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Omicron neutralising antibodies after COVID-19 vaccination in haemodialysis patients

The SARS-CoV-2 variant of concern (VOC) B.1.1.529 omicron is now the predominant VOC in the UK.¹ The burden of more than 30 mutations in omicron spike suggests at least a degree of vaccine evasion,² and UK Health Security Agency estimates of vaccine efficacy against infection are reduced compared to delta.¹ The critical question is how well existing vaccines will protect clinically extremely vulnerable groups against infection. In the UK, the COVID-19 death rate for in-centre haemodialysis (IC-HD) patients during the delta wave was 14.65 (95% CI 11.49–18.67) per 1000 patient-years, the highest rate for any OpenSAFELY-defined comorbidity.³ The increased transmissibility of omicron is likely to prove challenging in haemodialysis units, where in-unit transmission with prior VOCs has occurred.⁴ We therefore sought to determine the neutralising antibody (nAb) titres (nAbTs) in IC-HD patients, a cohort we have previously shown to have attenuated nAb responses to delta.⁵

In the UK, the IC-HD vaccination schedule is complex. Most IC-HD patients are considered fully vaccinated after two doses and boosted after three. Boosting eligibility criteria were finalised on Sept 14, 2021.⁶ A subset of IC-HD patients, due to their use of additional immunosuppression (eg, for failed renal transplants) or other comorbidities, are eligible for a three-dose primary course (announced Sept 1, 2021).⁷ These patients are already permitted a fourth booster dose 3 months after their third dose.

To assess the induction, maintenance, and diversity of nAbs we convened the UK-wide NAOMI consortium study assessing neutralising antibody after COVID-19 vaccination in haemodialysis patients.⁵ This is an observational

multicentre meta-cohort study to compare nAb responses between different vaccine regimens, and in pre-specified patient subgroups. Previously, we compared nAb responses after two doses of the adenoviral vector Oxford–AstraZeneca vaccine (ChAdOx-1 nCoV-19; AZD1222) or the Pfizer–BioNTech mRNA vaccine (BNT162b2). mRNA vaccine neutralising responses against wildtype virus and VOCs were similar to those seen in health-care or laboratory workers.^{5,8,9}

Here we report the first nAbTs against omicron in the at-risk IC-HD population (n=98) a median of 158 days [IQR 146–163] after second dose and 27 days [21–35] after third dose. We used live virus microneutralisation assays as previously described,⁵ and report delta as a comparator VOC, with full demographics listed in the appendix (p 2). First and second doses were either AZD1222 (n=30) or BNT162b2 (n=68). All third doses were BNT162b2 (at full dose). Earlier timepoints from one HD centre have already been reported.⁵ Given the urgency of these data, we locked this first set once more than 50 serum samples were available after third dose. These patients were vaccinated from September to November, 2021, and are from two UK HD centres (appendix p 2), reflecting the local variation in the deployment of third doses.

First, we assessed nAbTs against omicron and delta at a median of 158 days after two doses of either AZD1222 or BNT162b2 (appendix p 3). After two doses of AZD1222, the median nAbT against either VOC was less than the lower limit of detection of our assay (<1:40), in keeping with our previous report of delta nAbTs 1 month after the second dose⁵ (omicron IQR <40 to <40; delta IQR <40 to 110). At 158 days after two doses of BNT162b2, median nAbTs against delta were 112 (IQR <40 to 342), and median omicron nAbTs were below the range of the assay (appendix p 3; IQR <40 to 157).

Next, we considered the effect of an additional full dose of BNT162b2 (n=50, appendix p 3). For recipients of two doses of AZD1222 followed by a dose of BNT162b2 (AZD–AZD–BNT; n=21), delta nAbTs increased after a third dose to a median of 282 (IQR <40 to 1250). A third dose provided a significant increase in the proportion of patients in this vaccination group with nAbTs above 40 against delta (McNemar's test p=0.023) or omicron (p= 0.0077). However, the median titres against omicron remained below the quantitative range (<40 [IQR <40 to 270]). Recipients of three doses of BNT162b2 (BNT–BNT–BNT, n=29) had boosted nAbTs against delta, from 112 to 461 (4.1 fold change [IQR 171 to 1214]) and developed detectable nAbTs against omicron, with a median nAbT of 236 (IQR <40 to 603) after a third dose. A third dose provided a significant increase in the proportion of patients in this vaccination group with nAbT above 40 against delta (McNemar's test, p=0.0077) or omicron (p=0.0094).

For both AZD–ZD–BNT and BNT–BNT–BNT recipients, a proportion of IC-HD patients do not mount nAbT responses to either VOC. Seven (33%) and 11 (52%) of 21 patients who received AZD–AZD–BNT showed 50% inhibitory concentration (IC₅₀) below 40 against delta and omicron, respectively, after a third dose. This contrasts with the patient group that received BNT–BNT–BNT, of which one (3%) and eight (28%) of 29 patients showed IC₅₀ below 40 against delta and omicron, respectively. We hypothesised that these patients could be taking immunosuppressants or have immunosuppressive comorbidities (beyond the immunosuppression associated with end-stage renal disease and haemodialysis itself), so we stratified the analysis by the presence of or absence of an immunosuppressed state (appendix p 2). The immunosuppressed AZD–AZD–BNT patients (n=5) had a median nAbT against



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omicron below the lower limit of the assay (IQR <40 to <40) and immunosuppressed BNT-BNT-BNT patients (n=6) had a median nAbT against omicron of 135 (about 50% of the response of the rest of the cohort [IQR <40 to 491]). In the non-immunosuppressed recipients, the median omicron nAbT after third dose was 107 for AZD-AZD-BNT recipients (n=16; IQR <40 to 578) and 236 for BNT-BNT-BNT recipients (n=23; IQR 67-777).

The main limitation of our study is its observational nature, risking unbalanced groups for comparisons. For example, the AZD-AZD-BNT and BNT-BNT-BNT cohorts are matched imperfectly, with AZD1222 recipients being older (mean age 68.8 years [SD 11.2] vs 60.3 [12.1], t test $p=0.001$). Therefore, we have reported responses within these vaccine cohorts, not between. We temper this limitation by the importance of these data: IC-HD patients are at increased risk of severe disease or death,³ and our data inform strategies to mitigate that risk over the coming weeks and months. Vaccine-induced cellular responses are likely to contribute to the protective effect of vaccination. Preliminary data suggest that in healthy individuals, T-cell responses to omicron spike-derived peptides appear comparable to peptide pools from other VOCs.¹⁰ In contrast, in infection-naïve IC-HD patients, a reduction in T-cell responsiveness to peptides of ancestral S1 and S2 after two doses of either vaccine has been suggested.¹¹ Together, these observations suggest that omicron infection in previously vaccinated HD patients might result in diminished cellular responses compared to healthy individuals.

In summary, we report the first nAbTs against omicron in IC-HD, a highly vulnerable population to COVID-19, frequently requiring hospital treatment and with an excess risk of death. Homologous vaccination with BNT-BNT-BNT generated quantifiable nAbTs against delta and

omicron in most IC-HD patients. Heterologous vaccination with AZD-AZD-BNT provides quantifiable nAbTs against delta in more than 50% of IC-HD patients but not against omicron, where more than 50% of IC-HD patients had nAbTs below the quantifiable range. A significant fraction of IC-HD patients would appear to remain at risk from omicron.

There are several implications of these data. First, the deployment of third doses in the UK took about 8 weeks between eligibility announcements for third or booster doses and their receipt in this highly vulnerable patient group. This contrasts with their very rapid access to first doses.⁵ Second, a lack of a quantifiable response (non-response) after two doses does not predict ongoing non-response to a third dose. We suggest that each further dose reduces this fraction. Some of these non-responders are already eligible for four doses in the UK, as their primary course has already been deemed three doses because of immunosuppression use or comorbidities.⁷ Third, adequate nAbTs against delta in IC-HD patients required three doses of vaccine, and this is reflected in the epidemiological data from the delta wave.³ Finally, omicron neutralisation will require at least three vaccine doses, perhaps four doses, in UK IC-HD patients, particularly as the kinetics of waning of omicron nAbs are unknown. Together, our data show that the current generation vaccines still have utility in clinically extremely vulnerable patient groups and that the number of doses that constitute an appropriate primary course differs between VOCs: for omicron, three doses in IC-HD might be insufficient.

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For data and full R code see <https://github.com/EdjCarr/Crick-HD-Omicron-2021-12>

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