Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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placed in non-COVID-19 areas with different infection prevention control processes.[3] Enteric features, and the ability of SARS-CoV-2 to persist on surfaces, raise the possibility of faecal-oral transmission in care settings under severe pressure, although the role of this transmission route is uncertain.[5]

As SARS-CoV-2 is likely to persist as an endemic or seasonal virus in coming years, it is critical to use the lessons learned so far in the pandemic to minimise the burden of hospital-acquired infections, and to consider new approaches to reduce the burden further. Surveillance afforded by this study has helped to rapidly identify changes in hospital-acquired infection incidence in different health-care settings. Unlike at the beginning of the pandemic, there are opportunities to pre-empt hospital-acquired infections and break chains of transmission through regular patient, resident, and staff testing including point-of-care diagnostics, as recently introduced for NHS staff, coupled with robust hospital infection prevention and control policies that include staff vaccination, environmental disinfection, and appropriate isolation, all supported by sentinel monitoring systems.

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Neutralising antibodies after COVID-19 vaccination in UK haemodialysis patients

Vaccination against COVID-19 induces highly protective immune responses in most 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 might experience 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 are a particularly vulnerable group. During the first wave of the COVID-19 pandemic (March 1 to Aug 30, 2020), 4666 cases and 1373 deaths in in-centre haemodialysis patients were reported to the UK's Renal Registry,[1] a case fatality rate of 29%. In the UK, although these patients were treated as clinically extremely vulnerable, they were unable to fully shield because of mandatory life-sustaining attendance at haemodialysis (typically three 4-h sessions per week), and instances of in-unit transmission have been shown by sequencing viral isolates.[2]

Vaccine responses are substantially attenuated in patients who need haemodialysis. For example, the subunit hepatitis B vaccine had to be re-formulated for this patient group to deliver a higher antigenic dose.[3] There is uncertainty whether an mRNA or an adenoviral-vectored COVID-19 vaccine could provide clinical protection in this population or how long that protection lasts given the known waning of SARS-CoV-2 antibodies after natural infection.[4]

In the UK, most in-centre haemodialysis 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 (appendix p 2). Phase 3 studies of authorised vaccines in the UK either excluded this particular patient group or did not report their renal disease subgroups.[5–7] Whereas anti-Spike (anti-S) antibody dynamics in in-centre haemodialysis patients have been described,[8] the levels of neutralising antibodies (nAbs) to the prevalent variants of concern (VOCs), which are emerging as the crucial serological correlate of protection,[9,10] have not been widely reported.

To assess the induction of nAbs in in-centre haemodialysis patients after vaccination with BNT162b2 (Pfizer–BioNTech) or AZD1222 (Oxford–AstraZeneca), we are curating a meta-cohort of haemodialysis patients from around the UK. In this multi-centre cohort study, antibody responses after vaccination were compared between prespecified cohorts of interest. Details of the study design, a definition of seronaive patients, and methodology are available in the appendix (pp 2, 14). We have used our high throughput live-virus neutralisation assays[11,12] against a variant with a spike identical to the virus first identified (wild type), a variant with an Asp614Gly mutation (D614G), and VOCs alpha (B.1.1.7), beta (B.1.351), and delta (B.1.617.2). Here, we report the first interim analysis of this study, testing the hypothesis that there is no difference in neutralising antibody responses elicited by BNT162b2 or AZD1222. Serum was drawn pre-vaccination, at a median of 28 days after first dose [IQR 26–35], and at a median of 33 days [IQR 26–48] after the second dose, in 178 patients (appendix p 2). Three centres had available data for this analysis: Oxford, Leicester, and the Royal Free Hospital; demographic characteristics of the whole interim report cohort, grouped by vaccine, are shown in the appendix (p 5). Although 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 (34·0% *vs* 38·1% female), ethnicity, the presence of diabetes or the immunosuppression state of AZD1222 and BNT162b2 recipients. We focused initially on seronaive patients (n=108; appendix p 6), defined by pre-vaccination sera that lacked detectable anti-S IgG by ELISA, or nAbs against wild type or D614G and who had never returned a positive PCR (before commencing vaccination) and assessed nAb responses 33 days after two vaccine doses of either AZD1222 or BNT162b2. BNT162b2 induced nAb titres (nAbTs) across all five variants (median nAbT concentration needed to achieve 50% inhibition [IC_{50}]=582 against wild type, IC_{50}=327 against D614G, IC_{50}=174 against alpha, IC_{50}=136 against beta, and IC_{50}=267 against delta; appendix p 3). The response to AZD1222 was markedly reduced compared to BNT162b2 and might fall below the likely 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 range) variants (appendix p 3). Stratifying the nAbTs better illustrates the differing distributions of responses with patients with low (IC_{50}<40), medium (IC_{50} 40–256), and high (IC_{50}>256) titres after two doses of AZD1222 compared to BNT162b2 (p<0·0001 by ANOVA for vaccine effect in ordered logistic regression; appendix pp 3, 7). The corresponding analysis for infection-experienced patients revealed smaller differences between AZD1222 and BNT162b2, with AZD1222 achieving median nAbT IC_{50}>150 for all variants (appendix pp 10–11), suggesting a potential utility for adenoviral-vectored vaccines in certain settings. A similar pattern of improved responses in infection-experienced patients, in anti-S titres rather than neutralising antibody, has been reported for the single-dose adenoviral-vectored vaccine Ad26.CoV.2.[13]

We sought to compare neutralising antibody responses between seronaive haemodialysis patients and the healthy individuals we have already reported on as part of the Legacy study.[11,12] As a control group, we selected Legacy participants who had never reported COVID-19 symptoms (therefore probably infection-naive and sero-naive) and had received two doses of either vaccine. A comparison of demographic characteristics between haemodialysis patients and the Legacy cohort is provided in the appendix (p 8). Patients and healthy volunteers (both infection-naive) had similar responses to the mRNA vaccine, despite the age difference between the cohorts. As expected, haemodialysis patients had an attenuated response to AZD1222 (appendix pp 4, 8–9).

Given the ability of BNT162b2 to induce nAbTs across all variants in haemodialysis patients, we assess other vaccine response associations (appendix p 12). The response to BNT162b2 was attenuated in older patients (age grouped as greater or less than 65 years), but this was not discernible in the AZD1222 response due to its low titres. A gender effect was apparent in responses to BNT162b2, but not AZD1222. Stratifying by diabetes showed no effect. As expected, immunosuppressed patients showed attenuated responses.

There are several limitations to our study, most importantly the potential for confounding factors to exist between haemodialysis centres. However, it is unlikely that the same confounder would be present between several different centres since they are physically separated over more than one site (a hub–satellite model), and although the hub and satellite have used BNT162b2 or AZD1222, they share medical, nursing staff, haemodialysis protocols, and a single dialysis supplier. Restricting the analysis to a single centre that had delivered both BNT162b2 (n=48) and AZD1222 (n=12) to seronaive patients recapitulated the previous

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findings (appendix p 13). Although we have stringently tried to exclude previous antigenic exposure in our seronaive group (by anti-S ELISA, by nAbT to relevant variants, and PCR data, where available), we cannot fully exclude the possibility that some of the patients we considered seronaive had an undetected previous infection in early 2020, before PCR became widely available. Other patients might not have generated 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. First, an mRNA vaccine induces comparable nAb titres in haemodialysis patients and healthy controls. This is an important initial step in improved vaccinations against other pathogens in haemodialysis patients. We note that an mRNA influenza vaccine is in phase 1/2 development, and haemodialysis patients are a population that stands to benefit from a novel influenza vaccine. Second, 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. Third, AZD1222 alone in seronaive individuals induces suboptimal nAbT against all VOCs, including the delta variant that is dominant globally. Fourth, the very high proportion of previously infected haemodialysis patients might 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.

The delivery of any approved vaccine will probably mitigate morbidity and mortality, but the optimal strategy for haemodialysis patients who are yet to start a vaccination course remains to be determined. Our data suggest that 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 third doses, in principle, for many vulnerable groups.[14] 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 vaccination strategies for haemodialysis patients, have used two doses of mRNA vaccines,[8] and results of three studies testing a third dose of BNT162b2 in 132 haemodialysis patients in France suggest further augmentation of responses.[15–17] We suggest that in-centre haemodialysis patients should be prioritised for a third dose, particularly AZD1222 recipients who have not already survived infection.

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For **data and R code** see https://github.com/EdjCarr/Crick-HD-AZD-BNT-VOCs-2021-07/

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SARS-CoV-2 delta variant neutralisation after heterologous ChAdOx1-S/BNT162b2 vaccination

Safety considerations associated with the Oxford–AstraZeneca COVID-19 ChAdOx1-S vaccine (AZD1222) have led many public health agencies to recommend a heterologous boost with an mRNA vaccine after prime vaccination with ChAdOx1-S instead of a homologous boost. The first results of a phase 2 trial from Spain[1] and additional reports from observational studies suggest robust immune responses accompanied by acceptable reactogenicity after ChAdOx1-S prime and BNT162b2[2,3] (Pfizer–BioNTech) or mRNA-1273[4] (Moderna) boost vaccination. Given the strong immune response after heterologous prime-boost vaccination, mixing of vaccines has been suggested as a suitable strategy to contain emerging SARS-CoV-2 variants.[5]

Heterologous boosting with BNT162b2 has been shown to induce higher counts of spike-specific CD4+ and CD8+ T cells and, in particular, high titres of neutralising antibodies in a surrogate test against the SARS-CoV-2 variants of concern (VOCs) alpha, beta, and gamma.[3] However, the rapid spread of the delta variant is a concern for both ChAdOx1-S-primed vaccinees who are expecting a boost vaccination and for individuals who have been fully vaccinated with ChAdOx1-S.

We analysed plasma from ChAdOx1-S-primed vaccinees at a mean 16·3 days (range 14–22 days) after homologous ChAdOx1-S (group 1; n=12, seven women) or heterologous BNT162b2 (group 2; n=11, eight women) boost[3] to compare neutralising activity against SARS-CoV-2 VOCs, including the delta variant. Detailed methodology is available in the appendix. The mean dose interval between prime and boost was 73·5 days (range 71–85 days) and did not differ between the groups (appendix p 1). We used a vesicular stomatitis virus-based pseudotyped virus assay to analyse neutralisation.[6] This study was approved by the Internal Review Board of Hannover Medical School. All participants gave written informed consent.

Mean anti-spike IgG (QuantiVac, Euroimmun, Lübeck, Germany) was 171·9 relative units (RU) per mL (SD 121·8 RU/mL) in group 1 and 611·0 RU/mL (SD 104·5 RU/mL) in group 2 (p<0·0001; appendix p 1). Plasma from individuals in group 1 had moderate 50% neutralisation titre (NT_{50}) against the wild type and alpha variant, and this activity was further diminished against beta, gamma, and delta variants (appendix p 2). In contrast, all heterologous ChAdOx1-S/BNT162b2 vaccinated individuals achieved at least NT_{50}=25 against all variants, including the delta variant (NT_{50}≥100 in 85% of vaccinees; appendix p 2). Mean anti-spike IgG correlated highly significantly to NT_{50} against the delta variant across both groups (r=0·901; p<0·0001, Pearson correlation; appendix p 3).

The statistical analysis in this small study does not account for potential confounding factors. However, the robust inhibition of variants including the delta variant further supports heterologous ChAdOx1-S/BNT162b2 vaccination. If confirmed in a large study, our data also support a heterologous boost vaccination of individuals with completed homologous ChAdOx1-S vaccination, once humoral immunity is declining and patients become susceptible to infection.

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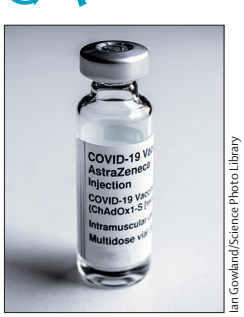

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