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Neutralising antibodies after COVID-19 vaccination in haemodialysis patients

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Vaccination against COVID-19 induces highly protective immune responses in the great majority of people. As some countries switch from suppression to acceptance of transmission of SARS-CoV-2 within a largely vaccinated adult population, vulnerable patient groups that have not mounted adequate immune responses to vaccination may suffer significant morbidity and mortality. There is an urgent need to identify such patient groups and to optimise medical advice and vaccination strategies for them.

In-centre haemodialysis patients (IC-HD) represent a particularly vulnerable group. During the first wave of the COVID-19 pandemic (1 March 2020 to 30 August 2020), there were 4,666 cases and 1,373 deaths in IC-HD patients reported to the United Kingdom's Renal Registry[1], a case fatality rate of 29%. In the UK, whilst IC-HD patients were treated as 'clinically extremely vulnerable', they were unable to fully 'shield' due to mandatory life-sustaining attendance at HD (typically three 4-hourly sessions per week), and instances of in-unit transmission have been shown by sequencing viral isolates[2].

Vaccine responses are substantially attenuated in haemodialysis patients. For example, the subunit hepatitis B vaccine had to be re-formulated for HD patients with a higher antigenic dose[3]. There is uncertainty that either an mRNA or an adenoviral-vectored vaccine could provide clinical protection in the IC-HD population.

The majority of IC-HD patients were vaccinated by their dialysis care team, as part of the Joint Committee on Vaccination and Immunisation (JCVI) priority group 4[3], resulting in rapid delivery of doses to this at-risk population (Figure 1A). Phase 3 studies of authorised vaccines in the UK either excluded IC-HD or did not report their 'renal disease' subgroups[4–6]. While multiple reports regarding anti-S antibodies (reviewed recently[7]) in IC-HD patients have been published, they do not widely report the levels of neutralising antibodies (nAbs) to the prevalent variants of concern (VOCs), which have emerged as the crucial serological correlate of protection[8].

To assess the induction of nAbs in IC-HD patients, after vaccination with BNT162b2 (Pfizer-BioNTech) or AZD1222 (Oxford-AstraZeneca), we are curating a meta-cohort of HD patients from around the UK (appendix, p 2). We have used our previously reported high throughput live virus neutralisation assays[9,10], against a strain with a spike identical to the virus first identified in Wuhan, China (wildtype), a strain with an Asp614Gly mutation isolated during the UK's first wave, and three VOCs: alpha (B.1.1.7, first isolated in Kent, UK), beta (B.1.351, first isolated in South Africa) and delta (B.1.617.2, one of several variants described in India in early 2021 and now predominant). Here, we report the first interim analysis of this study, using sera drawn pre-vaccination, at a median of 28 days after dose 1 [IQR 26-35], and at a median of 33 days [IQR 26-48] after the second dose (appendix, p 2), in 178 IC-HD patients. Three centres had

available data for this analysis: Oxford, Leicester and Royal Free Hospital (appendix, p 4). Whilst there were differences with the deployment of vaccines - two centres predominantly administered AZD1222, one centre predominantly BNT162b2 - there were no significant differences in age (median 63.2 vs 63.1 years), gender (34% vs 37.3% female), ethnicity, the presence of diabetes or the immunosuppression state of AZD1222 and BNT162b2 recipients (appendix, p 3).

We focused initially on seronaïve patients (n=115) - defined by pre-vaccination sera that lacked detectable anti-S IgG by ELISA, or nAbs against wildtype or D614G and who had never returned a positive PCR prior to commencing vaccination - and assessed nAb responses 33 days after two vaccine doses of either AZD1222 or BNT162b2 (appendix, p 2,4). We found that BNT162b2 induced nAb titres (nAbTs) across all 5 strains (median NAbT IC_{50}=719, 344, 182, 135, 266 against wildtype, D614G, alpha, beta and delta respectively; appendix, p 2 & 4). For AZD1222 the response was markedly reduced compared to BNT162b2 (appendix, p 5), and may fall below the correlate of protection from severe disease against alpha (>4 fold reduction, falling below the limit of detection of IC_{50}>40), beta (>3 fold reduction, falling below the limit of detection), or delta (>6 fold reduction, falling below the quantitative limit of detection) variants (appendix, p 2 & 5). Stratifying the nAbTs (appendix, p 2) better illustrates the differing distributions of responses with patients with low (<40), medium (40-256) and high (>256) titres after two doses of AZD1222 compared to BNT162b2 (P<0.001 by ANOVA for vaccine effect in ordered logistic regression; appendix, p 2, 5). The corresponding analysis for infection-experienced patients revealed smaller differences between AZD1222 and BNT162b2, with AZD1222 achieving median NAbT IC_{50}>256 for all strains (appendix, p 8-9).

Next, we sought to compare with the healthy individuals we have already reported from the LEGACY study. As a control group, we selected LEGACY participants who had never reported COVID symptoms (likely infection and sero-naive) and had received two doses of either vaccine (appendix, p 2, 6-7). We found that an mRNA vaccine performed similarly in IC-HD as in healthy volunteers (both infection naive), despite the age difference between the cohorts (appendix, p 7). As expected, we found an attenuated response in the IC-HD AZD1222 recipients (appendix, p 2, 6).

Given the ability of BNT162b2 to induce nAbTs across all strains in IC-HD, we wanted to assess other vaccine response associations. The response to BNT162b2 exhibits age associated waning (age grouped as greater or less than 65; (appendix, p 9), this is not discernible in the AZD1222 response due to its low titres (appendix, p 9). Stratifying by gender or diabetes found no effect (appendix, p 10. As expected, immunosuppressed patients showed attenuated responses (appendix, p 10).

There are several limitations to our study, most importantly the potential for confounding factors to exist between HD centres. However, it is unlikely that the same confounder would be present between several different centres since they are physically split over more than one site (a hub – satellite model), and the hub and satellite have used BNT162b2 or AZD1222, but share medical, nursing staff, HD protocols and a single dialysis supplier. Whilst we have stringently tried to exclude prior antigenic exposure in our seronaive group (by anti-S ELISA, by nAbT to relevant strains, and PCR data where available), we cannot fully exclude the possibility that there were infections in early 2020, before widespread PCR and whose patients either did not generate an antibody response, or their response had waned below the level of detection in our baseline sampling.

We draw several conclusions from this interim report on a subset of the full UK cohort. Firstly, an mRNA vaccine induces nAb titres in IC-HD patients comparable to healthy controls. This represents an important initial step in improved vaccinations in IC-HD for other pathogens. We note that there is a mRNA influenza vaccine in phase 1/2 development, and IC-HD are a cohort of patients that stand to benefit from a novel influenza vaccine. Secondly, two doses of either vaccine consolidates antibody immunity in infection-experienced individuals. A caveat to this conclusion is presence of survivor bias for individuals infected in the first wave. Thirdly, AZD1222 alone in seronaïve individuals induces sub-optimal nAbT against all VOCs, including the delta variant dominant in the UK and globally. Fourthly, the very high proportion of previously infected IC-HD patients may obfuscate calculations of vaccine efficacy if based on epidemiological parameters alone. Overall, our data highlight an urgent need for similar studies assessing vaccine responses in at-risk populations.

Whilst delivery of any approved vaccine will likely mitigate morbidity and mortality, the optimal strategy for IC-HD patients yet to start a vaccination course remains to be determined. Our data suggest two doses of mRNA vaccine or a heterologous boosting strategy are likely to offer the broadest VOC nAb coverage. The UK's JCVI has announced, in principle, booster doses for many vulnerable groups[11]. The precise start date for this programme, which vaccines are used, and the ordering of the groups is under review. Internationally, most countries with pre-existing IC-HD vaccination strategies (Israel, USA, Canada, France, Germany, Portugal), have used two doses of mRNA[7] and there are two studies reporting a third dose response in solid organ transplant patients[12,13]. We suggest that IC-HD patients should be prioritised for a third dose, particularly AZD-1222 recipients that have not already survived infection.

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Appendix for

Neutralising antibodies after COVID-19 vaccinations in the UK haemodialysis population

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Contents

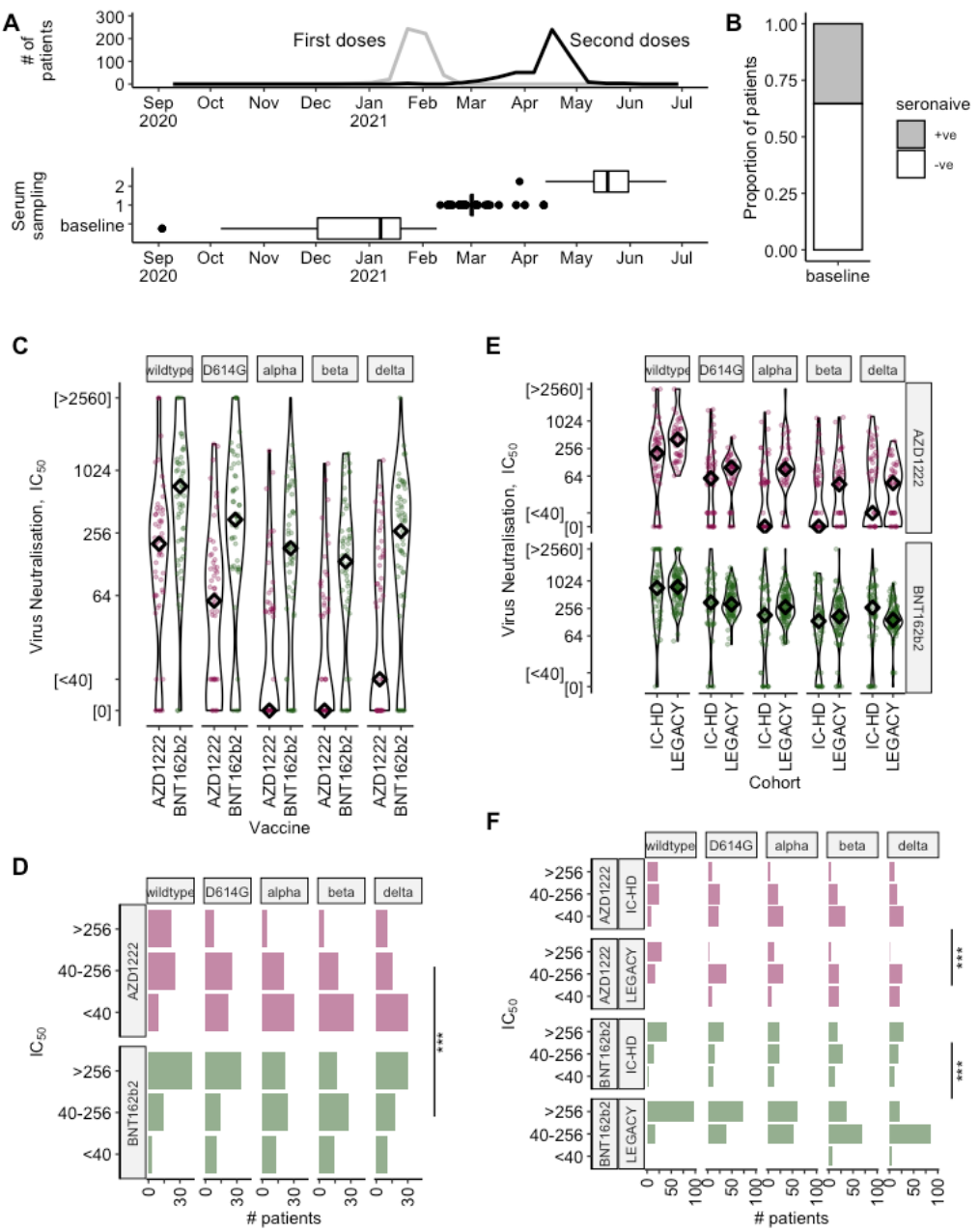


Figure 1: Neutralising antibody responses after two doses of AZD1222 or BNT162b2 in seronaïve haemodialysis patients

(A) Study design. Dates of vaccine administration and serum sampling times are shown in the top and bottom panels respectively. N=178 patients.

(B) The proportion of patients defined as seronaïve at the time of first vaccination. Seronaïve was defined as (i) no detectable anti-S IgG by ELISA (143 patients of 178 had no anti-S IgG), no positive PCR results before first dose (140 patients) and no detectable neutralising antibodies to either wildtype SARS-CoV-2 or SARS-CoV-2 carrying the D614G spike mutation at baseline (115 patients).

(C) Live virus microneutralisation titres against SARS-CoV-2: wildtype, the D614G spike mutant, and VOCs - alpha, beta and delta - 33 days after two doses in seronaïve haemodialysis patients comparing AZD1222 and BNT162b2 responses (AZD1222 n=56, BNT162b2 n=59).

(D) Data as in (C) plotted with stratification of titres into three categories (see also Supplementary Table 5 for ordinal logistic regression). P<0.001 is indicated by *** for the vaccine term.

(E) and (F) Microneutralisation titres as in (C) and (D), comparing two doses in seronaïve haemodialysis patients (IC-HD) with two doses in never-symptomatic healthy individuals (LEGACY) for AZD1222 and BNT162b2. (Supplementary Tables 6-8). P<0.001 is indicated by *** for the cohort term from ANOVA of ordinal linear regression models.

In (C) and (E), the medians are plotted as a black diamond. Note that the median is below the quantitative range (IC_{50}<40) in some instances.

Supplementary tables 1-9

Supplementary table 1: Demographics of the whole interim report cohort, grouped by vaccine

	AZD1222	BNT162B2	P-VALUE
	n = 94	n = 84	
AGE			**0.946**
	63.2 (13.5)	63.1 (13.3)	
GENDER			**0.685**
F	32 (34%)	32 (38.1%)	
M	62 (66%)	52 (61.9%)	
ETHNICITY			**0.139**
	0 (0%)	0 (0%)	
ASIAN	37 (39.4%)	38 (45.2%)	
BLACK	20 (21.3%)	7 (8.3%)	
MIXED	0 (0%)	1 (1.2%)	
OTHER	4 (4.3%)	3 (3.6%)	
WHITE	33 (35.1%)	35 (41.7%)	
DIABETIC			**0.921**
N	51 (54.3%)	44 (52.4%)	
Y	43 (45.7%)	40 (47.6%)	
IMMUNOSUPPRESSED			**0.133**
N	78 (83%)	77 (91.7%)	
Y	16 (17%)	7 (8.3%)	
DIALYSIS_CENTRE_CODE			**<.001**
A	19 (20.2%)	1 (1.2%)	
B	58 (61.7%)	15 (17.9%)	
C	17 (18.1%)	68 (81%)	

Supplementary table 2: Demographics of the seronaïve cohort

	AZD1222	BNT162B2	P-VALUE
	n = 56	n = 59	
AGE			**0.754**
	63.5 (13.7)	62.7 (12.6)	
GENDER			**0.685**
F	22 (39.3%)	20 (33.9%)	
M	34 (60.7%)	39 (66.1%)	
ETHNICITY			**0.142**
	0 (0%)	0 (0%)	
ASIAN	18 (32.1%)	26 (44.1%)	
BLACK	12 (21.4%)	4 (6.8%)	
MIXED	0 (0%)	1 (1.7%)	
OTHER	2 (3.6%)	1 (1.7%)	
WHITE	24 (42.9%)	27 (45.8%)	
DIABETIC			**1**
N	31 (55.4%)	33 (55.9%)	
Y	25 (44.6%)	26 (44.1%)	
IMMUNOSUPPRESSED			**0.357**
N	46 (82.1%)	53 (89.8%)	
Y	10 (17.9%)	6 (10.2%)	
DIALYSIS_CENTRE_CODE			**<.001**
A	10 (17.9%)	0 (0%)	
B	32 (57.1%)	7 (11.9%)	
C	**14 (25%)**	**52 (88.1%)**	

For supplementary tables 1 and 2, P values are t tests for single level continuous variables (eg age) and ANOVAs for higher levels (eg ethnicity). The Chi2 tests for categorical data (eg gender).

Supplementary table 3: Median NAbT fold changes between wildtype and variant SARS-CoV-2 for each vaccine, related to Figure 1E (demark medians below the quantitative [10*] or qualitative scales [5*]. Fold changes are calculated against 40, the lower limit of the quantification scale)*

VACCINE	COMPARISON	MEDIAN1	MEDIAN2	MEDIANFC	LL	UL	LEVEL
AZD1222	wt_vs_D61G	201	56	3.53	2.20	3.45	**0.95**
AZD1222	wt_vs_alpha	201	5	5.03			
AZD1222	wt_vs_beta	201	5*	5.03			
AZD1222	wt_vs_delta	201	10*	5.03			
AZD1222	alpha_vs_delta	5*	10*				
AZD1222	beta_vs_delta	5*	10*				
BNT162B2	wt_vs_D61G	719	344	2.09	1.73	2.39	**0.95**
BNT162B2	wt_vs_alpha	719	182	3.94	1.80	4.86	**0.95**
BNT162B2	wt_vs_beta	719	135	5.29	4.11	6.13	**0.95**
BNT162B2	wt_vs_delta	719	266	2.69	2.31	4.17	**0.95**
BNT162B2	alpha_vs_delta	182	267	0.68	0.76	1.02	**0.95**
BNT162B2	**BETA_VS_DELTA**	**136**	**267**	**0.51**	**0.53**	**0.88**	**0.95**

Supplementary table 4: Median NAbT fold changes between AZD1222 and BNT162b2 for each SARS-CoV-2 variant, related to Figure 1C (demark medians below the quantitative [10*] or qualitative scales [5*]. Fold changes are calculated against 40, the lower limit of the quantification scale)*

STRAIN	MEDIAN BNT162B2	MEDIAN AZD1222	MEDIAN FC	LL	UL	LEVEL
WILDTYPE	719	201	3.57	0.71	5.25	**0.95**
D614G	344	57	6.04		9.30	**0.95**
ALPHA	182	5*	4.55*			
BETA	136	5*	3.40*			
DELTA	**267**	**10***	**6.75***			

*Supplementary table 5: Ordered logistic regression model of effect of strain and vaccine type on neutralising antibody titres 33 days after 2 doses in seronaïve IC-HD patients, relating to Figure 1D. Model: ic50_binned ~ strain * vaccine*

FACTOR	*COEF*	*SE*	*WALD Z*	*PR(>|Z|)*
STRAIN (VS WILDTYPE)				
D614G	-1.1438	0.3490	-3.28	0.0010
ALPHA	-1.721	0.3613	-4.76	<0.0001
BETA	-1.9063	0.3683	-5.18	<0.0001
DELTA	-1.5055	0.3635	-4.14	<0.0001
VACCINE (VS AZD1222)				
BNT162B2	1.272	0.3765	3.38	0.0007
INTERACTION (STRAIN * VACCINE)				
D614 * BNT162B2	0.3934	0.5199	0.76	0.4492
ALPHA * BNT162B2	0.2704	0.5168	0.52	0.6009
BETA * BNT162B2	0.1996	0.5185	0.39	0.7002
DELTA * BNT162B2	0.5259	0.5246	1	0.3161

ANOVA

Wald Statistics Response: ic50_binned

FACTOR	COEF	SE	WALD Z
STRAIN (INCL. HIGHER ORDER FACTORS	58.33	8	<0.0001
VACCINE (INCL. HIGHER ORDER FACTORS)	84.74	5	<0.0001
INTERACTION	1.16	4	0.8852

Supplementary table 6: Demographics comparison between IC-HD and LEGACY cohorts

	IC-HD	LEGACY	P-VALUE
	n = 115	n = 162	
AGE			**<.001**
	63.1 (13.1)	40.5 (11.4)	
GENDER			**<.001**
F	42 (36.5%)	102 (63%)	
M	**73 (63.5%)**	**60 (37%)**	

*Supplementary table 7: Ordered logistic regression model of effect of strain and vaccine type on neutralising antibody titres after 2 doses of AZD1222 in seronaïve IC-HD patients or LEGACY participants, relating to Figure 1F.Model: ic50_binned ~ strain * cohort*

FACTOR	COEF	SE	WALD Z	PR(>|Z|)
STRAIN (VS WILDTYPE)				
D614G	-1.4783	0.3791	-3.28	0.0010
ALPHA	-2.3635	0.3934	-6.01	<0.0001
BETA	-1.9119	0.3914	-4.88	<0.0001
DELTA	-2.3635	0.3934	-6.01	<0.0001
COHORT (VS IC-HD)				
LEGACY	1.223	0.3972	3.08	0.0021
INTERACTION (STRAIN * COHORT)				
D614 * LEGACY	-0.7809	0.5409	-1.44	0.1488
ALPHA * LEGACY	0.4523	0.552	0.82	0.4125
BETA * LEGACY	-0.6477	0.5573	-1.16	0.2451
DELTA * LEGACY	-1.1936	0.5529	-2.16	0.0309

ANOVA

Wald Statistics Response: ic50_binned

Factor	Coef	SE	Wald Z
Strain (incl. Higher Order Factors	103.57	8	<.0001
Cohort (incl. Higher Order Factors)	103.57	8	<.0001
Interaction	11.46	4	0.0219

*Supplementary table 8: Ordered logistic regression model of effect of strain and vaccine type on neutralising antibody titres after 2 doses of BNT162b2 in seronaïve IC-HD patients or LEGACY participants, relating to Figure 1F. Model: ic50_binned ~ strain * cohort*

FACTOR	COEF	SE	WALD Z	PR(>|Z|)
STRAIN (VS WILDTYPE)				
D614G	-0.8328	0.3973	-2.1	0.0361
ALPHA	-1.7238	0.3961	-4.35	<0.0001
BETA	-2.0854	0.3969	-5.25	<0.0001
DELTA	-1.1083	0.3943	-2.81	0.0049
COHORT (VS IC-HD)				
LEGACY	0.9569	0.394	2.43	0.0151
INTERACTION (STRAIN * COHORT)				
D614 * LEGACY	-0.3408	0.5174	-0.66	0.5101
ALPHA * LEGACY	0.1285	0.5115	0.25	0.8016
BETA * LEGACY	-0.3135	0.5094	-0.62	0.5383
DELTA * LEGACY	-1.6829	0.5093	-3.3	0.001

ANOVA

Wald Statistics Response: ic50_binned

FACTOR	COEF	SE	WALD Z
STRAIN (INCL. HIGHER ORDER FACTORS	126.67	8	<.0001
COHORT (INCL. HIGHER ORDER FACTORS)	28.97	5	<.0001
INTERACTION	19.13	4	7.00E-04

Whilst there is a significant cohort effect, there is also (unlike for AZD1222) an opposing interaction effect is seen with delta, such that the two cohorts have equivalent delta responses.

*Supplementary table 9: Ordered logistic regression model of effect of strain and vaccine type on neutralising antibody titres after 2 doses of either vaccine in IC-HD patients, relating to Supplementary Figure 1F. Model: ic50_binned ~ strain * vaccine*

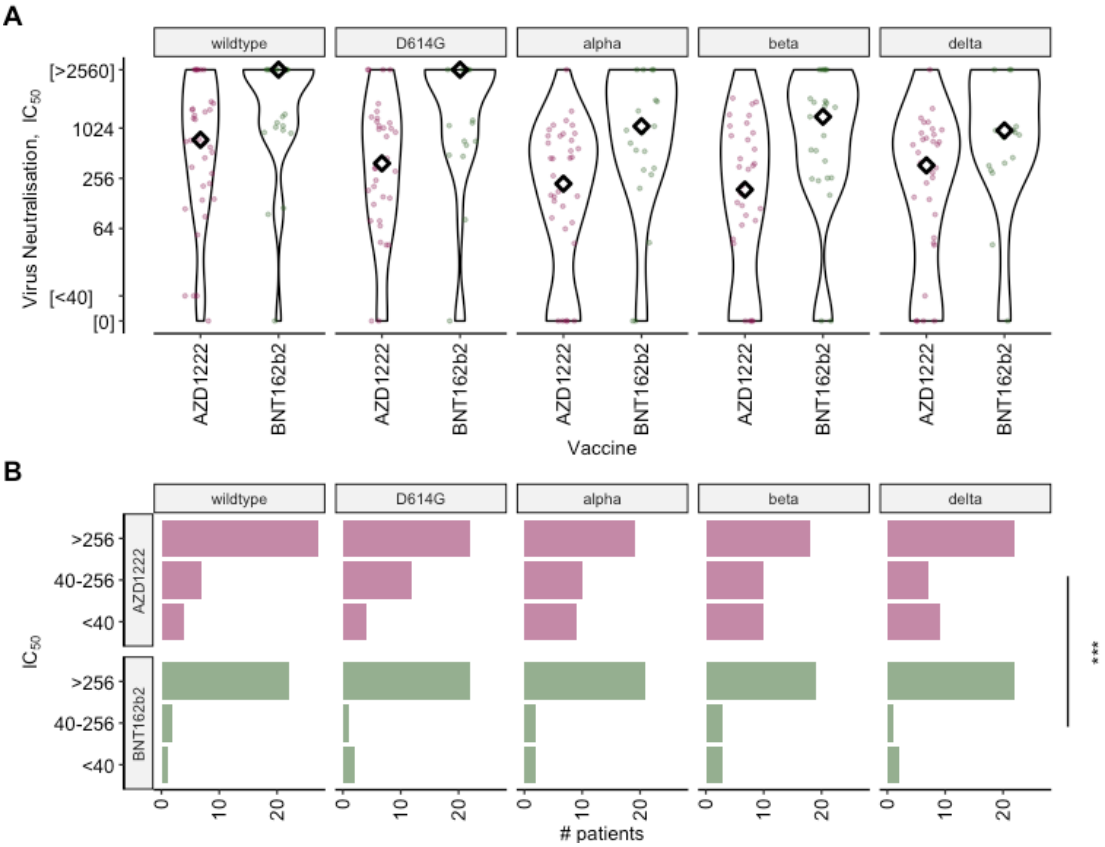
FACTOR	COEF	SE	WALD Z	PR(>|Z|)
STRAIN (VS WILDTYPE)				
D614G	-1.8444	0.2731	-6.75	<0.0001
ALPHA	-1.9491	0.2787	-6.99	<0.0001
BETA	-2.6846	0.2844	-9.44	<0.0001
DELTA	-2.4913	0.282	-8.83	<0.0001
VACCINE (VS AZD1222)				
BNT162B2	1.4435	0.2727	5.29	<0.0001
INTERACTION (STRAIN * VACCINE)				
D614 * BNT162B2	0.865	0.3685	2.35	0.0189
ALPHA * BNT162B2	0.4226	0.3679	1.15	0.2507
BETA * BNT162B2	0.518	0.3688	1.4	0.1602
DELTA * BNT162B2	0.3446	0.3666	0.94	0.3473

ANOVA

Wald Statistics Response: ic50_binned

FACTOR	COEF	SE	WALD Z
STRAIN (INCL. HIGHER ORDER FACTORS)	211.2	8	<.0001
VACCINE (INCL. HIGHER ORDER FACTORS)	242.58	5	<.0001
INTERACTION	5.84	4	0.2116

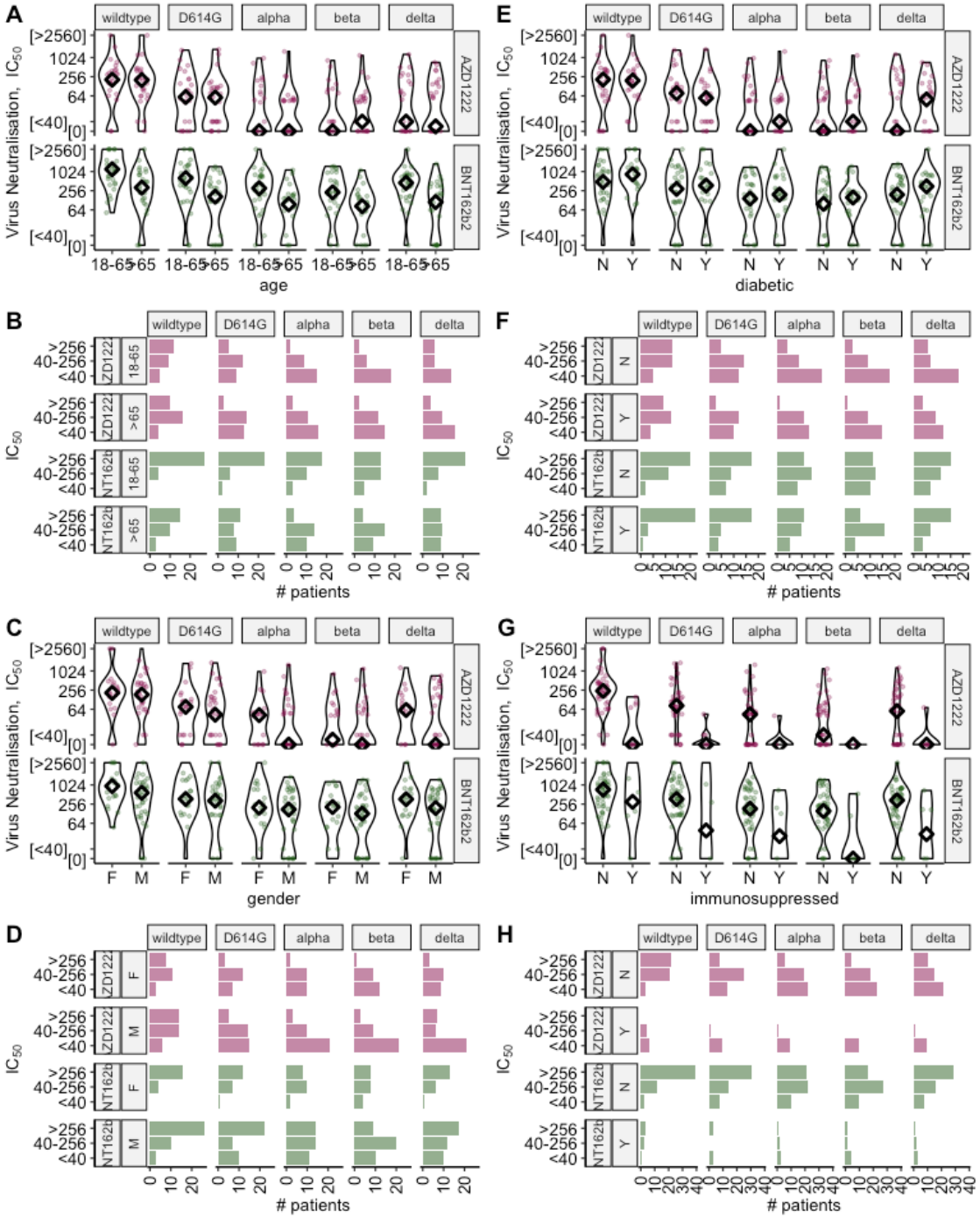
Supplementary figure 1: Live-virus microneutralisation antibody titres in infection-experienced IC-HD patients



(A) Live virus microneutralisation titres against SARS-CoV-2: wildtype, the D614G spike mutant, and VOCs - alpha, beta and delta - 33 days after two doses in seronaïve haemodialysis patients comparing AZD1222 and BNT162b2 responses (63 patients in total (AZD1222 n=38; BNT162b2 n=25).

(B) Data as in (A) plotted with strafication of titres, P < 0.001 from denoted by *** (ANOVA of regression model; see also Supplementary Table 7 for ordinal logistic regression).

Supplementary figure 2: Comparing nAbT responses by age group, gender, diabetes and immunosuppression in seronaïve IC-HD patients



NAbTs are compared 33 days after two doses in seronaïve haemodialysis patients. The data is grouped by age (18-65 or >65 years old, A & B), gender (C & D), the presence of diabetes (E & F), or the presence of immunosuppression (G & H) and each vaccine is shown separately. *P* values from ANOVA for the effect of age (*P*=0.76, *P*<0.0001), gender (*P*=0.72, *P*=0.17), diabetes (*P*=0.99, *P*=0.29), or immunosuppression (*P*<.0001, *P*=0.02), performed on ordinal linear regression models are provided (AZD1222, BNT162b2).

Supplementary Methods

Clinical cohorts

Three haemodialysis centres are included in this interim report, and one healthy control cohort. In centre haemodialysis patients were included if they were able to consent into their local study. Home haemodialysis patients and peritoneal dialysis patients were not included. 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].

Leicester cohort (IC-HD)
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].

Royal Free Hospital cohort (IC-HD)
Patients were consented to join the UCL-RFH biobank approved study "ANALYSIS OF ANTI-SARS COV2 IMMUNE RESPONSE". The UCL-RFH Biobank has been given a favourable ethics opinion for conduct in the NHS by the Wales research ethics Committee 4 (REC: 16/WA/0289).

Oxford cohort (IC-HD)
Patients were consented to join the Oxford Radcliffe Biobank approved study "Immunological responses to COVID-19 vaccines in transplant and haemodialysis patients" (ref: ORB 21/A014). The Oxford Radcliffe Biobank has a favourable ethics opinion from the South Central Oxford Committee C (REC: 19/SC/0173). This work was conducted locally with funding support by the Oxford Transplant Foundation and the Oxfordshire Health Services Research Committee, part of Oxford Hospitals Charity.

LEGACY cohort (Healthy volunteers)
The LEGACY cohort (NCT04750356) has been described recently[2,3]. It comprises of healthcare workers from University College London Hospital and scientists from the Francis Crick Institute, London. The LEGACY study was approved by London Camden

and Kings Cross Health Research Authority (HRA) Research and Ethics committee (REC: 20/HRA/4717) and sponsored by University College London. The full dataset was kindly made available by the LEGACY team for analysis in this report. Please see Wall et al. for access details[2,3].

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 serological analyses, including in-house anti-Spike IgG ELISA and live-virus microneutralisation were performed as described previously[4].

Data analysis, statistics

Data analysis was performed in R/Rstudio, using Rmarkdown to knit to pdf. Anonymised data wrangling used a mix of base R and tidyverse. As previously[2,3], 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. NAbT are compared between vaccines, age groups, gender, diabetes (as a categorical variable) or immunosuppression using unpaired Mann-Whitney tests. 95% confidence intervals of the fold changes of median NAbT were estimated using *bootstrap* and *boot.ci*, with *type="basic"* argument, which does not assume normality. Where the median is below the quantitative range of the assay and estimated effect is shown using the lower bound of the quantitative range (IC_{50}=40), and confidence intervals are not reported. Stratified IC_{50} NAbT were compared using ordinal logistic regression using the model: IC_{50} binned ~ strain * vaccine and the rms package. Correlation between log2 NAbT and age was performed using Spearman's correlation coefficient. Plots were generated using ggplot2 and ggpubr packages.

Data Sharing

All R code to reproduce all figures and analyses is freely available at XXX. The public dataset omits dialysis centre, age and dates, to ensure an individual participant cannot be identified. The LEGACY data is already available as outlined in their original publications[2,3].

Ethics

This work is covered by the following REC approvals: REC: 21/WM/0031, REC: 16/WA/0289, REC: 19/SC/0173, REC: 20/HRA/4717, as described in the cohort descriptions above. Within REC: 21/WM/0031, central processing in the Crick was included.

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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