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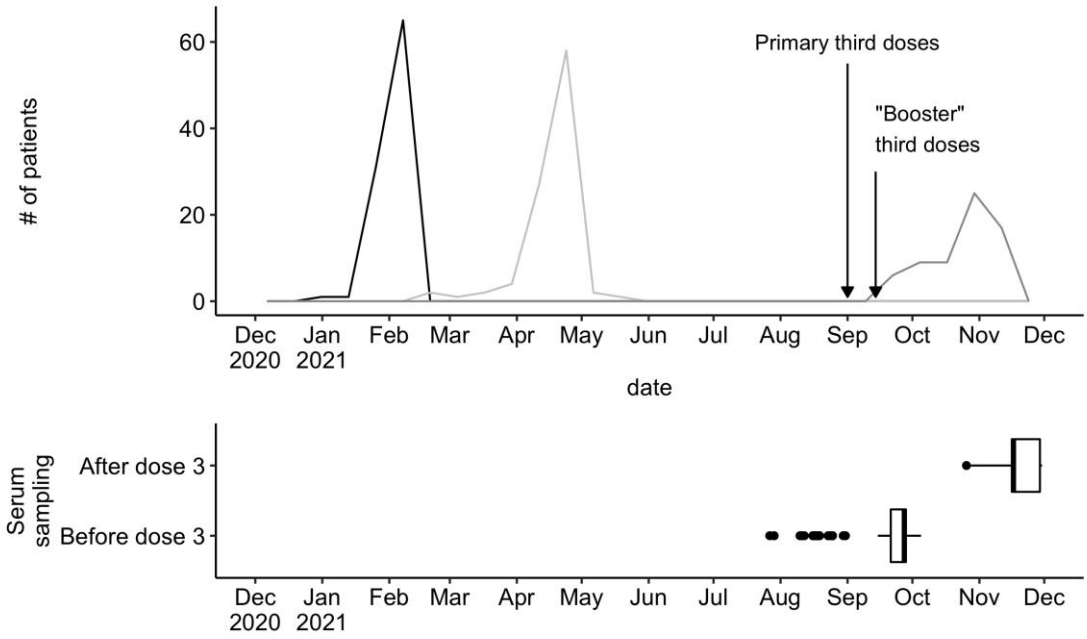

Figure 1 - Study design

The dates of vaccination and venepuncture are shown. Vaccinations (upper panel) 1, 2 and 3 are shown in black,light grey and dark grey respectively. Dates of serum sampling (lower panel), are shown as boxplots. The median and IQR define the box, and the whiskers extend to the furthest datapoint, upto 1.5x IQR from the median. Data beyond the whisker is shown as a dot.

The JCVI announcement of primary third doses is indicated (1 September 2021, https://www.gov.uk/government/publications/third-primary-covid-19-vaccine-dose-for-people-who-are-immunosuppressed-jcvi-advice/joint-committee-on-vaccination-and-immunisation-jcvi-advice-on-third-primary-dose-vaccination). This allowed a small portion of IC-HD patients to access third doses, due to immunosuppression use. “Booster” doses were announced for all CEV patients were authorised on 14 September https://www.gov.uk/government/news/jcvi-issues-updated-advice-on-covid-19-booster-vaccination.

	AZD1222	BNT162b2	P-Value
	n = 30	n = 68	
vaccine			<.001
AZD1222	30 (100%)	0 (0%)	
BNT162b2	0 (0%)	68 (100%)	
dialysis_centre			<.001
A	16 (53.3%)	6 (8.8%)	
B	14 (46.7%)	62 (91.2%)	
age_in_years			0.001
	68.8 (11.2)	60.3 (12.1)	
gender			0.696
F	13 (43.3%)	25 (36.8%)	
M	17 (56.7%)	43 (63.2%)	
immunosuppressed			0.326
N	24 (80%)	61 (89.7%)	
Y	6 (20%)	7 (10.3%)	

Table 1 - Demographics of the third dose cohort

IC-HD cohort stratified by the formulation of their first two vaccines

COVID infections are defined as: 'before' infection identified prior to first dose; 'during' infection identified between doses 1 and 2; 'breakthrough' infection >14d after dose 2. Immunosuppression defined as previously [1]. Age is shows as mean (standard deviation) and is compared used a t test; all other comparisons are χ^2 test.

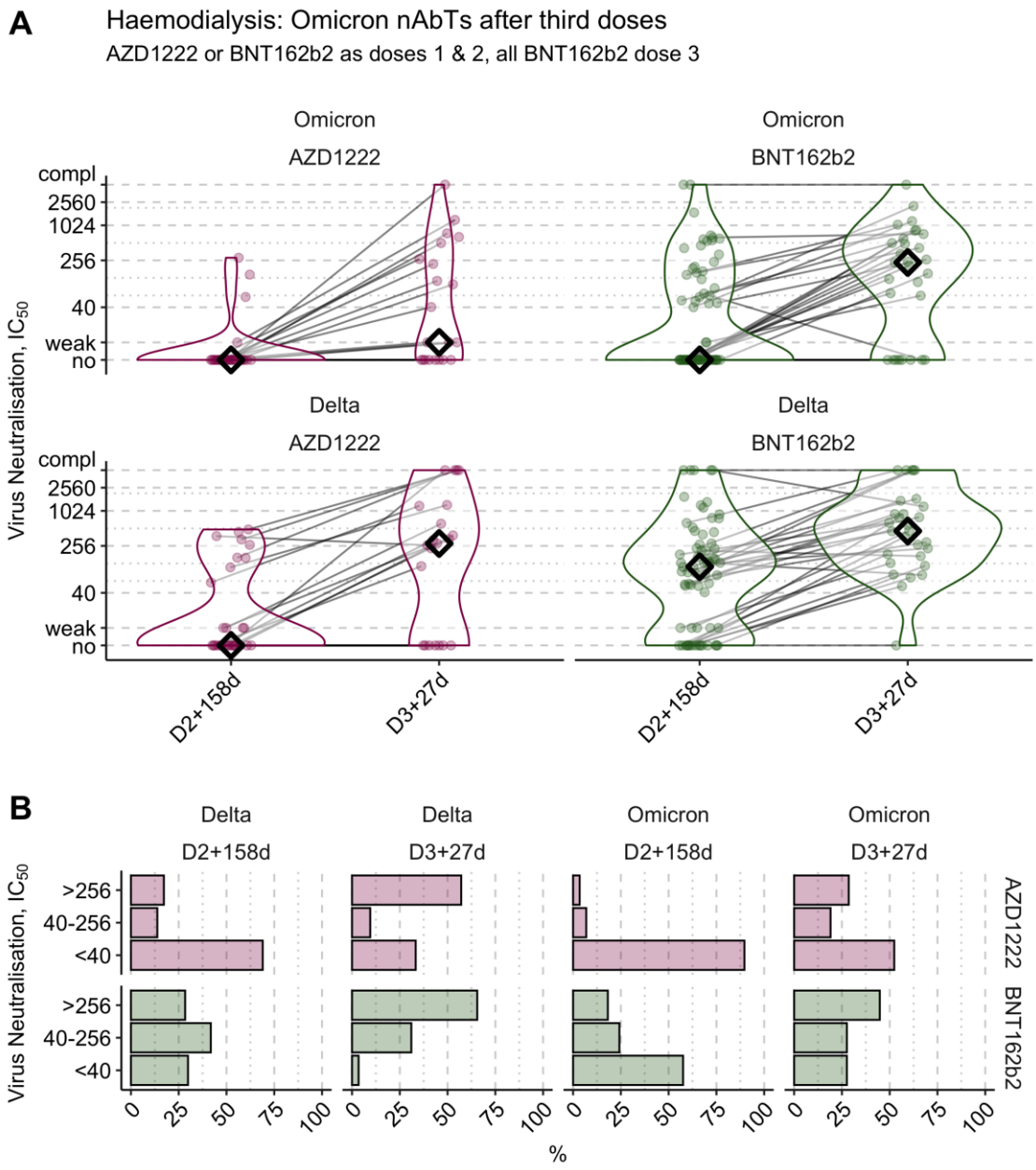

Figure 2 – The neutralising antibody titres against Omicron and Delta SARS-CoV-2 VOCs before and after third doses

(A) Live virus microneutralisation titres for either the Omicron or Delta SARS-CoV-2 variants-of-concern, reported as IC_{50}, are shown at 158 days [146-163, n=98] after the second dose and 27 days [21-35, n=51] after dose 3 (medians [inter-quartile ranges, number of patients]). Each individual is a point, and samples from the same individual are joined by a line (21 paired AZ samples; 30 paired BNT samples). No, weak and complete (compl) inhibition are shown, with gridlines to indicate IC_{50} of 64,128,512 and 2048. Median IC_{50} are marked by a black diamond.

(B) The percentages of IC50s after stratification in low (<40), medium (40-256) or high (>250) neutralising antibody titres are shown at the dates in (A) for both Delta and Omicron. after two doses of either AZD1222 or BNT162b2 and after a subsequent dose of BNT162b2. In (A)-(B), recipients of doses 1 and 2 AZD1222 or BNT162b2 are plotted in purple or green respectively.

Methods

Study objectives and design

We are performing a cohort study of 1,200 IC-HD patients across the UK [2]. The study has several objectives:

1. Confirm the immunogenicity of BNT162b2 and AZD1222 in IC-HD patients, including the generation of neutralising antibodies.
    a. Confirm augmentation of the antibody response with the second dose of vaccine
    b. Assess the longevity of the antibody response, including neutralising antibody.
2. Compare the profiles of neutralising antibodies generated between BNT1262b and AZD1222 IC-HD recipients.
3. Compare the profiles of neutralising antibodies generated by either vaccine between different age groups, different genders, different ethnicities, and different primary renal diseases.
4. Compare the profiles of neutralising antibodies generated between patients with and without diabetes or with and without immunosuppression.
5. Exploratory / discovery phase, where novel patterns / correlations are identified to provide hypothesis for testing in other cohorts / specifically targeted studies.

For any cohort comparison we expect, given the nature of the UK's IC-HD population (its ethnicities, the frequencies of diabetes, immunosuppression) to be able to assemble groups of >100 patients for each comparison.

We planned serum collections were before vaccination, 28 days after each vaccination, and 6 & 12 months after commencing vaccination.

The study design is pragmatic and serum collection dates are reviewed in light of changing vaccination policy.

Clinical cohorts

Two haemodialysis centres is used in this report. In centre haemodialysis patients were included if they were able to consent into their local study and were clinically

eligible to receive the available vaccine. Home haemodialysis patients and peritoneal dialysis patients were not included. The data shown is censored for individuals who received two doses of vaccine, and had available sera ~28 days after their third dose. Anonymised (coded only against a research identifier) sera and phenotype data were provided for central analysis: age, gender, ethnicity, diabetes, immunosuppression, primary renal disease, alongside the dates of vaccine, vaccine manufacturer and the dates of serum sampling. Ethnicity was recorded as Asian, Black, Mixed, White or Other (in line with UK government advice at the time of commencing the study https://webarchive.nationalarchives.gov.uk/20210224165417/https://design-system.service.gov.uk/patterns/ethnic-group/). Diabetes was recorded as Y/N, and we defined immunosuppression as Y/N as in Billany et al. [1]. Individuals were vaccinated intramuscularly as part of their usual care, with either 0.5mL [not less than $2.5x10^8$ infectious units] AZD-1222, ChAdOx1-S [recombinant] (Oxford-AstraZeneca) or 30ug BNT162b2 (Pfizer-BioNTech), at the interval indicated in Figure 1.

Leicester cohort

Patient samples were collected as part of the study "PHENOTYPING SEROCONVERSION FOLLOWING VACCINATION AGAINST COVID-19 IN PATIENTS ON HAEMODIALYSIS", with REC approval from (West Midlands - Solihull Research Ethics Committee, REC: 21/WM/0031) sponsored by the University of Leicester and included consent for samples to transfer to the Francis Crick Institute. This work was conducted locally with support from the NIHR Leicester Biomedical Research Centre and funding from the Leicester Hospitals Charity, University Hospitals of Leicester NHS Trust. Data from these patients have been published previously [1–3].

Cambridge cohort

This prospective observational cohort study, "SARS CoV-2 antibody responses in immunocompromised patients" includes patients recruited from the Department of Nephrology, at Cambridge University Hospitals NHS Foundation Trust, (East Midlands- Leicester Central Research Ethics Committee: REC 20/EM/0180). The study is sponsored by Cambridge University Hospitals NHS Foundation Trust.

Consent was obtained as part of the study to allow for anonymised blood samples to analysed by academic and/or industry collaborators, both within and outside the UK. This work was funded by Addenbrooke's Charitable Trust, and supported by the Cambridge University Biomedical Research Centre.

Serological Analysis and live-virus neutralisation

All serum samples were collected during routine IC-HD sessions from the HD circuit, without additional venepuncture. Sera were separated from blood in local laboratories and stored frozen. Sera were shipped to the Crick on dry ice, and barcoded whilst frozen. All live-virus microneutralisation were performed as described previously [3].

Data analysis, statistics

Data analysis was performed in R4.0.4/Rstudio, using Rmarkdown. Anonymised data wrangling used a mix of base R and tidyverse. As previously [2–4], IC_{50} values above the quantitative limit of detection of the assay (>2560) were re-coded as 5120; IC_{50} values below the quantitative limit of the assay (< 40) but within the qualitative range were re-coded as 10 and data below the qualitative range (i.e. no response observed) were re-coded as 5. IC_{50} values are shown on a log2 scale throughout. 95% confidence intervals of the fold changes of median neutralising antibody titres were estimated using bootstrapping as implemented in the infer package. Plots were generated using ggplot2 and ggpubr packages.

Data Sharing

All R code to reproduce all figures and analyses is freely available at (https://github.com/EdjCarr/Crick-HD-Omicron-2021-12/[EC1]). The public dataset omits dialysis centre, age, gender and dates, to maintain anonymity.

Ethics

This work is covered by the following REC approvals: REC: 21/WM/0031 and REC 20/EM/0180.

Role of the funding source

This work was supported by Kidney Research UK, NKF, PKD charity, Kidney Wales and several Kidney Patient Associations [Exeter, North Staffs and South Cheshire, Northamptonshire, South Eastern and Wessex], the MRC and core funding from the Francis Crick Institute, which receives its funding from Cancer Research UK, the UK Medical Research Council, and the Wellcome Trust. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data and the final responsibility to submit for publication.

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Acknowledgements

We thank the patients, their families, and the dialysis and renal unit staff who have delivered this at the frontline of a fast-moving pandemic, and the responsive rapid funding from Kidney Research UK and partners.

This research was funded in whole, or in part, by the Wellcome Trust [FC011104, FC011233, FC001030, FC001159, FC001827, FC001078, FC001099, FC001169]. For the purpose of Open Access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission. The authors would like to thank all the study participants, the dialysis and renal unit staff, the staff of the NIHR Clinical Research Facility at UCLH including Kirsty Adams and Marivic Ricamara. We would like to thank Jules Marczak, Gita Mistry, Nicola Bex, Simon Caiden, Bobbi Clayton, and the staff of the Scientific Technology Platforms (STPs) and COVID-19 testing pipeline at the Francis Crick Institute. We thank Prof. Wendy Barclay of Imperial College and the wider Genotype to Phenotype consortium for the B.1.617.2 variants used in this study, and Max Whiteley and Thushan I de Silva at The University of Sheffield and Sheffield Teaching Hospitals NHS Foundation Trust for providing source material. We thank Dr Laura McCoy of UCL for the CR3009 antibody. We also thank Marg Crawford, Robert Goldstone, Jerome Nicod, and Harshil Patel for generation and processing of sequencing data. We

acknowledge support from the NIHR Leicester Biomedical Research Centre and the Cambridge University Biomedical Research Centre EJC acknowledges the support of Health Education East of England, in particular Drs Francesca Crawley, Sarah Fluck, Lisa Willcocks and John Firth, to facilitate his out-of-programme experience. This work was supported by the Francis Crick Institute which receives its core funding from Cancer Research UK (FC011104, FC011233, FC001030, FC001159, FC001827, FC001078, FC001099, FC001169), the UK Medical Research Council (FC011104, FC011233, FC001030, FC001159, FC001827, FC001078, FC001099, FC001169), and the Wellcome Trust (FC011104, FC011233, FC001030, FC001159, FC001827, FC001078, FC001099, FC001169) and funded by the MRC [MRC-Pandemic Award-PRJ-20009 to RCLB, EJC; and MR/W010011/1 to LH] and Kidney Research UK [SP/VACCINE/2021 to MW, SM, EJC & RCLB], with KRUK supported by the NKF, the PKD charity, Kidney Wales and several Kidney Patient Associations [Exeter, North Staffs and South Cheshire, Northamptonshire, South Eastern and Wessex], and the Royal Free Charity, the Leicester Hospitals Charity, Oxford Hospitals Charity, and Addenbrooke's Charitable Trust.

Supplementary references

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