled repeatedly for two weeks and monitored for symptoms.

Result: In total 82 (cumulative incidence 22%) omicron infections were detected, divided between BA.1, BA.1.1 and BA.2. Only 10% of infected participants remained asymptomatic. Viral load peaked at day 3 and live virus could be detected for up to 9 days after first PCR-positive sample. Presence of symptoms correlated to elevated viral load ($p<0.0001$), but despite resolution of symptoms most participants showed Ct levels <30 at day 9. While post-booster antibody titers were similar in those with and without subsequent breakthrough infection ($p>0.05$), high antibody titers were linked to reduced viral load ($p<0.01$) and time to viral clearance ($p<0.01$). No significant differences were observed for viral load and time to viral clearance between BA.1, BA.1.1 and BA.2 infected individuals.

Conclusion: We report high incidence of omicron infections despite recent booster vaccination in triple vaccinated individuals. Vaccine-induced antibody titres seem to play a limited role in risk of omicron infection. High viral load and secretion of live virus for up to nine days may increase transmission in a triple vaccinated population.

Introduction

The SARS-CoV-2 B.1.1.529 (omicron) variant has caused a considerable surge in Covid-19 cases, including in populations with high vaccine uptake [1]. While the now widely administered booster mRNA vaccine (third doses) have been shown to be effective against severe Covid-19 [1 2] caused by omicron, protection against infection appears limited and not sufficient to prevent viral transmission [3]. Vaccine induced serological responses correlated well with the risk of infection with the ancestral virus and pre-omicron SARS-CoV-2 variants of concern [4-7], but less is known regarding correlations between serological responses and protection against omicron infection.

The omicron surge has been caused by sublineages including BA.1, BA.1.1 and BA.2 [8]. Real worl data show that BA.2 carries a transmission advantage, taking over as the dominating sublineage in several countries [9]. Mutations in the antibody target spike protein distinguish the omicron sublineages from each other, but *in vitro* neutralization data suggest similar vaccine induced neutralizing capacity against BA.1 and BA.2 [10]. Viral characteristics and variations in viral abundance and clearance between the sublineages are, however, not fully characterized [11-13].

Here we investigated breakthrough infections in triple-vaccinated healthcare workers (HCW) with and without prior SARS-CoV-2 infection. During the study period BA.1, BA.1.1 and BA.2 circulated in Stockholm, Sweden, allowing for a comparison of breakthrough infections with the three sublineages [8]. Serological correlates of protection against infection, symptoms and viral RNA trajectories were analyzed.

Remarkably, 22% of study participants became infected during the study period, with no significant impact of pre-infection antibody titers. Viral RNA trajectories were similar and suggestive of infectivity by all omicron sublineages, implying that three vaccine doses offer limited protection against BA.1, BA.1.1 and BA.2 infections and onward transmission.

Methods

Study cohorts

The COMMUNITY study comprises 2149 HCW at Danderyd Hospital, Stockholm, Sweden, enrolled between April and May, 2020. Study participants are followed every four months since inclusion [14-17]. SARS-CoV-2 infection prior to vaccination was confirmed by seroconversion at any of the follow-up visits and/or by PCR. All HCW were offered

vaccination with either BNT162b2 (BNT) or ChAdOx1 nCoV-19 (ChAd), depending on availability, starting in January 2021. Vaccine and date of vaccination is obtained through the Swedish vaccination register (VAL Vaccinera) and data regarding PCR-confirmed SARS-CoV-2 infection is obtained through SmiNet (Swedish Public Health Agency).

To investigate serological responses to an mRNA-1273 (MOD) booster dose, 300 participants were stratified into groups depending on primary vaccine regimen and on occurrence of SARS-CoV-2 infection prior to primary vaccination. Inclusion criteria was the administration of a MOD booster dose between December 13 – 23, 2021, after primary SARS-CoV-2 vaccination with either two doses of BNT (dose interval 33-53 days) with second dose between May 23 and June 30, two doses of ChAd (dose interval 70-108 days) with second dose between May 10 and June 14, or one dose of ChAd followed by one dose of BNT (dose interval 68-115 days) with second dose between May 18 and June 21, 2021. Blood samples were collected 13 weeks (median 90 days, IQR 82-98 days) after second vaccine dose and 5 weeks (median 35 days, IQR 33-40 days) after the booster dose. Exclusion criteria was PCR-confirmed SARS-CoV-2 infection between first vaccination and up to 6 days after post booster blood sampling (n=40). Demographics are presented in Table 1.

To analyze viral characteristics and risk of breakthrough infections, we invited 375 participants shortly after their booster vaccine dose to a twice-weekly qPCR screening with self-administered naso-oropharyngeal/saliva swabs [18] for four weeks. All participants who had completed primary vaccination and received a BNT or a MOD booster were invited. Blood samples and qPCR tests were obtained at inclusion. Positive qPCR tests after a negative inclusion test were followed up by an extended set of self-administered swabs for qPCR every other day until 15 days post first positive sample. Participants that were qPCR positive at inclusion (n=21) were included in further screening but excluded from time-dependent analyses. All study participants engaged in the extended follow-up responded to a questionnaire including a pre-defined set of symptoms (fever, sore throat, cough, headache, anosmia and rhinorrea). After a 15 days completion of follow-up sampling, participants continued in the twice-weekly screening until the end of the study period. PCR, whole genome sequencing (WGS) and virus isolation was performed as previously described [19].

The study was approved by the Swedish Ethical Review Authority (dnr 2020-01653) and conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all study participants.

Serological investigation

SARS-CoV-2 anti wild-type (WT) IgG, cross-reactive IgG capable of binding omicron (BA.1, BA.1.1 and BA.2), and IgG capable of blocking WT and omicron (BA.1, BA.1.1 and BA.2) spike ACE2 binding (surrogate neutralization), were measured in post vaccination samples drawn at start of the screening study (V-PLEX SARS-CoV-2 Panel 22, 23 and 25, Meso Scale Diagnostics, Maryland, USA). Antibody titers are expressed as arbitrary units (AU)/ml, except for anti-WT IgG, which are expressed in the WHO-standard binding antibody units (BAU)/ml. An in-house calibration curve (starting dilution 1:2) was generated for the ACE2 competitive binding assay using a serum sample obtained from a previously omicron-infected study participant with a live microneutralization titer of 270 against omicron.

Live-virus microneutralization

In a sub-set of 86 participants (66 SARS-CoV-2 naïve and 20 recovered), neutralizing capacity against WT and omicron was performed using a micro-neutralization assay as previously described [20]. Briefly, heat-inactivated serum was 3-fold serially diluted, mixed with virus, incubated for 1 hour and finally added, in duplicates, to confluent Vero E6 cells in 96-well plates. Original SARS-CoV-2 WT and omicron BA.1 (both isolated from Swedish patients) were used. After 5 days incubation, the wells were inspected for signs of CPE by optical microscopy. Serum neutralizing activity was measured by 100% CPE inhibition (IC_{100}). Each well was scored as either neutralizing (if no signs of CPE was observed) or non-neutralizing (if any CPE was observed). The arithmetic mean neutralization titer of the reciprocals of the highest neutralizing dilutions from the two duplicates for each sample was then calculated.

Statistics

Risk of breakthrough infection over four weeks screening was evaluated using survival analysis by logistic regression model adjusted for age and sex. For statistical comparisons, negative qPCR-samples were given a value of 46. Mann-Whitney U test was performed for comparisons of antibody titers between groups, peak Ct levels and number of positive days between groups, using GraphPad Prism version 9.2.0 (GraphPad Software, San Diego, California, USA).

Results

Serological responses following MOD booster vaccine dose

We recently reported increased cross-neutralization potency against SARS-CoV-2 variants following primary vaccination with two doses BNT or heterologous ChAd followed by BNT compared to two doses of ChAd [21]. Using blood samples taken before (figure 1A) and five weeks after (figure 1B) MOD booster vaccination, we found comparable booster anti-WT spike IgG (figure 1B), anti-WT RBD IgG (figure S1A), cross-reactive IgG capable of binding omicron BA.1 spike (figure S1B) and RBD (figure S1C) and neutralizing titers against both WT (figure S1D) and omicron BA.1 (figure S1E). As previously reported [22] SARS-CoV-2 recovered vaccinees showed stronger antibody responses than SARS-CoV-2 naïve vaccinees following primary vaccination (Figure 1C). This difference still remained after the booster dose (Figure 1D), although not as strong (fold change 2.5 vs. 8.2 for anti-spike WT IgG (Figure 1D), 1.3 vs. 4.5 for cross-reactive IgG capable of binding Omicron BA.1 spike (Figure S1F), 2.7 vs. 7.6 for neutralizing titers against WT (Figure S1G) and 1.5 vs. 18 for neutralizing titers against Omicron BA.1 (Figure S1H) after booster dose as compared to after primary vaccination).

Consistent with recent reports [23-25], post booster neutralization of omicron BA.1 was substantially lower compared to neutralization of WT both in SARS-CoV-2 naïve participants (10.2 fold-change, $p<0.001$) (Figure 1E) and in SARS-CoV-2 recovered participants (fold change 19.2, $p<0.0001$) (Figure 1F).

Taken together, these findings show that while booster vaccination may level out differences due to various prior immunizations the serological responses against omicron is clearly lower than against WT SARS-CoV-2.

High rate of Omicron breakthrough infection in triple-vaccinated HCW January – February 2022.

To investigate risk for post booster breakthrough infections with omicron, 375 triple-vaccinated participants were enrolled in a qPCR-screening study early 2022. Demographics and vaccine regimens are presented in Table 2. During this period, BA.1, BA.1.1 and BA.2 circulated in Sweden. Self-administered naso-oropharyngeal/saliva tests were performed twice weekly for four weeks (median adherence 2 samples per week, IQR 1.75-2). The total time-at-risk was 1485 person-weeks, total number of screening samples 2502.

A total of 82 (22% of all tested participants) omicron breakthrough infections were detected during the four-week screening period, among which 21 were detected at study

inclusion. 61 participants who were negative at first sample and subsequently tested positive during the four week screening were enrolled in a 14-day follow up with self-administered samples every second day. Adherence to these follow-up samplings was high with a median of 7 (IQR 7-7) self-administered follow-up samples. Analysis of viral RNA levels revealed a peak day three after initial positive test, and that the majority of the participants were positive with Ct < 30 nine days after initial positive test (figure 2A). Six participants, all with Ct values >30 in the initial positive sample, were qPCR negative in all follow-up samples. 23 of 61 (38%) participants remained asymptomatic > 48 hours after first qPCR-positive sample, with a median pre-symptomatic Ct value of 28.9 (range 19.4-38). Six participants (9%) remained asymptomatic throughout the whole course of their infection (Figure 2B). Peak viral load and time to viral clearance was not significantly different between participants with asymptomatic course of infection and those with symptoms at any time point during the infection (p=0.06 and p=0.095, respectively).

Post booster antibody titers are associated to viral load and time to clearance

To address whether individuals with breakthrough infections had lower antibody responses before infection, we compared antibody titers in samples obtained at inclusion in the qPCR screening in participants that subsequently tested positive to those that remained negative throughout the screening period. Post booster anti-WT spike IgG titers (Figure 2C) and neutralizing titers against both WT (figure 2D) and omicron BA.1 (figure 2E) were similar in those with and without subsequent breakthrough infection (p>0.05). High binding and neutralizing antibody titers were, however, associated with lower peak viral RNA levels (p=0.001) and a faster viral clearance (p<0.005) (figure 2F-G).

Symptomatology is associated to levels of viral RNA

Among the 55 participants with symptomatic infection (91%), “common cold” symptoms dominated. Presence of symptoms at time of sampling correlated to higher viral load compared to samples from asymptomatic participants (p<0.0001) (Figure 2H). There was a trend towards shorter duration of symptoms in participants with pre-infection anti-WT spike IgG titers in the upper quartile compared to the bottom quartile, but this did not reach significance (median duration of symptoms 5 vs 8 days, p=0.18). Symptoms in relation to median Ct value the initial seven days of infection are depicted in figure S2A-E. Fever, cough, headache and anosmia at any time point throughout the course of infection were associated with an increased viral load.

No significant association between prior SARS-CoV-2 infection and risk of breakthrough infection or viral load and clearance

Logistic regression revealed no significant protection against infection by SARS-CoV-2 infection prior to booster immunization (p=0.06, table S1); 23.0% of the SARS-CoV-2 naïve (n=50) and 20.4% of the SARS-CoV-2 recovered (n=32) participants became infected. Furthermore, no significant correlation between prior infection and peak viral load (p=0.59), time to viral clearance (p=0.51) or symptom duration (p=0.14) was observed (Figure 2I and S2F).

Comparisons between omicron sublineages BA.1, BA.1.1 and BA.2 breakthrough infections

As shown above (Figure 1E-F), post booster cross-reactive antibody responses capable of neutralizing omicron BA.1 were substantially lower compared to antibodies neutralizing WT SARS-CoV-2. When comparing cross-reactive antibody responses capable of neutralizing omicron sublineages we found slightly but significantly higher titers capable of neutralizing BA.2 as compared to BA.1 (Figure 3A).

WGS was successful in 71/72 cases with at least one sample with Ct < 35, identifying 26 BA.1 (of which 20 were included in follow-up), 21 BA.1.1 (13 in follow-up), and 24 BA.2 (22 in follow-up) infections. Notably, pre-infection anti-WT spike IgG were comparable in participants that subsequently became infected, and those that remained qPCR negative, regardless of omicron sublineage (Figure 3B).

Median Ct value of first positive sample was 29.4 in BA.1 vs. 25 in BA.2 infections (Figure 3C), corresponding to an approximate 100-fold higher level of viral RNA in BA.2 infected individuals early in the course of infection. These differences were however not significant (p=0.06). There was also a trend towards a longer time to viral clearance in BA.2 infections as compared to BA.1 infections (p=0.13) (Figure 3C). Symptom duration was significantly longer in BA.2 infected compared to BA.1 (median duration of symptoms 8 vs 6 days), p<0.01 (Figure 3D). There were no asymptomatic cases among BA.2 infections (n=22).

Isolation of infectious viruses was successful from nine individuals (three infected with BA.1 and six with BA.1.1). Interestingly, isolation of viable viruses was possible from one sample with Ct 27 and from one sample drawn at day 9, showing that

samples with relatively high Ct levels and samples from late in the course of infection can contain infectious viruses.

Discussion

We report a high rate of breakthrough infections (22% over a period of 4 weeks) in a HCW cohort recently receiving a booster immunization and with a high rate of prior infection, supporting previous *in vitro* [23 24 26] and epidemiological [2 9] reports of omicron immune evasion. Further, post booster antibody titers were similar in participants with and without subsequent breakthrough infection, exemplifying limitations of vaccine induced antibody titres as a marker of protection against omicron breakthrough infection.

Although identification of SARS-CoV-2 RNA through qPCR is not equivalent to the detection of infectious virus, low Ct values have repeatedly been shown to correspond to viable virus in cell cultures for both omicron [11 13] and other SARS-CoV-2 variants [27 28]. Consequently, Ct values are often used as a proxy of viral load. Fall et al., reported presence of infectious omicron virus in samples obtained up to eight days after symptom onset, and that the presence of infectious omicron virus was similar in non vaccinated, vaccinated and boosted individuals, implying that vaccine has little effect on viral load once infected [11]. In line with this, we here demonstrate high viral RNA levels up to nine days after first qPCR positive sample, including after symptom resolution, in the majority of omicron breakthrough infections occurring shortly after a vaccine booster dose. Together, this suggests that recently vaccinated omicron-infected individuals may transmit the virus for a longer time period than the five days quarantine from symptom onset recommended by current guidelines [29]. This is of particular importance in vulnerable environments such as healthcare settings. Our data are furthermore in line with a recent report demonstrating a peak in omicron viral load 2-5 days after symptom onset [13], where virus isolation was positive in 19% of vaccinated but not boostered infected individuals nine days after first positive qPCR test.

Although post booster antibody titres were similar in participants with and without subsequent breakthrough infection in our cohort, high pre-infection titres ameliorated viral load once infected. Waning antibody titres have been shown following both primary vaccination and booster doses [30-32]. The observed association between high post booster antibody titers and a lower viral load once infected may contribute to the proposed short-term

mRNA booster effectiveness against onward omicron viral transmission [3 9], but longer follow-ups are needed to address the duration of this effect.

Asymptomatic and pre-symptomatic transmissions play important roles in transmission dynamics. Accurate estimations of the number of asymptomatic infections are key in mathematic modelling and assumptions of population immunity. Less than 10% of cases in our study had an entirely asymptomatic course of infection, contradicting an early report suggesting a high rate of asymptomatic omicron infection [33]. Importantly, although Ct values were generally higher among asymptomatic and pre-symptomatic participants, several asymptomatic cases displayed low Ct values, emphasizing the role of asymptomatic transmission also in populations with a high vaccine uptake.

Global surveillance data suggest a higher transmissibility of BA.2 than BA.1 and BA.1.1, and BA.2 is becoming dominant [9 34]. The reasons for the increasing frequency of BA.2 is unclear. Our findings of similar post booster antibody titres capable of neutralizing the three sublineages are in line with recent data reporting similar neutralizing antibody titres against BA.2 and BA.1 in mRNA boostered individuals [10], suggesting that the surge in BA.2 infections is related to increased transmissibility rather than to enhanced immunologic escape as compared to BA.1. Although we could not demonstrate any significant differences in viral load between the sublineages, there was a trend toward higher initial viral load and a longer duration of viral shedding in BA.2 infections, which may contribute to an increased transmission. Further studies will determine if, and how, BA.2 may be linked to an increase in overall transmissibility or an enhanced immune evasion unrelated to circulating antibody titres.

This study is limited by the observational design, in a cohort that is comprised of predominantly young and healthy individuals with a female dominance. The study is strengthened by the comprehensive screening program with high adherence to testing, thereby limiting the risk of missing transient and asymptomatic cases. The relatively large number of qPCR positive cases during a period with high circulation of BA.1, BA.1.1 and BA.2 furthermore allowed us to perform a characterization of omicron sublineage breakthrough infections. Vaccine status and prior infection were obtained from high-quality national registries, and prior infection was also determined through regular serology in the cohort, which has been followed since the start of the Covid-19 outbreak.

In conclusion, identifying potential immune correlates of protection from infection and understanding the kinetics of SARS-CoV-2 omicron shedding in vaccinated individuals is crucial to guide infection control measures and vaccination policy. We show a

high incidence of omicron infection in a recently triple vaccinated HCW cohort. These breakthrough infections were associated with high viral load, which likely contributes to the global surge in cases. Finally, our findings emphasize that vaccine-induced antibody titres play a limited role in omicron infection risk prediction.

Declaration of Interests

The authors declare no competing interests.

Acknowledgments

This work was funded by Jonas & Christina af Jochnick foundation (CT) Lundblad family foundation (CT); Region Stockholm (CT); Knut and Alice Wallenberg foundation (CT, JK); Jonas Söderquist's scholarship (CT); Science for Life Laboratory (PN); Erling-Persson family foundation (SoH); Center for Innovative Medicine (JK, KB); and Swedish Research Council (JK). The funders above had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Tables and Figures

	SARS-CoV-2 Naive	SARS-CoV-2 Recovered
Vaccination: BNTx2 + MOD		
N	21	73
Age, m (IQR)	50 (35-54)	51 (42-58)
Female, n (%)	19 (90)	66 (90)
Vaccination: ChAdx2 + MOD		
N	36	34
Age, m (IQR)	52 (49-60)	50 (44-54)
Female, n (%)	32 (89)	28 (82)
Vaccination: ChAd + BNT + MOD		
N	88	48
Age, m (IQR)	51 (45-56)	49 (42-54)
Female, n (%)	78 (89)	41 (85)

Table 1. Demographics, frequency of prior SARS-CoV-2 infection and vaccine regimen of the study cohort included in the investigation of serological booster responses. m; median, IQR; interquartile range; ChAd; ChAdox1 n-CoV 19 vaccine, BNT; BNT162b2 mRNA vaccine, MOD; mRNA-1273 vaccine.

	qPCR Positive	qPCR Negative
N	82	293
Age, m (IQR)	51 (43-57)	53 (45-59)
Female, n (%)	75 (91)	260 (88)
SARS-CoV-2 recovered at inclusion, n (%)	32 (39)	130 (44)
Days from booster vaccine to inclusion, m (IQR)	34 (31-35)	34 (32-37)
Primary vaccine regimen		
BNTx2, n	53	187
ChAdx2, n	9	48
ChAd + BNT, n	20	58
Booster vaccine, n		
BNT, n	20	70
MOD, n	62	223

Table 2. Demographics, frequency of prior SARS-CoV-2 infection and vaccine regimen of the study cohort included in the qPCR screening. m; median, IQR; interquartile range; BNT; BNT162b2 mRNA vaccine, ChAd; ChAdox1 n-CoV 19 vaccine, MOD; mRNA-1273 vaccine.

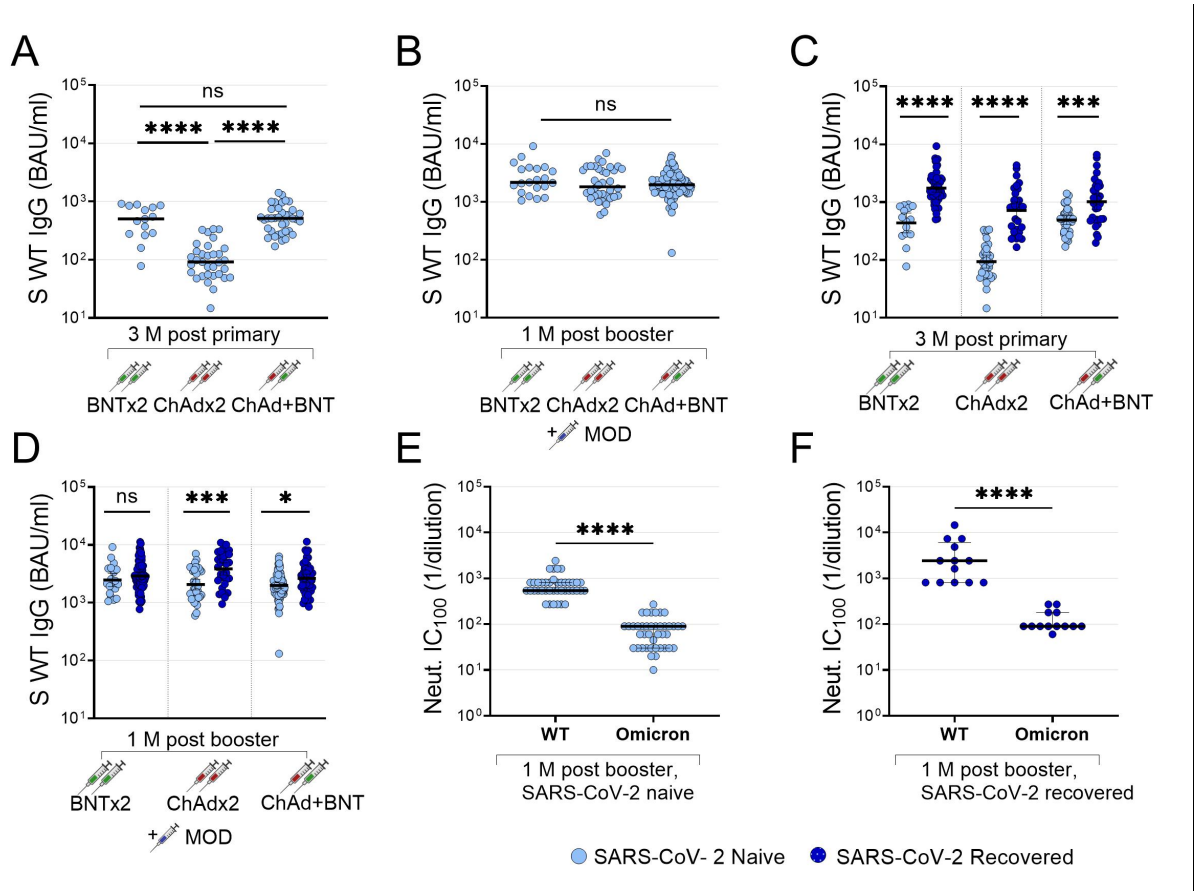

Figure 1. Impact of primary vaccine regimens and prior infection on booster antibody responses. Anti-WT spike IgG three months after primary vaccination series with two doses BNT, two doses ChAd or one dose ChAd followed by one dose BNT (**A**), and anti-spike IgG one month after MOD booster vaccine dose in the same participants (**B**).

Anti-WT spike IgG in SARS-CoV-2 naïve (light blue dots) and recovered (dark blue dots) participants 3 months after primary vaccination series with two doses BNT, two doses ChAd or one dose ChAd followed by one dose BNT (**C**) and one month after MOD booster vaccine dose in the same participants (**D**). Microneutralizing titers against SARS-CoV-2 WT and omicron BA.1 in SARS-CoV-2 naïve (**E**) and recovered (**F**) participants one month after MOD booster vaccine dose. IgG titers are presented as binding antibody units (BAU)/ml and microneutralizing titers are presented as lowest neutralizing dilution (1/Y). Lines depict geometric mean titers and bars depict 95% confidence interval. S; spike, WT; wild-type, Neut; microneutralizing titer, BAU; binding antibody units; BNT; BNT162b2 mRNA vaccine, ChAd; ChAdox1 n-CoV 19 vaccine, MOD; mRNA-1273 vaccine, M; months, ns; $P > 0.05$, *; $P \leq 0.05$, **; $P \leq 0.01$, ***; $P \leq 0.001$, ****; $P \leq 0.0001$.

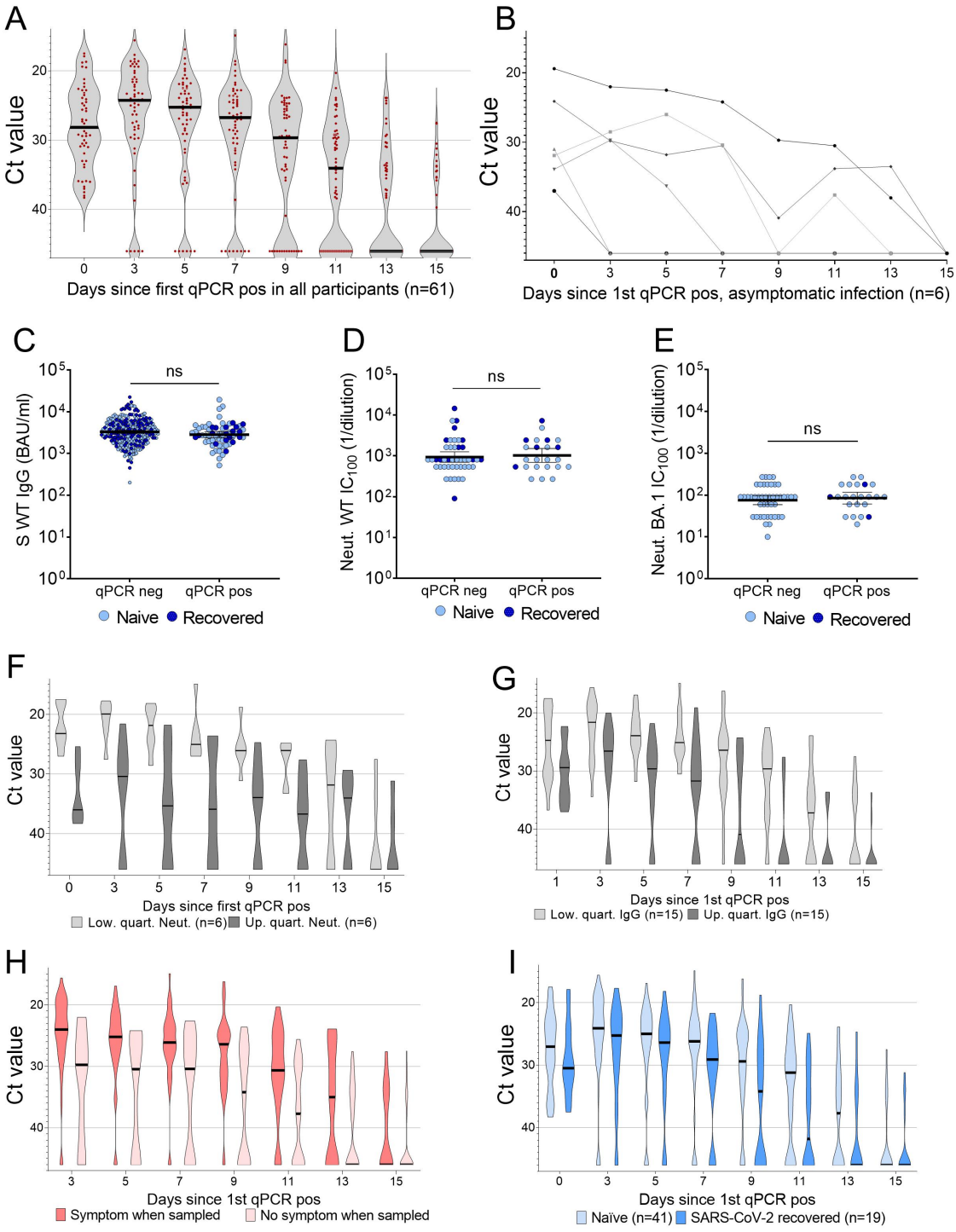

Figure 2. SARS-CoV-2 omicron viral load, time to viral clearance and impact of pre infection antibody titers, symptoms and prior infection. Ct value during the first 15 days of breakthrough infection in all qPCR positive participants (**A**), and in participants with an asymptomatic course of infection (**B**). Post booster microneutralizing titers against SARS-CoV-2 WT (**C**), omicron BA.1 (**D**) and anti-WT spike IgG (**E**) and in participants that

remained qPCR negative and participants that tested qPCR positive during the screening period. Ct values in qPCR positive participants with pre-infection anti-WT microneutralization titers (**F**) and anti-WT IgG titers (**G**) in the lower (light grey) and upper (dark grey) quartile. Ct values in participants who were symptomatic (dark red) or asymptomatic (light red) at time of sampling (**H**) and in participants with (dark blue) and without (light blue) infection prior to booster vaccine dose (**I**). Ct; cyclic threshold, Pos; positive, neg; negative, S; spike, WT; wild-type; BAU; binding antibody units; Neut; microneutralizing titer, Low; lower, Up; upper, quart; quartile, sympt; symptom, ns; $P > 0.05$.

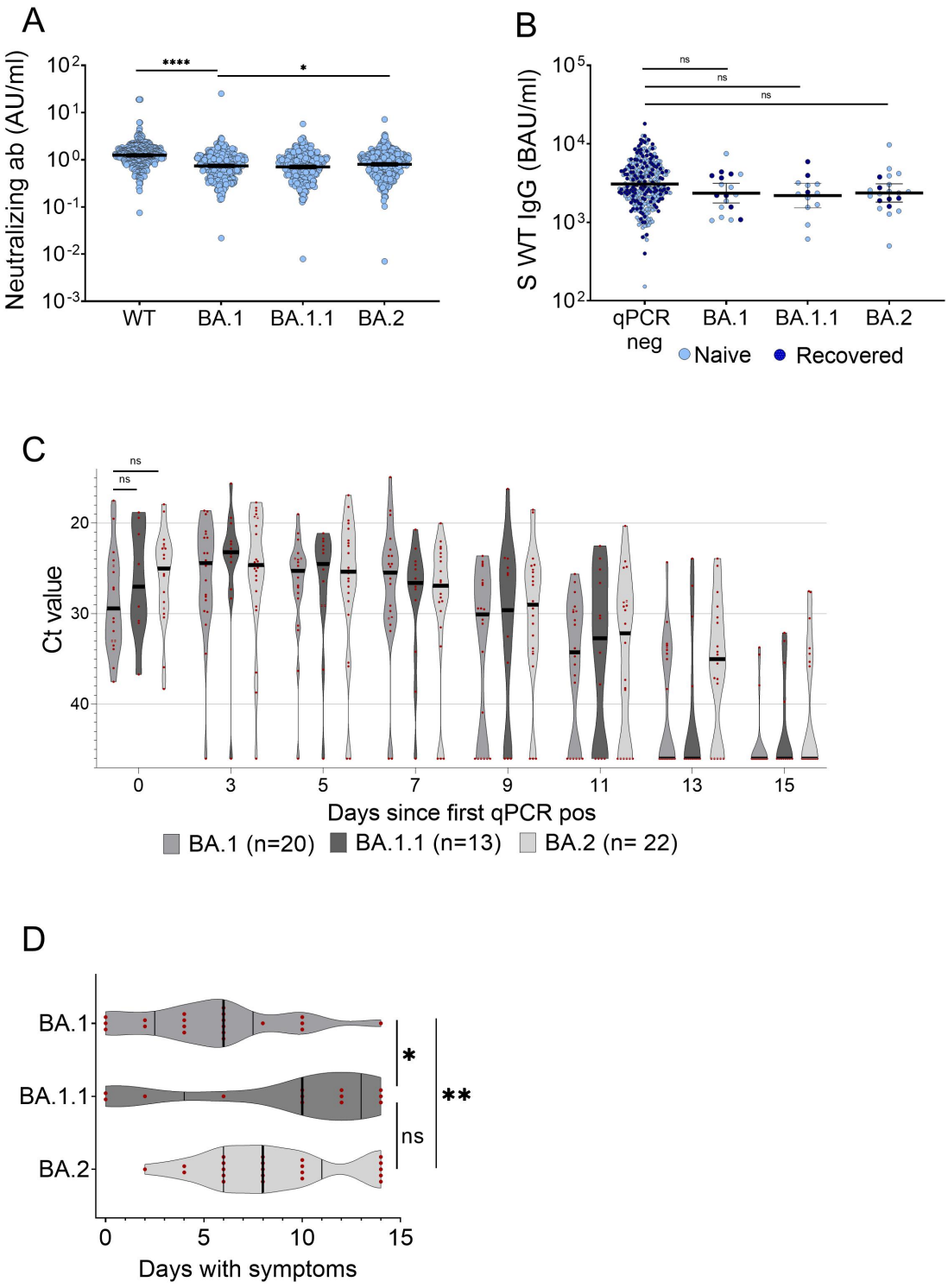

Figure 3. Post booster cross-reactive antibody responses capable of binding and neutralizing omicron sub lineages and comparisons between subsequent omicron sub lineage breakthrough infections.

Post booster cross-reactive anti-spike IgG capable of blocking ACE-2 WT, BA.1, BA1.1 and BA.2 spike binding (**A**). Post booster anti-WT spike IgG titers in participants that remained

qPCR negative and in participants who tested positive with BA.1, BA1.1 or BA.2 infection during the screening period (**B**). Ct values in qPCR positive participants the first 15 days of breakthrough infection with BA.1, BA.1.1 and BA.2 (**C**). Number of symptomatic days for participants who tested positive with BA.1, BA1.1 or BA.2 infection during the screening period (**D)**. Lines depict geometric mean titers and bars depict 95% confidence interval. Pos; positive, neg; negative, S; spike, WT; wild-type; Ct; cyclic threshold, AU; arbitrary units; BAU; binding antibody units, ns; $p > 0.05$, *; $p \leq 0.05$; **$p \leq 0.01$

Supplemental figures and tables

	OR	95% CI	P-value
Anti-WT spike IgG quantile			
Mid	Ref	-	-
Bottom	2.04	(0.09 to 22.6)	0.6
Top	0.45	(0.16 to 1.03)	0.080
Sero group			
Sero -	Ref	-	-
Sero +	0.56	(0.30 to 1.01)	0.061
Vaccine combination			
BNT x 2	Ref	-	-
ChAd & BNT	1.41	(0.71 to 2.72)	0.3
ChAd x 2	0.91	(0.37 to 2.02)	0.8

Table S1. Survival analysis by age and sex adjusted logistic regression of risk of infection over four weeks qPCR screening.

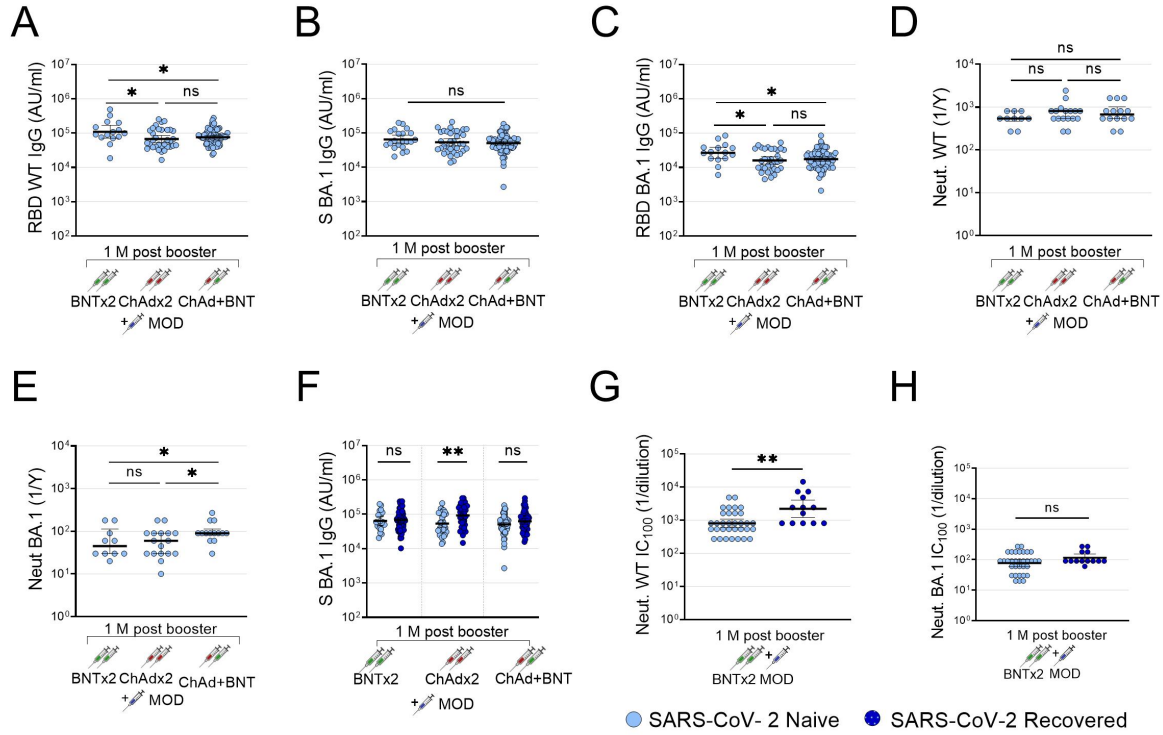

Figure S1. Impact of primary vaccine regimens and prior infection on booster immune responses. Anti-WT RBD IgG (**A**), cross-reactive IgG capable of binding BA.1 spike (**B**) and BA.1 RBD (**C**), microneutralizing titers against WT (**D**) and omicron BA.1 (**E**) one month after mRNA-1273 (MOD) booster vaccine dose in participants with primary vaccination series with two doses BNT, two doses ChAd or one dose ChAd followed by one dose BNT. Cross-reactive IgG capable of binding BA.1 Spike in SARS-CoV-2 naïve (light-blue dots) and recovered (dark-blue dots) participants one month after MOD booster vaccine dose in participants with primary vaccination series with two doses BNT, two doses ChAd or one dose ChAd followed by one dose BNT (**F**). Microneutralizing titers against WT (**G**) and omicron BA.1 (**H**) one month after MOD booster vaccine dose in participants with primary vaccination with two doses BNT. IgG titers are presented as arbitrary units (AU)/ml and microneutralizing titers are presented as lowest neutralizing dilution (1/Y). Lines depict geometric mean titers and bars depict 95% confidence interval. S; spike, WT; wild-type, Neut; microneutralizing titer, AU; arbitrary units; BNT; BNT162b2 mRNA vaccine, ChAd; ChAdox1 n-CoV 19 vaccine, MOD; mRNA-1273 vaccine, M; months, ns; $P > 0.05$, *; $P \leq 0.05$, **; $P \leq 0.01$, ***; $P \leq 0.001$, ****; $P \leq 0.0001$

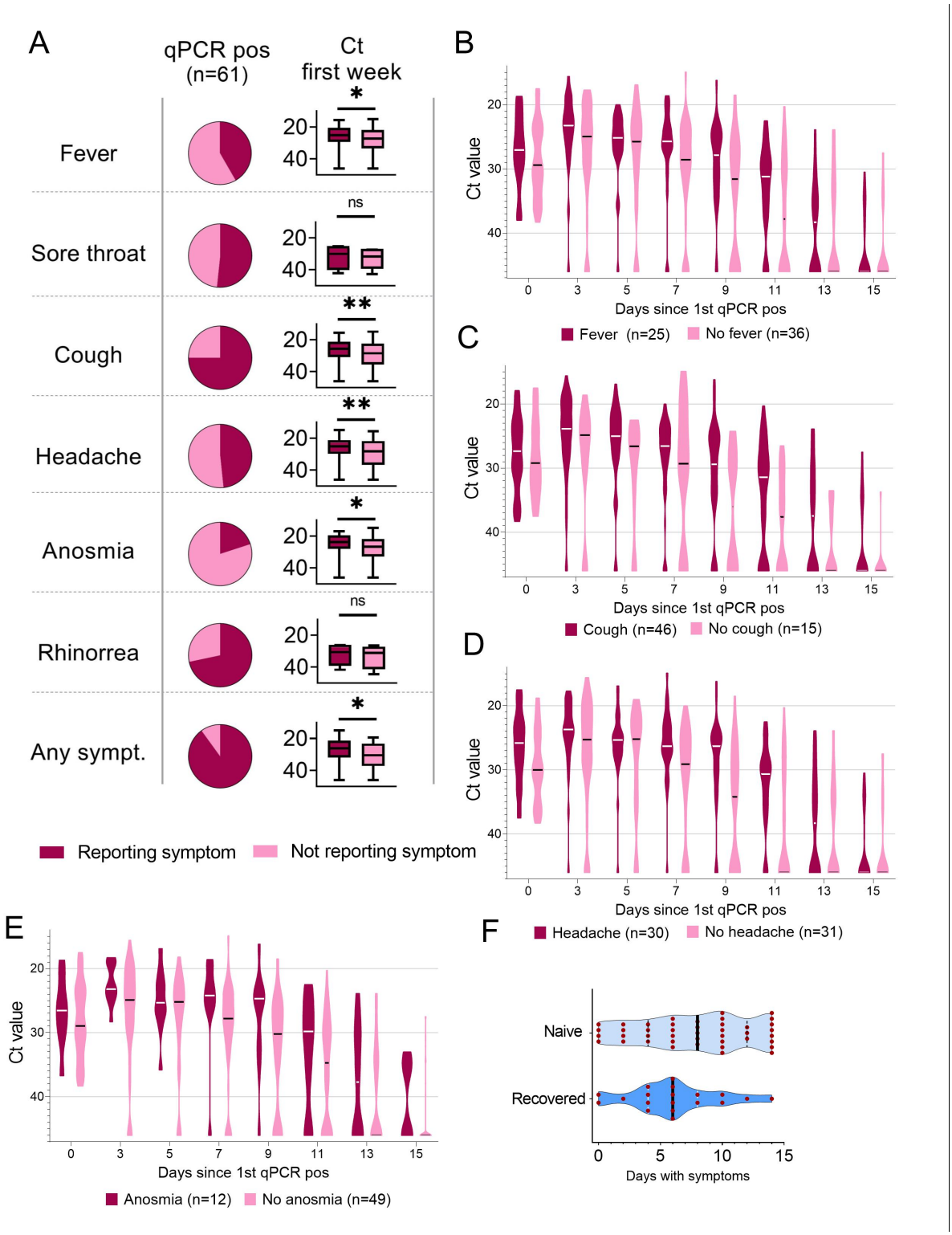

Figure S2. Self-reported symptomatology during omicron breakthrough infections and correlation to Ct value. Prevalence and median Ct values during the first week of infection in qPCR positive participants with (purple) and without (pink) fever, sore throat, cough, headache, anosmia and rhinorrea (**A**). Box plots depict medians and interquartile ranges. Ct values for qPCR positive participants with (purple) and without (pink) fever (**B**), cough (**C**),

headache (**D**), and anosmia (**E**). Number of symptomatic days among participants with (light blue) and without (dark blue) prior infection (**F**). Pos; positive, sympt; symptom, Ct; cyclic threshold, ns; $P > 0.05$, *; $P \leq 0.05$, **; $P \leq 0.01$.