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.

which is the same number as in 2000 (241 [226–260] million).[1] Has the global burden of malaria really not changed over 20 years, after spending more than US$30 billion on malaria control activities, and after distributing more than 2·5 billion insecticide-treated bednets, 3 billion rapid diagnostic tests, and 3·5 billion artemisinin combination treatments?

A major problem with the WMR is that the method of calculation changes every year. For example, WMR 2020 reported an estimated 453 000 deaths from malaria (422 000–496 000) in 2015,[2] whereas WMR 2021 reports 566 000 deaths (524 000–619 000) in 2015 (appendix).[1] The WMR 2021 method of estimation is considered most robust,[1] but is it accurate? There has been substantial progress in malaria control in Asia and the Americas, so what is really going on in Africa? 20 years ago, the malaria situation in Africa was dire. There was little distribution of insecticide-treated bednets, and the increasingly ineffective chloroquine was still the first-line antimalarial treatment across the continent. Even adjusting for population increases in Africa, and the uncertain effect of COVID-19, returns on investments in the past 20 years seem profoundly disappointing. If these WHO estimates are correct, then deploying insecticide-treated bednets, rapid diagnostic tests, and artemisinin combination treatments across the continent, in addition to deploying seasonal malarial chemoprevention, has had little effect.

See Online for appendix

The WHO Global Malaria Programme messaging is confusing and contradictory. WMR 2020 documented an impressive 60% reduction in global malaria mortality since 2000.[2] In 2021, the reduction became 30% for the same years! In 2015, WMR 2015[3] announced a "dramatic decline in the global malaria burden over 15 years" and WHO proudly reported that target 6C of the Millennium Development Goals—namely, a decline in the global incidence of malaria—had unquestionably been achieved. This accomplishment was reiterated as a key message in the 2019 WMR: "on a global scale there was exceptional headway in reducing the burden of malaria in 2000–2015—proof that progress is possible".[4] Where are those claims now?

Each year WHO proposes that a substantial increase in international funding is needed. But a clear understanding of what is happening, what is going wrong, and why, are needed to justify this request.

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Omicron neutralising antibodies after COVID-19 vaccination in haemodialysis patients

The SARS-CoV-2 variant of concern (VOC) B.1.1.529 omicron is now the predominant VOC in the UK.[1] The burden of more than 30 mutations in omicron spike suggests at least a degree of vaccine evasion,[2] and UK Health Security Agency estimates of vaccine efficacy against infection are reduced compared to delta.[1] The critical question is how well existing vaccines will protect clinically extremely vulnerable groups against infection. In the UK, the COVID-19 death rate for in-centre haemodialysis (IC-HD) patients during the delta wave was 14·65 (95% CI 11·49–18·67) per 1000 patient-years, the highest rate for any OpenSAFELY-defined comorbidity.[3] The increased transmissibility of omicron is likely to prove challenging in haemodialysis units, where in-unit transmission with prior VOCs has occurred.[4] We therefore sought to determine the neutralising antibody (nAb) titres (nAbTs) in IC-HD patients, a cohort we have previously shown to have attenuated nAb responses to delta.[5]

In the UK, the IC-HD vaccination schedule is complex. Most IC-HD patients are considered fully vaccinated after two doses and boosted after three. Boosting eligibility criteria were finalised on Sept 14, 2021.[6] A subset of IC-HD patients, due to their use of additional immunosuppression (eg, for failed renal transplants) or other comorbidities, are eligible for a three-dose primary course (announced Sept 1, 2021).[7] These patients are already permitted a fourth booster dose 3 months after their third dose.

To assess the induction, maintenance, and diversity of nAbs we convened the UK-wide NAOMI consortium study assessing neutralising antibody after COVID-19 vaccination in haemodialysis patients.[5] This is an observational multicentre meta-cohort study to compare nAb responses between different vaccine regimens, and in pre-specified patient subgroups. Previously, we compared nAb responses after two doses of the adenoviral vector Oxford–AstraZeneca vaccine (ChAdOx-1 nCoV-19; AZD1222) or the Pfizer–BioNTech mRNA vaccine (BNT162b2). mRNA vaccine neutralising responses against wildtype virus and VOCs were similar to those seen in health-care or laboratory workers.[5,8,9]

Here we report the first nAbTs against omicron in the at-risk IC-HD population (n=98) a median of 158 days [IQR 146–163] after

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

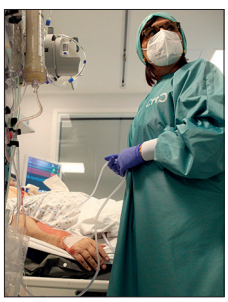
First, we assessed nAbTs against omicron and delta at a median of 158 days after two doses of either AZD1222 or BNT162b2 (appendix p 3). After two doses of AZD1222, the median nAbT against either VOC was less than the lower limit of detection of our assay (<1:40), in keeping with our previous report of delta nAbTs 1 month after the second dose[5] (omicron IQR <40 to <40; delta IQR <40 to 110). At 158 days after two doses of BNT162b2, median nAbTs against delta were 112 (IQR <40 to 342), and median omicron nAbTs were below the range of the assay (appendix p 3; IQR <40 to 157).

Next, we considered the effect of an additional full dose of BNT162b2 (n=50, appendix p 3). For recipients of two doses of AZD1222 followed by a dose of BNT162b2 (AZD–AZD–BNT; n=21), delta nAbTs increased after a third dose to a median of 282 (IQR <40 to 1250). A third dose provided a significant increase in the proportion of patients in this vaccination group with nAbTs above 40 against delta (McNemar's test p=0·023) or omicron (p=0·0077). However, the median titres against omicron remained below the quantitative range (<40 [IQR <40 to 270]). Recipients of three doses of BNT162b2 (BNT–BNT–BNT, n=29) had boosted nAbTs against delta, from 112 to 461 (4·1 fold change [IQR 171 to 1214]) and developed detectable nAbTs against omicron, with a median nAbT of 236 (IQR <40 to 603) after a third dose. A third dose provided a significant increase in the proportion of patients in this vaccination group with nAbT above 40 against delta (McNemar's test, p=0·0077) or omicron (p=0·0094).

For both AZD–AZD–BNT and BNT–BNT–BNT recipients, a proportion of IC-HD patients do not mount nAbT responses to either VOC. Seven (33%) and 11 (52%) of 21 patients who received AZD-AZD-BNT showed 50% inhibitory concentration (IC_{50}) below 40 against delta and omicron, respectively, after a third dose. This contrasts with the patient group that received BNT–BNT–BNT, of which one (3%) and eight (28%) of 29 patients showed IC_{50} below 40 against delta and omicron, respectively. We hypothesised that these patients could be taking immunosuppressants or have immunosuppressive comorbidities (beyond the immunosuppression associated with end-stage renal disease and haemodialysis itself), so we stratified the analysis by the presence of or absence of an immunosuppressed state (appendix p 2). The immunosuppressed AZD–AZD–BNT patients (n=5) had a median nAbT against omicron below the lower limit of the assay (IQR <40 to <40) and immuno-suppressed BNT–BNT–BNT patients (n=6) had a median nAbT against omicron of 135 (about 50% of the response of the rest of the cohort [IQR <40 to 491]). In the non-immunosuppressed recipients, the median omicron nAbT after third dose was 107 for AZD–AZD–BNT recipients (n=16; IQR <40 to 578) and 236 for BNT–BNT–BNT recipients (n=23; IQR 67–777).

The main limitation of our study is its observational nature, risking unbalanced groups for comparisons. For example, the AZD–AZD–BNT and BNT–BNT–BNT cohorts are matched imperfectly, with AZD1222 recipients being older (mean age 68·8 years [SD 11·2] *vs* 60.3 [12·1], *t* test p=0·001). Therefore, we have reported responses within these vaccine cohorts, not between. We temper this limitation by the importance of these data: IC-HD patients are at increased risk of severe disease or death,[3] and our data inform strategies to mitigate that risk over the coming weeks and months. Vaccine-induced cellular responses are likely to contribute to the protective effect of vaccination. Preliminary data suggest that in healthy individuals, T-cell responses to omicron spike-derived peptides appear comparable to peptide pools from other VOCs.[10] In contrast, in infection-naive IC-HD patients, a reduction in T-cell responsiveness to peptides of ancestral S1 and S2 after two doses of either vaccine has been suggested.[11] Together, these observations suggest that omicron infection in previously vaccinated HD patients might result in diminished cellular responses compared to healthy individuals.

In summary, we report the first nAbTs against omicron in IC-HD patients, a highly vulnerable population to COVID-19, frequently requiring hospital treatment and with an excess risk of death. Homologous vaccin-ation with BNT-BNT-BNT generated quantifiable nAbTs against delta and omicron in most IC-HD patients. Heterologous vaccination with AZD–AZD–BNT provides quantifiable nAbTs against delta in more than 50% of IC-HD patients but not against omicron, where more than 50% of IC-HD patients had nAbTs below the quantifiable range. A significant fraction of IC-HD patients would appear to remain at risk from omicron.



Valeria Mongelli/Bloomberg/Getty Images

See **Online** for appendix

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

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

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Department of Error

GBD 2019 Adolescent Mortality Collaborators. Global, regional, and national mortality among young people aged 10–24 years, 1950–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet *2021;* **398:** *1593–618*—In figure 8 of this Article, the total deaths and proportion in each age group in 1950 were incorrect. These corrections have been made to the online version as of Feb 24, 2022.

Stuart ASV, Shaw RH, Liu X, et al. Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com-COV2): a single-blind, randomised, phase 2, non-inferiority trial. Lancet *2022;* **399:** *36–49*—In this Article, the X axis for figure 3B has been updated to read 14 days since boost vaccination. This correction has been made to the online version as of Feb 24, 2022.

Jaffe S. The next steps for US vaccine mandates. Lancet *2022;* **399:** *425–26*—In this World Report, Professor Laurence Tribe's first name was misspelled. This correction has been made to the online version as of Feb 24, 2022.