Reduced neutralisation of SARS-COV-2 Omicron-B.1.1.529 variant by post-immunisation serum

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SARS-CoV-2 is estimated to have caused 265 million infections and 5.25 million deaths over the last 2 years (1). Current vaccines are based on the original SARS-CoV2 strain and are designed primarily to raise an antibody response against the spike protein (S), although elicited T-cell responses may also contribute to protection from severe disease.

The SARS-CoV2 RNA polymerase is intrinsically error prone which results in mutation to the genome. In the last year, several variants containing multiple mutations in S have been reported: Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1) and Delta (B.1.617.2). These variants contain mutations in the Receptor Binding Motif (RBM), a small 25 amino acid patch at the tip of S that mediates interaction with the ACE2 receptor (Alpha-1, Beta-3, Gamma-3, Delta-2). These changes may lead to increased transmissibility by increasing affinity to ACE2 (Alpha -7x, Beta -19x, Gamma -19x , Delta -2x) (2) or lead to immune escape. First Alpha and then Delta spread globally causing successive waves of infection, whilst Beta and Gamma led to large localised outbreaks in Southern Africa and South America respectively.

Currently, Delta is estimated to represent over 99% of infections worldwide, however, a new variant of concern Omicron (B.1.1.529) was reported first in South Africa on 24 November 2021 (3), but has since been reported in multiple countries. Early reports from South Africa suggest Omicron is highly transmissible, in a population where 60-80% already show serological evidence of previous infection or vaccination, suggesting Omicron is able to break through natural and vaccine-induced immunity, although early reports do not indicate more severe disease.

Omicron contains a large number of mutations in S compared to previous variants of concern, mostly concentrated around the RBM: 30 amino acid substitutions, deletion of six residues and insertion of three residues (2). Mutations are also present at other sites (Receptor Binding Domain and N-Terminal Domain) which may affect neutralising antibodies. There is concern that Omicron will lead to increased

propensity to infect individuals, who have received vaccines, whose antigens are based on the original S sequence.

Here, we report the results of neutralisation assays using an isolate of Omicron obtained from an infected case in the UK. Neutralisation assays were performed on sera from individuals from the immunology cohort of the Com-COV2 study, who were seronegative at enrolment (defined by anti-nucleocapsid IgG). Participants were vaccinated with two doses of Oxford-AstraZeneca AZD1222 (n=22), or two doses of Pfizer/BioNTech BNT162b2 (n=21) with a priming interval of 8-11 (median 9) weeks. Samples were obtained 28 days (range 25-32) following the second immunisation (Table S1) (4).

Live virus neutralisation titres against Omicron are compared with titres against Victoria, an early pandemic SARS-CoV2 strain, together with titres against Beta and Delta variants.

Neutralising titres on sera from participants who had received homologous AZD1222 dropped to below the detectable threshold in all but one participant (Figure 1A, B). Median neutralising titres on sera from participants who had received homologous BNT162b2 dropped 29.8-fold from 1609 (Victoria strain) to 54 (Omicron variant), with one participant dropping below the detection threshold. In most cases, samples which failed to neutralize with $FRNT_{50}$ at a dilution of <1/20 demonstrated some residual neutralizing activity (Figure 1C).

In summary, there was a substantial fall in neutralisation titre in recipients of both homologous AZD1222 and BNT162b2 primary courses, with evidence of some recipients failing to neutralise at all. This drop in neutralization titre will likely be more pronounced at later timepoints. These data, although derived from a relatively small sample size, are consistent with recently published data from datasets of similar size (5–7). Together they suggest Omicron is more antigenically distant from the

original SARS-CoV2 vaccine strain than the previously most distant strains, Beta and Delta. Preliminary data from the UK Health Security Agency (8) has shown reduced effectiveness against symptomatic infection following 2 doses of AZD1222 or BNT162b2 suggest this is leading to increased breakthrough infections in previously infected or double vaccinated individuals, which may drive a further wave of infection. The impact on disease severity is unknown, although there is currently no evidence of increased potential to cause severe disease, hospitalization or death. It may be that other aspects of the immune response such as non-neutralising antibodies and cellular immunity, which are not expected to be as severely impacted by this variant, may confer a degree of protection against severe disease. However, it should be noted that higher transmission, will inevitably lead to increased numbers of cases and a greater burden on health systems, even without proportional changes in severity.

It is clear that possessing a high starting titre against early pandemic strains gives a higher level of neutralisation of Omicron, which could be obtained by deploying third booster doses of vaccine. There is some reassurance that a third dose of a Covid-19 vaccine does indeed increase vaccine effectiveness against the Omicron variant (8), and testing of samples from Cov-Boost (9) will provide further information on the immunology underlying this. Together these will provide further understanding of the potential for a boosting strategy as a control measure for Omicron infection and transmission.

Should Omicron, as expected, become the dominant strain worldwide, given its antigenic distance from ancestral strains, it may be necessary to produce vaccines tailored to Omicron, however, these might be unlikely to give protection against previous strains. This may stimulate consideration of a switch from the current monovalent vaccine strategy towards multivalent formulations currently used in seasonal influenza vaccines. In the meantime reaching the unvaccinated with current vaccines remains a priority in order to reduce transmission levels and reduce the potential for severe disease in the immunologically naïve.

Figure 1 Neutralisation assays of SARS-CoV-2 Omicron. Neutralisation of Victoria, Beta, Delta and Omicron using (A) AZD1222 serum (ChAd) and (B) BNT162b2 (BNT) serum. Median values are indicated above each column. The data underpinning the Victoria, Beta and Delta neutralisation have been previously reported[4]. The horizontal dotted line indicates half the value of the lower limit of detection. (C) Percent neutralization at serum dilution of 1/20 for those sera which failed to achieve $FRNT_{50}$ at 1/20, the green dot represents the single BNT162b2 sample. The horizontal line in figure 1A and B represents the assay limit of detection

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ChAd/ChAd

BNT/BNT

133 42 52 10

1609 559 1358 54

Live virus neutralisation, $FRNT_{50}$

10000

1000

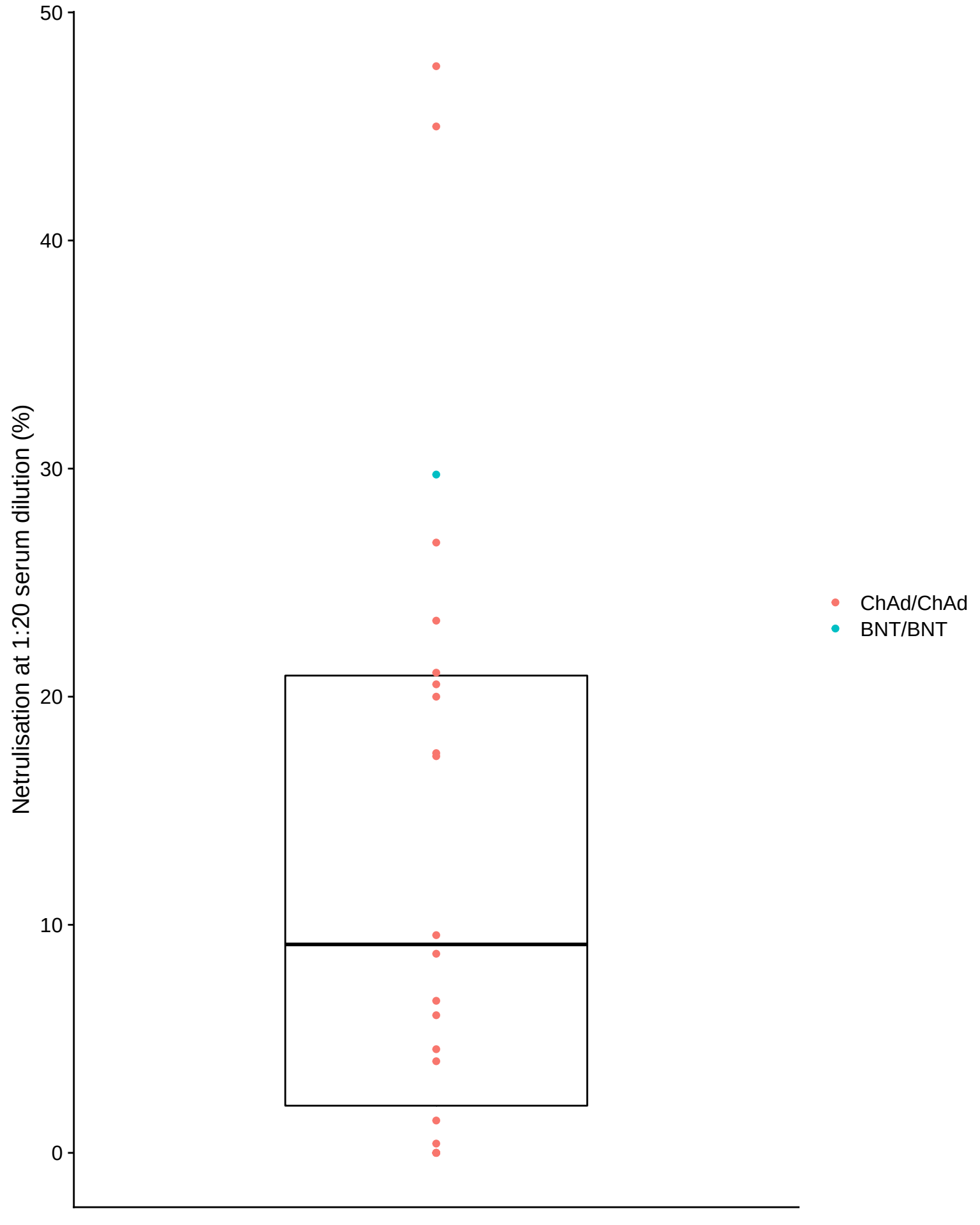
100

10

1

Victoria Beta Delta Omicron

Victoria Beta Delta Omicron


50
40
30
20
10
0
Netrulisation at 1:20 serum dilution (%)
ChAd/ChAd
BNT/BNT