Comparison of immunogenicity and clinical effectiveness between BNT162b2 and ChAdOx1 SARS-CoV-2 vaccines in people with end-stage kidney disease receiving haemodialysis: A prospective, observational cohort study

*Paul Martin,[a] Sarah Gleeson,[b] Candice L. Clarke,[b] Tina Thomson,[a] Helena Edwards,[a] Katrina Spensley,[a,b] Paige Mortimer,[b] Stacey McIntyre,[b] Alison Cox,[c] Graham Pickard,[c] Liz Lightstone,[a,b] David Thomas,[a,b] Stephen P. McAdoo,[a,b] Peter Kelleher,[c,d] Maria Prendecki,[a,b] and Michelle Willicombe [a,b]**

[a]Imperial College Renal and Transplant Centre, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London W12 0HS, United Kingdom
[b]Centre for Inflammatory Disease, Department of Immunology and Inflammation, Imperial College London, Hammersmith campus, Du Cane Road, London W12 0NN, United Kingdom
[c]Department of Infection and Immunity Sciences, Northwest London Pathology NHS trust, Charing Cross Hospital, Fulham Palace Road, London W6 6RF, United Kingdom
[d]Department of Infectious Diseases, Imperial College London, Chelsea and Westminster Campus, Fulham Road, London SW10 9NH, United Kingdom

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Summary

Background People with end-stage kidney disease, including people on haemodialysis, are susceptible to greater COVID-19 related morbidity and mortality. This study compares the immunogenicity and clinical effectiveness of BNT162B2 versus ChAdOx1 in haemodialysis patients.

Methods In this observational cohort study, 1021 patients were followed-up from time of vaccination until December 2021. All patients underwent weekly RT-PCR screening. Patients were assessed for nucleocapsid(anti-NP) and spike (anti-S) antibodies at timepoints after second(V2) and third(V3) vaccinations. 191 patients were investigated for T-cell responses. Vaccine effectiveness (VE) for prevention of infection, hospitalisation and mortality was evaluated using the formula VE=(1-adjustedHR)x100.

Findings 45.7% (467/1021) had evidence of prior infection. There was no difference in the proportion of infection-naïve patients who seroconverted by vaccine type, but median anti-S antibody titres were higher post-BNT162b2 compared with ChAdOx1; 462(152-1171) and 78(20-213) BAU/ml respectively, $p<0.001$. Concomitant immunosuppressant use was a risk factor for non-response, OR 0.12[95% CI 0.05−0.25] $p<0.001$. Post-V3 (all BNT162b2), median anti-S antibody titres remained higher in those receiving BNT162b2 versus ChAdOx1 as primary doses; 2756(187−1246) and 1250(439−2635) BAU/ml respectively, $p=0.003$.

Anti-S antibodies waned over time. Hierarchical levels of anti-S post-V2 predicted risk of infection; patients with no/low anti-S being at highest risk. VE for preventing infection, hospitalisation and death was 53% (95% CI 6−75), 77% (95% CI 30−92) and 93% (95% CI 59−99) respectively, with no difference seen by vaccine type.

Interpretation Serum anti-S concentrations predict risk of breakthrough infection. Anti-S responses vary dependent upon clinical features, infection history and vaccine type. Monitoring of serological responses may enable individualised approaches to vaccine boosters in at risk populations.

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*Corresponding author at: Department of Immunology and Inflammation, 9th floor Commonwealth Building, Imperial College London Hammersmith Campus, Du Cane Road, London, W12 0NN.
E-mail address: m.willicombe08@imperial.ac.uk (M. Willicombe).

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Research in context

Evidence Before this study

End stage kidney disease (ESKD) is strongly associated with COVID-19 related mortality. People with ESKD (including those on haemodialysis) and other immunocompromised conditions were excluded from the original SARS-CoV-2 vaccine studies, negating immunogenicity and efficacy data in this population prior to their clinical use.

We performed a literature search of MEDLINE in February 2022 using the following search strategy -((vaccin*) AND (Haemodialysis OR Hemodialysis OR dialysis)) AND (COVID-19 OR SARS-CoV-2 OR Coronavirus). Overall serological responses to SARS-CoV-2 vaccines in haemodialysis patients are good, with seroconversion rates of >88% reported. However, the majority of studies assess primary vaccine courses utilising mRNA vaccine platforms only. In addition, most studies investigate serological responses exclusively, despite the recognition that ESKD and uraemia are associated with T-cell exhaustion and suppression of IFN-γ production. A few studies have reported on vaccine effectiveness, with evidence available suggesting that ESKD is a risk factor for breakthrough infection. However, there are no prior studies which correlate effectiveness with immunogenicity data in patients who were asymptomatically screened.

Added value of this study

This large, prospective, longitudinal study compares immune responses and clinical effectiveness following vaccination with BNT162b2 versus ChAdOx1 in 1021 haemodialysis patients; 523 (51.2%) of whom received BNT162b2 and 498 (48.8%) ChAdOx1. Patients with prior infection, 467/1021 (45.7%), were identified, and all patients underwent weekly asymptomatic screening throughout the duration of the study. Whilst absolute seroconversion rates in infection-naïve patients were no different between those patients who received BNT162b2 compared with ChAdOx1; spike protein antibody concentrations (anti-S) were significantly higher in patients who had received BNT162b, with median concentrations of 462 (152−1171) BAU/ml versus 78 (20−213) BAU/ml following BNT162b2 and ChAdOx1 respectively, $p<0.000$. Concomitant use of immunosuppression, OR 0.12 (0.05−0.25), $p<0.0001$ was associated with non-seroconversion. T-cell responses were poor; only 17/94 (18.1%) of infection-naïve patients had detectable T-cell responses post-vaccination, with no proportional difference between those receiving BNT162b2, 2/19 (10.5%), compared with ChAdOx1, 15/75 (20.0%), $p=0.34$.

Vaccine effectiveness for preventing infection, hospitalisation and death was 53(6−75) %, 77(30−92) % and 93(59−99) % respectively, with no difference in risk of infection following BNT162b2 compared with ChAdOx1 in this cohort, HR 1.48 (0.84−2.63), $p=0.18$. **Anti-S concentrations post-vaccination were associated with risk of breakthrough infection, with** higher risk of infection seen in patients with lower antibody concentrations.

Anti-S concentrations waned over time, with significant boosting after a third vaccine (V3), all of which were BNT162b2. However, post-V3, anti-S remained higher in infection-naïve patients who received BNT162b2 versus ChAdOx1 as primary doses; 2756(1871246) and 1250(439−2635) BAU/ml respectively, $p=0.003$.

Implications of all the available evidence

The pandemic is not over; there remains a need to understand the immunogenicity and effectiveness of all vaccine platforms in people with ESKD and other immunocompromising health conditions. This study demonstrates that serological response to vaccination, irrespective of vaccine type, predicts the risk of subsequent SARS-CoV-2 infection. Monitoring of serological responses to vaccination in patients receiving haemodialysis, may enable targeted and individualised approaches to future vaccine booster strategies. This bespoke monitoring and intervention proposal could be explored in other people with immunocompromising conditions.

Introduction

Encouraging data on the immunogenicity of mRNA SARS-CoV-2 vaccines in people with end-stage kidney disease (ESKD) receiving haemodialysis has emerged globally, with seroconversion rates of >88% reported.[1−4] Whilst reports of corresponding clinical efficacy of mRNA vaccines in haemodialysis populations are now forthcoming, there remains limited data on the immunogenicity of SARS-CoV-2 vaccines that utilise viral vector biotechnology.

Most SARS-CoV-2 immunogenicity studies in haemodialysis patients have focused on serological responses alone. Whilst it is recognised that in healthy individuals, vector-based vaccines elicit a more robust

T-cell response compared with mRNA vaccines, the accelerated immunosenescence associated with ESKD may have a differential effect on the cellular and humoral components of the individual vaccine responses.[5,6] Understanding these differences may better inform booster vaccination strategies in this population.

Here we compare the immunogenicity of the BNT162b2 and ChAdOx1 vaccines in a large, well-characterised haemodialysis population, assessing humoral and cellular responses and comparing them with healthy controls. By prospective longitudinal surveillance, we also report on comparative clinical efficacy of these two vaccines and assess the correlation between immunogenicity and vaccine effectiveness, and the effect of homologous or heterologous third-vaccine doses on serological responses.

Methods

Patient selection

One-thousand and twenty-one patients who were receiving maintenance haemodialysis in nine community units in northwest London, who had received 2 doses of a SARS-CoV-2 vaccine and had a serological sample ≥14 days following their 2nd inoculation (V2), were included (Figure 1). No sample size calculation was performed prior to undertaking this study; the studied cohort is the total number of in-centre haemodialysis patients at Imperial College Healthcare NHS Trust who were eligible to participate in the study.. The type of vaccine administered was dependent on local availability at the time. Participants were vaccinated either at their haemodialysis centre, by their general practice doctor,

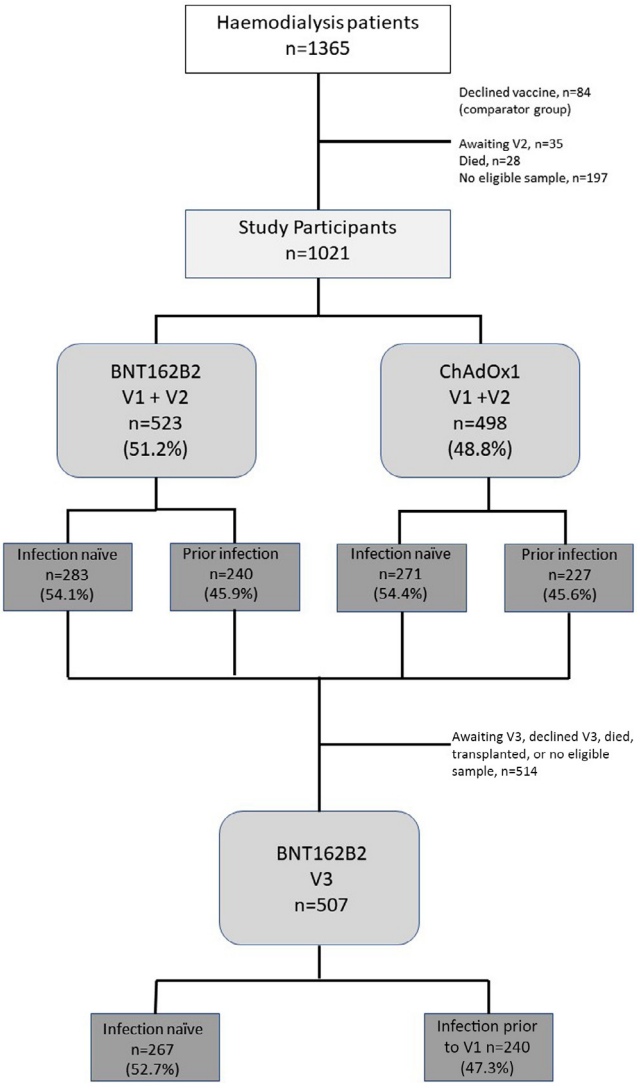

Figure 1. Study flow diagram.

or at community hubs. All patients were followed up post-V2 until 30th November 2021. Clinical data were obtained from electronic patient records and the institutional vaccine database. The study was approved by the Health Research Authority, Research Ethics Committee (20/WA/0123).

A subgroup of 191(18.7%) patients underwent more in-depth immunological analysis of both serological and cellular responses to SARS-CoV-2 vaccination. The clinical characteristics of this subgroup, along with a comparison with the remainder of the cohort, can be found in *Supplemental Information* (Table S1). Sixty-five healthcare workers (HCW), median age 38 (30–46) years, were used as a comparator group against the aforementioned subgroup only. Fifty and 15 HCW received the BNT162b2 and ChAdOx1 vaccines, respectively. The median interval between V1 and V2 in the subgroup was 68 (60–72) days, compared with 68 (61–70) days in the HCW control group, p=0.70. The median time to sampling post-V2 in the subgroup was 27 (26–28) days, compared with 28 (21–28) days in the HCW control group, p=0.06.

Serological responses to third-dose vaccines (V3) were assessed in 507 patients who had not developed breakthrough infection between V2 and V3; 267 were infection-naïve and 240 had evidence of infection prior to first vaccination. All third doses administered were BNT162b2, irrespective of vaccine received for the first two doses.

Eighty-four patients refused to be vaccinated. A summary of the clinical characteristics of this cohort can be found in the *Supplemental Information* (Table S2). This cohort was used as reference group when assessing event rates in the vaccinated cohort.

SARS-CoV-2 antibody detection

Serological sampling was performed during haemodialysis sessions. Serum was tested for antibodies to nucleocapsid protein (anti-NP) and spike protein (anti-S). Anti-NP was detected using the Abbott Architect SARS-CoV-2 IgG 2 step chemiluminescent immunoassay (CMIA) according to manufacturer's instructions. Samples were interpreted as positive or negative with a threshold index value of 1.4. For vaccine responses, anti-S IgG were assessed using the Abbott Architect SARS-CoV-2 IgG Quant II CMIA. Anti-S titres are quantitative, with a range of detection between 7.1 BAU/ml and 5680 BAU/ml.

Detection of cellular responses to SARS-CoV-2

SARS-CoV-2 specific T-cell responses were detected using the T-SPOT® Discovery SARS-CoV-2, and assays performed by Oxford Immunotec. In brief, peripheral blood mononuclear cells (PBMCs) were isolated from whole blood samples with the addition of T-Cell Xtend™ (Oxford Immunotec) where indicated. 250,000 PBMCs were plated into individual wells of a T-SPOT® Discovery SARS-CoV-2 plate. The assay measures immune responses to SARS-CoV-2 spike protein peptide pools (S1 protein and S2 protein), in addition to positive PHA (phytohemagglutinin) and negative controls. Cells were incubated and interferon-γ secreting T-cells were detected. Spot forming units (SFU) were detected using an automated plate reader (Autoimmun Diagnostika). Infection-naïve, unvaccinated participants were used to identify a threshold for a positive response using mean +3 standard deviation SFU/10^6 PBMC, as previously described.[7] This resulted in a cut-off for positivity of 40 SFU/10^6 PBMC, established by Imperial College London/North-West London Pathology.

Definition of prior SARS-CoV-2 infection

Prior exposure was defined as: positive viral detection from nasopharyngeal swab specimens via reverse-transcriptase polymerase chain reaction (RT-PCR) assays, positive anti-NP serology at any time point, or positive anti-S serology pre-vaccination. All patients were swabbed weekly throughout the study period. Protocolised three-monthly serological screening of haemodialysis patients commenced June 2020.

Assessment of vaccine effectiveness

Reported outcomes included RT-PCR proven SARS-CoV-2 infection, hospitalisation, and death. Death was recorded as SARS-CoV2-related if it occurred within 28-days of confirmed infection. Event rates for the outcomes of interest were reported as incidence per 1000-patient days at risk. Cox proportional hazards models were used to determine adjusted hazard ratios (HR) for the first PCR-positive test after 14 days post-V2. Patients who received a third dose of SAR-CoV-2 vaccine were censored on the day of third inoculation. Vaccine effectiveness (VE) was calculated using the formula VE= (1-adjusted HR) x100. Outcomes of unvaccinated haemodialysis patients were used as the reference group.

Statistical analysis

Statistical analysis was conducted using Prism 9.0 (GraphPad Software Inc., San Diego, California). Unless otherwise stated, all data are reported as median with interquartile range (IQR). The Chi-squared test was used for proportional assessments. The Mann-Whitney and Kruskal-Wallis tests were used to assess the difference between 2 or >2 groups, with Dunn's post-hoc test to compare individual groups. Multivariable analyses for vaccine immunogenicity were conducted using logistic regression using variables which were found to be significant on univariable analysis.

Role of the funding source
Funding of laboratory consumables and staff costs.

Results

1021 patients were tested for anti-S and anti-NP, at median time 41(37–42) days post-V2. Of these patients, 467/1021 (45.7%) had evidence of prior infection; 328 (70.2%) diagnosed via RT-PCR and 139(27.8%) serologically. Overall, 523(51.2%) patients received BNT162b2 and 498(48.8%) received ChAdOx1 (Figure 1). There was no difference in the proportion of patients with prior infection receiving BNT162b2, 240(45.9%), compared with ChAdOx1, 227(45.6%), p=0.92.

Serological responses in infection-naïve patients

The overall seroconversion rate in infection-naïve patients was 476/554(85.9%), with no proportional difference between those who received BNT162b2, 250/283(88.3%) patients, compared with ChAdOx1, 226/271 (83.4%) patients, p=0.09. However, median anti-S concentrations were significantly higher in patients who received BNT162b, at 462(152–1171) and 78(20–213) BAU/ml following BNT162b and ChAdOx1 respectively, p<0.0001 (Figure 2a).

Clinical characteristics associated with a reduced likelihood of seroconverting included length of time since ESKD diagnosis and need for renal replacement therapy, concomitant pharmacological immunosuppression, and history of failed kidney transplant (Table 1). Being active on the transplant waitlist and being of non-Caucasian ethnicity was associated with increased seroconversion rates (Table 1). Comparison of anti-S concentrations demonstrated lower levels in patients receiving immunosuppression compared with non-immunosuppressed patients, with median concentrations of 27(7.1–338) BAU/ml and 231(53–700) BAU/ml respectively, p<0.0001. Further analyses of anti-S by immunosuppression type and transplantation history are shown in the *Supplemental Information* (Figure S1). We found lower seroconversion rates in Caucasian patients, with a significant difference in anti-S between Caucasians and Indoasians, 147(11–448) and 230(48–650) BAU/ml respectively, p=0.02. There were no quantitative differences in anti-S according to gender, cause of ESKD, or diabetes status (*Supplemental Information* Figure S2). No correlation was seen between age and anti-S concentrations, p=0.24.

On multivariable analysis, use of immunosuppression, OR 0.12[95% CI 0.05–0.25], p<0.0001 was associated with non-seroconversion whilst being active on the transplant wait list remained an independent predictor of seroconversion, OR 2.52[95% CI 1.12–5.69], p=0.02 *Supplemental Information* (Table S3).

Serological responses in patients with prior infection

Of 467 patients with prior infection, 6(1.3%) remained anti-S seronegative post-V2; 3/227(1.32%) who received ChAdOx1 and 3/240(1.25%) who received BNT162b2, p=0.95. Five of the six patients had prior infection diagnosed by RT-PCR. One patient was diagnosed based on

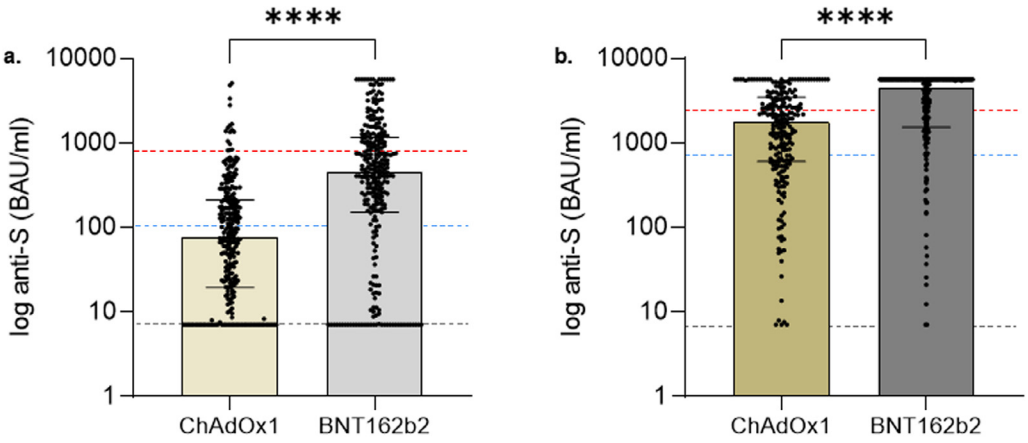

Figure 2. Comparison of spike protein antibodies in haemodialysis patients receiving BNT162b2 compared with ChAdOx1. a. In infection-naïve patients *n*=554. The median anti-S concentrations in the BNT162b and ChAdOx1 patients were 462 (152–1171) and 78 (20–213) BAU/ml respectively, p<0.0001. The dotted lines represent the median anti-S of infection-naive health care workers (HCW) who received the BNT162b2 vaccine, 815 (318-2033) BAU/ml (red/upper line) and ChAdOx1 vaccine, 88 (47–395) BAU/ml (blue/middle line). The black/lower dotted line indicates the positive cut-off of the assay 7.1 BAU/ml **b. In patients with prior infection *n*=467.** The median anti-S concentrations in the BNT162b and ChAdOx1patients were 4467 (1543–5680) and 1767 (610–3469) BAU/ml respectively, p<0.0001. The dotted lines represent the median anti-S of HCW with prior infection who received the BNT162b2 vaccine, 2189 (1236–3303) BAU/ml (red/upper line) and ChAdOx1 vaccine, 753 (574–867) BAU/ml (blue/middle line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Characteristics		Failure to seroconvert N=78 (%)	Seroconversion N=476 (%)	p-value
Gender	Male	44 (56.4)	293 (61.6)	0.39
	Female	34 (43.6)	183 (38.4)	
Age	Years – median (IQR)	68 (57–77)	67 (56–76)	0.56
Ethnicity	Caucasian*	33 (42.3)	145 (30.5)	**0.038**
	Black	12 (15.4)	90 (18.9)	
	Indoasian	17 (21.8)	168 (35.3)	
	Other	16 (20.5)	73 (15.3)	
Cause of ESKD	Polycystic kidney disease	5 (6.4)	22 (4.6)	0.33
	Glomerulonephritis*	17 (21.8)	82 (17.2)	
	Diabetic nephropathy	29 (37.2)	196 (41.2)	
	Urological	5 (6.4)	34 (7.1)	
	Unknown	11 (14.1)	103 (21.6)	
	Other	11 (14.1)	39 (8.2)	
Time at ESKD	Years – median (IQR)	3.8 (1.6–12.9)	2.7 (0.7–6.8)	**0.008**
Previous transplant	Yes	27 (34.6)	76 (16.0)	**0.0001**
	No	51 (65.4)	400 (84.0)	
Immunosuppression at time of vaccine	None	41 (52.6)	418 (87.8)	**<0.0001**
	Yes	37 (47.4)	58 (12.2)	
	CNI monotherapy	14 (17.9)	22 (4.6)	
	CNI/anti-proliferative	0	4 (0.8)	
	CNI/steroids	10 (12.8)	11 (2.3)	
	CNI/anti-proliferative/steroids	1 (1.3)	0	
	Anti-proliferative/steroids	4 (5.1)	0	
	Anti-proliferative alone	1 (1.3)	0	
	Rituximab based	2 (2.6)	0	
	Corticosteroids alone	5 (6.4)	18 (3.8)	
	Other	0	3 (0.6)	
Diabetes	No	41 (52.6)	235 (49.4)	0.60
	Yes	37 (47.4)	241 (50.6)	
Active on transplant wait list	No	70 (89.7)	382 (80.3)	**0.045**
	Yes	8 (10.3)	94 (19.7)	
Vaccine type	BNT1262b2	33 (42.3)	250 (52.5)	0.09
	ChAdOx1	45 (57.7)	226 (47.5)	
Time between vaccinations	Days – median (IQR)	62 (44–72)	63 (53–72)	0.16
Time of serological test post-V2	Days – median (IQR)	39 (28–48)	41 (28–48)	0.63

***Table 1*: Clinical characteristics associated with seroconversion following SARS-CoV-2 vaccination in 554 infection naïve haemodialysis patients.**
ESKD end-stage kidney disease, CNI calcineurin inhibitor, V2 vaccine dose two, * Comparator group for analysis.

positive anti-NP status prior to vaccination. Individual patient characteristics available in the *Supplemental Information* (Table S4). A summary of characteristics of patients with evidence of natural infection prior to vaccination, and a comparison with their infection-naïve peers, can be found in the *Supplemental Information* (Table S5).

The overall median anti-S antibody titre post-V2 was markedly higher in patients with prior exposure compared with infection-naïve patients; 2692(972–5680) BAU/ml and 189(27–631) BAU/ml respectively, $p<0.0001$. For patients with prior infection, those who received ChAdOx1 had a median anti-S of 1767(610–3469) BAU/ml, which was lower than patients who had received BNT162b2, 4467(1543–5680) BAU/ml, $p<0.0001$ (Figure 2b). There was no difference in median anti-S in those patients who were diagnosed by RT-PCR compared with serology. Patients receiving BNT162b2 testing positive via PCR had a median anti-S of 5184(1689-5680) BAU/ml versus 3354(1390–5680) BAU/ml following a serological diagnosis, $p=0.97$. For those receiving ChAdOx1, a median anti-S of 1954(642–3747) BAU/ml and 1420(533–2907) BAU/ml were seen following PCR and serological diagnoses respectively, $p=0.71$ (*Supplemental Information* Figure S3). There was a negative correlation between anti-NP and time

from COVID diagnosis, $r=-0.30$, $p<0.0001$. The co-existence of anti-NP post-V2 was associated with higher anti-S; anti-NP positive and anti-NP negative patients receiving BNT162b2 had a median anti-S of 5680(3644–5680) BAU/ml and 2519(737–5680) BAU/ml respectively, $p<0.0001$; and those receiving ChAdOx1, 2152(956–4133) BAU/ml and 1872(301–2709) BAU/ml respectively, $p=0.04$ (*Supplemental Information* Figure S3).

Cellular and humoral responses in infection-naïve patients

A subgroup of 191 patients had paired assessment of T-cell and serological responses at a median time of 27(26–28) days post-V2. Fifty of 191 (26.2%) patients received BNT162b2 and 141 (73.8%) ChAdOx1. Nineteen of 50 (38.0%) patients who received BNT162b2 and 75(53.1%) who received ChAdOx1 were infection-naïve, $p=0.052$.

Overall, 17/94(18.1%) of infection-naïve patients had detectable T-cell responses post-V2. There was no proportional difference in ELISpot positivity in infection-naïve patients who received BNT162b2, 2/19(10.5%), compared with ChAdOx1, 15/75(20.0%), $p=0.34$. On quantification of cellular responses, there was no difference in the median number of SFUs between infection-naïve patients who received BNT162b2 compared with ChAdOx1, with 2(0–16) SFU/10^6 PBMCs and 10(4–28) SFU/10^6 PBMCs respectively, $p=0.35$. However, compared with infection-naïve HCW, responses were significantly weaker in patients, with infection-naïve HCW receiving BNT162b2 and ChAdOx1 having a median 63(21–132) SFU/10^6 PBMCs, $p<0.0001$ and 68 (30–162) SFU/10^6 PBMCs, $p=0.0083$ respectively (Figure 3a). Paired serological assessment of these infection-naïve patients demonstrated no difference in seroconversion rates following either BNT162b2 or ChAdOx1, with 14/19(73.7%) and 57/75(76.0%) patients seroconverting respectively, $p=0.83$. Quantification of these responses showed significantly higher anti-S in patients who received BNT162b2 compared with ChAdOx1, at 557(7.1–1745) BAU/ml and 82(8–183) BAU/ml respectively, $p=0.02$ (Figure 3b). However, there were no differences in anti-S between infection-naïve HCW and patients who received the corresponding vaccine, with HCW receiving BNT162b2 having a median anti-S of 815(318–2033), $p=0.054$, and those receiving ChAdOx1 a median anti-S of 88(47–395) BAU/ml, $p=0.97$ (Figure 3b).

Cellular and humoral responses in patients with prior infection

Overall, 56/97(57.7%) of patients with prior exposure had detectable T-cell responses post-V2. There was no proportional difference in ELISpot positivity in patients with prior infection who received BNT162b2, 15/31 (48.4%), compared with ChAdOx1, 41/66(62.1%), $p=0.20$. On quantification of cellular responses, there was no difference in median SFU/10^6 PBMCs who received BNT162b2 compared with ChAdOx1, with 26 (6–144) SFU/10^6 PBMCs and 102(18–250) SFU/10^6 PBMCs respectively, $p=0.08$ (Figure 4a). No significant differences were seen between previously exposed HCW receiving ChAdOx1, 114(74–216) SFU/10^6 PBMCs, compared with patients who received ChAdOx1, $p=0.99$. However, previously exposed HCW who received BNT162b2 had significantly greater responses, 246(131–332) SFU/10^6 PBMCs, compared with patients receiving BNT162b2, $p=0.0017$ (Figure 4a).

Ninety-four of 97 (96.9%) patients with prior evidence of infection had detectable anti-S. There was no difference in anti-S in patients with prior infection who received BNT162b2, 2380(544–5680) BAU/ml, compared with ChAdOx1, 1446(357–4063) BAU/ml, $p=0.45$. There were also no differences between patients and HCW with prior exposure who received BNT162b2, median anti-S 2189(1236–3303) BAU/ml, $p=0.99$, or HCW who received ChAdOx1, median anti-S 753(574–867) BAU/ml, $p=0.92$ (Figure 4b).

Assessment of vaccine effectiveness

The median surveillance period for vaccine effectiveness was 206(186–235) days. During this period, 76/1021 (7.4%) patients received a transplant or transferred care, and 80/1021(7.8%) patients died in the absence of a diagnosis of SARS-CoV-2. In total, 208,046 patient days were included in the event rate analysis following vaccination (Table 2). Vaccine effectiveness for preventing infection, hospitalisation and death was 53% (95% CI 6–75), 77% (95% CI 30–92) and 93% (95% CI 59–99) respectively (Table 2). Considering effectiveness by vaccine type, VE of BNT162b2 against infection was 62% (95% CI 18–82) $p=0.011$, and 42% (95% CI -22–70) $p=0.13$ for ChAdOx1. There was no significant higher risk of infection following vaccination with ChAdOx1 compared with BNT162b2 in this cohort, HR 1.48 (95% CI 0.84–2.63) $p=0.18$ (*Supplemental Information* Table S6).

Within the vaccinated group, analysis of clinical characteristics associated with SARS-CoV-2 related clinical events revealed evidence of prior infection was associated with reduced likelihood of re-infection and its potential sequelae (*Supplemental Information* Table S6). No patient with prior infection was admitted to hospital or died due to SARS-CoV-2 infection following vaccination. Prior infection defined by either PCR (HR 0.07 [95% CI 0.01–0.23] $p=0.0002$) or serology alone (HR 0.24 [95% CI 0.06–0.67] $p=0.018$) reduced the risk of subsequent PCR proven infection following vaccination.

Correlation between post-vaccination serological responses and subsequent infection

As a binary value, a detectable serological response post-V2 was not associated with reduced likelihood of infection, HR 0.70 [95% CI 0.31–2.03] $p=0.46$.

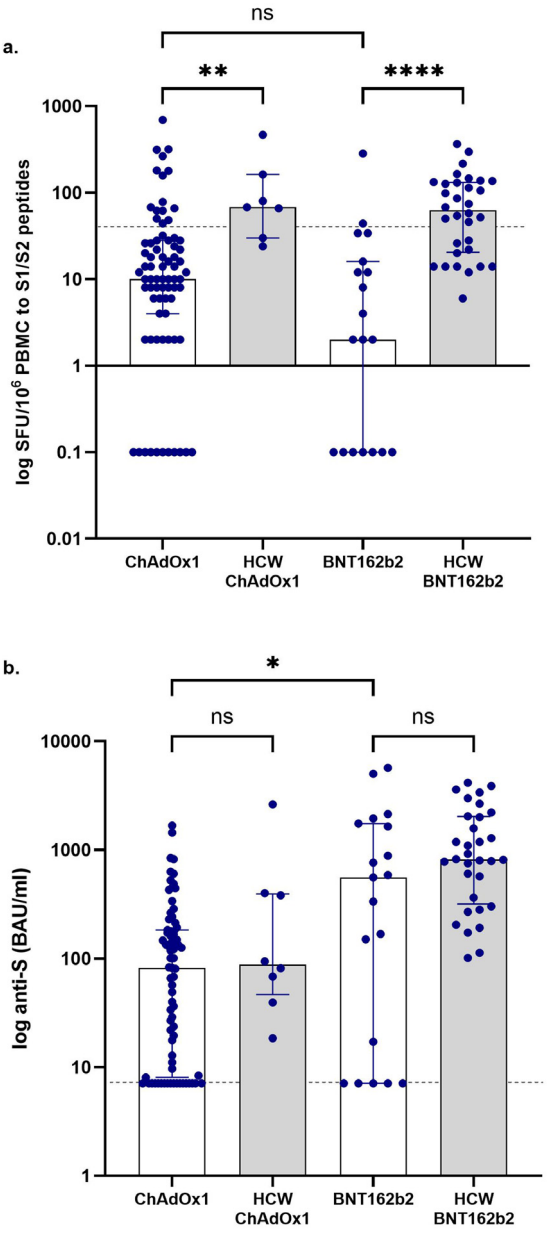

Figure 3. Comparison of post-vaccination T-cell and serological responses in infection-naïve patients (*n*=94) and healthcare workers (*n*=40). The median SFU in infection-naïve patients receiving ChAdOx1 and BNT162b2 were 10 (4–28) and 2 (0–16) SFU/10^6 PMBCs respectively. The median SFU in infection-naïve HCW receiving ChAdOx1A and BNT162b2 was 68 (30–162) SFU/10^6 and 63 (20.5–131.5) SFU/10^6 PMBCs respectively. The median anti-S concentrations in infection-naïve patients receiving ChAdOx1A and BNT162b2 were 82 (8.0–183) and 557 (7.1–1745) respectively. The median anti-S concentrations in infection-naïve HCW receiving ChAdOx1 and BNT162b2 were 88 (47–395) and 815 (318–2033) BAU/ml respectively. a. There was no difference in SFU in patients receiving ChAdOx1 compared with BNT162b2, p=0.35. Responses were significantly weaker in patients compared with HCW receiving the same vaccine; ChAdOx1, p=0.0083 and BNT162b2, p<0.0001. b. There was no difference in anti-S concentrations in patients compared with HCW receiving the same vaccine; ChAdOx1, p=0.97 and BNT162b2, p=0.054. Patients receiving BNT162b2 had significantly higher anti-S than those receiving ChAdOx1, p=0.02.

To investigate the impact of antibody waning on this lack of association, 783 patients with no new infection post-V2 who had paired antibody testing performed at a median time of 41(27–49) and 158(153–166) days post-V2, corresponding to time 1 (T1) and time 2 (T2) were assessed. Over a median period of 116(115–129) days between sampling, median anti-S concentrations fell from 735(143–3068) to 210(35–1110) BAU/ml, p<0.0001. In the 413/783(52.7%) patients who were infection-naïve, this equated to a fall from 202(28–628) to 46(9–134) BAU/ml, p<0.0001; 82(20–211) to 21(7.1–57) BAU/ml in those vaccinated with ChAdOx1, p<0.0001, and 441(162–1168) to 100(33–2234) BAU/ml in those receiving BNT162b2, p<0.0001 (Figure 5a). In the 370 patients who had prior infection, post-V2 concentrations fell from 2710(1090–5680) to 1094(384–2814), p<0.0001; a reduction from 1909 (634–3502) to 750(290–1867) BAU/ml in those vaccinated with ChAdOx1, p<0.0001, and 4390(1741–5680) to 1546(538–3690) BAU/ml in those receiving BNT162b2, p<0.0001. Notably, median anti-S was significantly higher at T2 in patients with prior infection compared with T1 in the infection naïve, p<0.0001 (Figure 5a).

Considering antibody waning over time, the protective effect of post-V2 anti-S concentrations were investigated using hierarchical levels determined by IQR: level 1 (7.1–120 BAU/ml), level 2 (121–652 BAU/ml), level 3 (653–2905 BAU/ml) and level 4 (2906–5680 BAU/ml). A higher risk of infection was seen in patients with lower levels of antibody. Using patients with antibody concentrations within level 1 as a reference point, the adjusted hazard ratios for subsequent infection were HR 0.79 [95% CI 0.41–1.50] p=0.47, HR 0.30 [0.12–0.69] p=0.007 and HR 0.08 [0.013–0.28] p=0.0008 in patients within level 2, 3 and 4 respectively (Figure 5b).

Serological responses post-V3 following homologous versus heterologous boosting

Further serial sampling was obtained in 507 patients, without evidence of interval infection, at a median of 52 (37–62) days post-V3. In infection-naïve patients (n=267), anti-S was significantly higher post-V3 compared with post-V2 at 1909(669–4853) and 210(27–653) BAU/ml respectively, p<0.0001. Higher concentrations were also seen in 240 patients with evidence of prior infection, with levels of 5680(3271–5680) and 2727(975–5680) BAU/ml post- V3 and V2 respectively, p<0.0001 (Figure 5c). Comparing post-V3 anti-S in

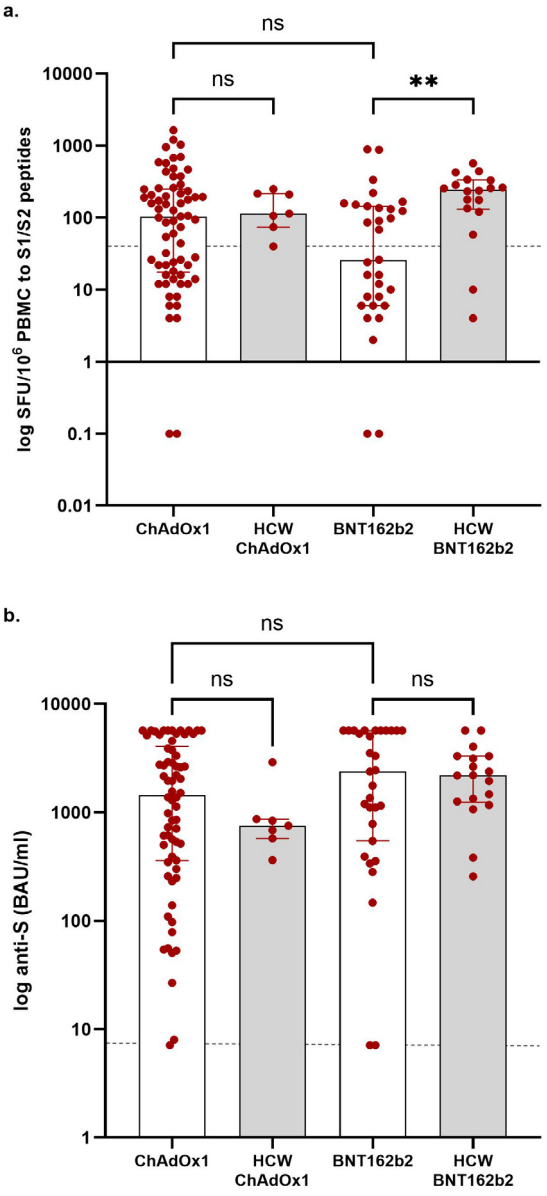

Figure 4. Comparison of post-vaccination T-cell and serological responses in patients (*n*=97) and healthcare workers (*n*=25) with prior exposure to SARS-CoV-2. The median SFU in previously exposed patients receiving ChAdOx1 and BNT162b2 were 102 (18–250) and 26 (6–144) SFU/10^6 PMBCs respectively. The median SFU in previously exposed HCW receiving ChAdOx1 and BNT162b2 were 114 (74–216) and 246 (131–332) SFU/10^6 PMBCs respectively. The median anti-S concentrations in previously exposed patients receiving ChAdOx1 and BNT162b2 were 1446 (357–4063) and 2380 (544–5680) respectively. The median anti-S in previously infected healthcare workers receiving ChAdOx1 and BNT162b2 were 753 (574–867) and 2189 (1236–3303) BAU/ml respectively. a. There was no difference in SFU in patients receiving ChAdOx1 compared with BNT162b2, p=0.08. Responses were significantly weaker in patients compared with HCW receiving BNT162b2, p=0.0017, but not ChAdOx1, p=0.99. b. There was no difference in anti-S concentrations in patients receiving ChAdOx1compared with BNT162b2, p=0.45. There was no difference in anti-S concentrations in patients compared with HCW receiving the same vaccine; ChAdOx1, p=0.99 and BNT162b2, p=0.92.

those with prior infection demonstrated no difference in levels post-V3 in patients who received a primary vaccine course of BNT162b2 (5680(3154–5680) BAU/ml) versus ChAdOx1 (5680(3560–5680) BAU/ml), p=0.32 (Figure 5d). However, for infection-naïve patients, those who had received BNT162b2 as a primary course had significantly higher anti-S compared with those who had received ChAdOx1 at 2756(187–1246) versus 1250 (439–2635) BAU/ml respectively, p=0.003 (Figure 5d).

Discussion

The susceptibility of in-centre haemodialysis patients to SARS-CoV-2 infection is highlighted by the high proportion of patients in our cohort, 45.8%, who were found to have infection prior to vaccination. As already recognised, there were distinct differences in the immunogenicity data in those who had prior infection, compared with those who remained infection naïve. After receipt of two vaccines, 936 (91.7%) patients had detectable anti-S, with seroconversion occurring in 475 (85.9%) infection-naïve patients. Whilst we found no difference in the proportion of patients seroconverting between BNT162b2 and ChAdOx1, quantitatively higher antibody concentrations were seen in patients who had received BNT162b2. This was evident in both infection-naïve and previously infected patients, with a difference remaining post-V3 in the naïve group.

Immunogenicity data from the vaccine clinical trials suggest that T-cell responses are more robust following ChAdOx1 compared with BNT162b2.[5,8,9]. Within a previously defined subgroup, we found no difference in T-cell responses between the vaccines in infection-naïve patients, but we observed overall blunted responses compared with corresponding healthy controls. However, only patients with previous exposure who had received BNT162b2 had weaker T-cell responses compared with healthy controls. The observation that HCWs had greater T-cell responses than patients following BNT162b2, but similar responses with ChAdOX1 suggests that T-cell responses may be more robust following ChAdOx1 in dialysis patients. Other studies have reported cellular responses to mRNA vaccines using different measurement techniques and with variable outcomes[10–13]. Our data may reflect the peptide pools used in the ELISpot assays or differing thresholds used to define positivity. Irrespectively, it is recognised that ESKD and uraemia are associated with T-cell exhaustion and suppression of IFN-γ production, and the attenuated responses we found are in keeping with this[6,14,15].

Event		Per patient days of follow up	Number of patients	Number of events	Rate per 1000-patient days	Adjusted Hazard Ratio (95% CI)	*p* value	Vaccine Efficacy % (95% CI)
Infection	Unvaccinated	18,396	84	12	0.65	1		
	Vaccinated	2,08,046	1021	49	0.24	0.47 (0.25−0.94)	0.023	53 (6−75)
Hospitalisation	Unvaccinated	18,396	84	6	0.33	1		
	Vaccinated	2,08,046	1021	18	0.09	0.23 (0.08−0.70)	0.0062	77 (30−92)
Death	Unvaccinated	18,396	84	4	0.22	1		
	Vaccinated	2,08,046	1021	8	0.038	0.068 (0.008−0.41)	0.005	93 (59−99)

***Table 2*: SARS-CoV-2 infection event rates and vaccine efficacy.**

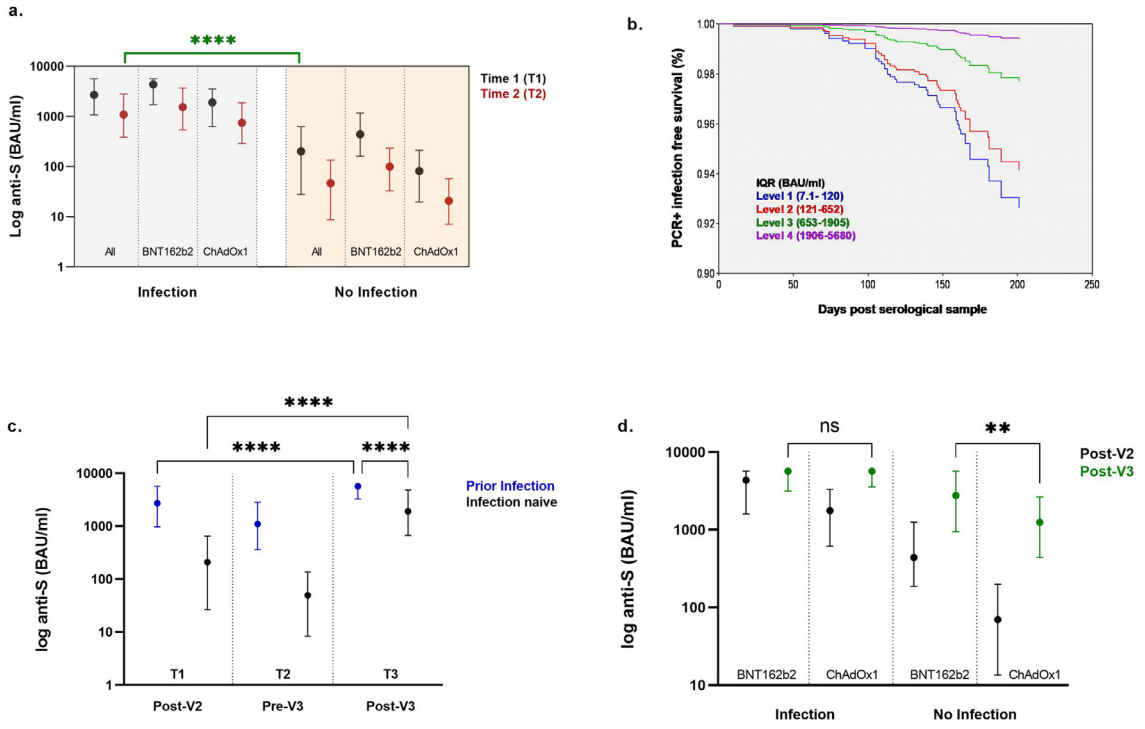

Figure 5. Waning of post-V2 antibody responses and correlation between anti-S and risk of infection. a. Waning of anti-S concentrations over time. Over a median period of 116 days, anti-S fell from 202 (628−28) to 46 (9−134) BAU/ml, $p<0.0001$, in 413 infection-naïve patients; 82 (20−211) to 21 (7.1−57) BAU/ml in those vaccinated with ChAdOx1, $p<0.0001$, and 441 (162−1168) to 100 (33−2234) BAU/ml in those receiving BNT162b2, $p<0.0001$. In 370 patients who had prior infection, post-V2 concentrations fell from 2710 (1090−5680) to 1094 (384−2814), $p<0.0001$; a reduction from 1909 (634−3502) to 750 (290−1867) BAU/ml in those vaccinated with ChAdOx1, $p<0.0001$, and 4390 (1741−5680) to 1546 (538−3690) BAU/ml in those receiving BNT162b2, $p<0.0001$. Median anti-S was significantly higher at T2 in patients with prior infection compared with T1 in the infection naïve, $p<0.0001$. **b. Adjusted risk for subsequent PCR-positive SARS-CoV-2 infection by anti-S concentration post-vaccination.** Compared with patients with an anti-S concentration of 7.1-120BAU/ml (level 1) following 2 doses of vaccine, patients with concentrations of 121−652 BAU/ml (Level 2), 653−2905 BAU/ml (Level 3) and 2906−5680 BAU/ml (Level 4) had an adjusted risk of 0.79 (0.41−1.50), $p=0.47$, 0.30 (0.12−0.69), $p=0.007$ and 0.08 (0.013−0.28), $p=0.0008$ respectively. **c. Serological responses post-V3 by prior infection status.** . In 267 infection-naïve patients, anti-S was significantly higher post-V3 compared with post-V2 at 1909 (669−4853) and 210 (27−653) BAU/ml respectively, $p<0.0001$. Higher concentrations were also seen in 240 patients with evidence of prior infection, with levels of 5680 (3271−5680) and 2727 (975−5680) BAU/ml post- V3 and V2 respectively, $p<0.0001$. **d. Serological responses post-V3 by vaccine type and infection status.** Post-V3 anti-S in 240 patients with prior infection demonstrated no difference in levels post-V3 in patients who received a primary vaccine course of BNT162b2 (5680 (3154−5680) BAU/ml) versus ChAdOx1 (5680 (3560−5680) BAU/ml), $p=0.32$. In 267 infection-naïve patients, those who had received BNT162b2 as a primary course had significantly higher anti-S compared with those who had received ChAdOx1 at 2756 (187−1246) versus 1250 (439−2635) BAU/ml respectively, $p=0.003$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Overall, given that T-cell responses were analysed in a smaller subgroup and may lack statistical power, we cannot confidently determine the clinical relevance of the cellular response in this studied cohort.

This study demonstrates that vaccine effectiveness against infection in haemodialysis patients is relatively low, in keeping with registry reports of higher incidence of breakthrough infections in patients with ESKD on haemodialysis, and consistent with the weaker immunogenicity properties we report.[16] However, it is also important to consider the additional impact of routine asymptomatic detection on the reported effectiveness, a practice performed by all UK renal centres at the time of the study. Interestingly, a recent prospective study of UK healthcare workers undergoing regular surveillance has described a comparable vaccine effectiveness (51%) against infection over a similar period.[17] Unfortunately, despite similar breakthrough infection rates, there is a stark difference in COVID-19 related clinical outcomes between patients with ESKD on haemodialysis and the general population.[16] Interestingly, we did not see a difference in clinical effectiveness between BNT162b2 and ChAdOx1, a finding also reported in a recent Scottish renal registry analysis, which contrasts with data in healthcare workers.[17,18] Within our analysis, this may be due to underpowering as demonstrated by the broad confidence intervals reported. Nevertheless, data from this and other studies do not support the withdrawal of viral vector vaccines in haemodialysis populations, especially at the expense of ensuring global vaccine coverage.[16,18] Our study strongly underscores the clinical benefit of vaccination in haemodialysis patients; when compared with unvaccinated peers, we report a vaccine efficacy of 77% for preventing hospitalisation, and 93% for preventing death due to COVID-19 (Table 2).

We have shown that factors other than vaccine type and prior infection contribute to immunogenicity. The concomitant use of immunosuppression also influenced sero-responses, as did transplant waitlist status. The former observation is in keeping with immunogenicity studies in other immunosuppressed populations showing weakened responses to SARS-CoV-2 vaccines[19,20]. The latter observation was more unexpected as we did not see a significant impact of age on vaccine responses. It may be reasonable to infer that those patients active on the transplant waitlist are physiologically less frail than their peers who are not waitlisted. We therefore hypothesise that, within this cohort, immunosenescence may be more closely related to physiological age than chronological age.[21]

Our haemodialysis cohort is heterogenous in nature; yet, apart from those taking immunosuppressives, each patient was vaccinated according to the same standard schedule. We propose it may be beneficial to consider routine monitoring of sero-responses in this population to guide individualised immunisation strategies. This study shows an inverse correlation between quantitative sero-responses and risk of infection; data which are supported by other studies and consistent with the finding that anti-S binding antibodies correlate with the presence of neutralising antibodies, which are considered the best correlate of protection.[22,23] Certainly, our finding that infection-naïve haemodialysis patients who received ChAdOx1 had the lowest anti-S concentrations complements the finding of inadequate neutralising antibodies in haemodialysis patients with these shared clinical features in a previous study.[24] All infection-naïve patients who contracted infection after vaccination had anti-S concentrations which fell below 284 BAU/ml, the binding antibody level which best correlated with neutralising antibodies against the Alpha variant in haemodialysis patients.[23] By providing post-V3 data, we demonstrate how effectively antibody concentrations respond to booster doses. Clearly, one challenge of this targeted approach would be the need to establish new parameters with different variants. Certainly, the Omicron variant has demonstrated significant immune evasion properties, which may render this proposal of individualised boosting redundant. However, the strategy from the UK at the time of this study was to prevent morbidity and mortality with vaccination rather than infection itself. Registry data reports mortality in haemodialysis patients is significantly less with Omicron infection compared with previous variants, and it has been shown that booster doses aided this outcome.[25,26] It should also be considered that for people receiving haemodialysis there is regular opportunity for serological sampling, as all patients undergo monthly blood tests as part of clinical monitoring. Furthermore, considering hepatitis-B as an example, there is a precedent for individualised approaches to vaccine administration and serological monitoring in this population.[27]

There are several limitations to our study; we were unable to control for vaccine effectiveness against different SARS-CoV-2 variants, we do not report on neutralising antibody properties, and our assessment of cellular immunity is in a smaller subgroup that may lack statistical power and is limited to a single T-cell cytokine readout. Incidentally, there are demographic differences between the subgroup who underwent T-cell analysis and the remainder of the cohort. Beyond age and sex, our volunteer control group of HCWs is not well characterised. The control group is not matched for age, giving an overestimate of the immune responses in healthy controls.[7] In addition, the control group, especially those receiving ChAdOx1, is relatively small and therefore susceptible to type II error. However, there are also several strengths to our study; we report on both humoral and cellular responses to ChAdOx1 vaccine, and correlate immunogenicity with clinical effectiveness. We also make a comparison with BNT162b2 and compare homologous versus heterologous post-V3 responses. Moreover, our ethnically diverse cohort has

been characterised in depth throughout the pandemic with asymptomatic screening via PCR and serological testing, enabling accurate identification of individuals with prior exposure.[28–30]

The efficacy of both BNT162b2 and ChAdOx1 vaccines in preventing infections and hospitalisations in the general population has been clearly demonstrated. Although breakthrough infection remains a cause for concern for haemodialysis patients, the clinical benefit of vaccination in our cohort is clear. Further improvements of vaccine effectiveness for preventing COVID-19 related hospitalisation and death, by the integration of bespoke monitoring and interventions in this population with individualised complexities, should be explored.

Contributors

Conceptualisation and supervision - Michelle Willicombe, Liz Lightstone, David Thomas, Stephen McAdoo, Peter Kelleher
Data curation - Paul Martin, Sarah Gleeson, Candice Clarke, Tina Thomson, Helena Edwards, Katrina Spensley
Laboratory work - Paige Mortimer, Stacey McIntyre, Alison Cox, Graham Pickard, Maria Prendecki
Formal analysis - Michelle Willicombe
Writing of drafts - Paul Martin, Michelle Willicombe
Review of draft- all authors

Data sharing statement

The data reported in this manuscript is not freely available. However, reasonable requests to access the data will be considered by the corresponding author.

Declaration of interests

Peter Kelleher and Michelle Willicombe have received support to use the T-SPOT Discovery SARS-CoV-2 by Oxford Immunotec. All other authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanepe.2022.100478.

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