UK Kidney Association guidance on COVID-19 vaccination in highly vulnerable people with kidney disease

Aims

To provide guidance on the use of COVID-19 vaccines in highly vulnerable people with kidney disease

Overview of guidance

This is a consensus opinion of a group of kidney professionals. The guidance is based on the relatively limited data available so far on the effect of COVID-19 vaccination in people with kidney disease and should be used in conjunction with local or national guidance. We have tried to include recommendations but are limited by the lack of firm evidence; there is an urgent need for further research and clarity of messaging. The guidance was written in June 2021 and will be further updated as more information emerges.

Summary of recommendations

This guidance applies specifically to all people on haemodialysis or peritoneal dialysis, all those with a kidney transplant, people with chronic kidney disease Stage G5 not yet receiving dialysis, and those with kidney disease receiving immunosuppressive treatment (hereafter referred to as Highly Vulnerable Kidney Patients, HVKPs). For these purposes, immunosuppressive treatment includes steroids (equivalent of prednisolone 20mg/day for >= 4 weeks), lower doses of steroids in combination with other immunosuppressant drugs, and receipt of rituximab within the previous 6 months. National (government) guidance applies to patients with earlier stage kidney disease.

Vaccinations

We recommend that all HVKPs receive two doses of a vaccine approved by the Joint Committee on Immunisation and Vaccination (JCVI). This includes both COVID-19 infection naive patients and those who had a previously

documented COVID-19 PCR positive infection or serological evidence of previous infection. The only contra-indication to vaccination is a history of systemic allergic reaction caused by a previous dose of the COVID-19 vaccine to be used or by any component (excipient) of the COVID-19 vaccine. In the event of an allergic or other adverse reaction to a first dose, we suggest completing the course with an alternative vaccine.

We recommend that all adult household contacts of all HVKPs receive two doses of COVID-19 vaccine, prioritised for all household contacts over the age of 16 in the case of severely immunosuppressed individuals in line with JCVI recommendations[1].

We recommend that all HVKPs who are on the waiting list for kidney transplantation or who may be listed for transplantation receive 2 doses of a JCVI-approved vaccine prior to activation on the transplant list, with the 2-dose schedule being completed prior to commencing immunosuppression: in this situation, the JCVI have recommended that the second dose be offered at the recommended minimum time interval (3 or 4 weeks)[2].

We recommend that all HVKPs who have previously declined COVID-19 vaccination be offered further education to inform them about their increased vulnerability to COVID-19, to counter misinformation and build trust in vaccine safety and potential efficacy, as demonstrated by early data on good laboratory based responses to COVID-19 vaccines in many HVKPs.

We recommend that all HVKPs accept a third dose of vaccine should it become available.

We cannot currently recommend routine testing of HVKPs for anti-COVID-19 antibodies following vaccination for the following reasons:

- There is no consistent single reliable antibody test established across the UK.
- We need greater clarity as to the level of antibody which provides clinical protection.
- Currently the results of an antibody test would not change the recommendations for vaccination or prevention of exposure to COVID-19 for an individual.

- The community are working on which tests may more reliably inform about protection.

Enhanced precautions to reduce exposure to COVID-19

We recommend that all HVKPs and their household contacts continue to use enhanced precautions (avoidance of high risk environments, including discussion with your employer about optimising COVID-19 safety prior to returning to work; continued use of face masks; social distancing; handwashing; meeting others outside or in well ventilated areas) and seeking advice from a specialist clinician before making plans to travel abroad, even after the government lifts restrictions for the general population. This recommendation particularly applies to patients who have been vaccinated within 6 months of receiving rituximab or other B-cell depletion therapy, and recent transplant recipients.

These recommendations also apply to kidney patients who elect not to receive the vaccine.

We recommend that HVKPs and their households access and use the NHS's free, twice weekly lateral flow tests for asymptomatic adults (symptoms should prompt an NHS PCR test either via 111 or the NHS app).

Treatment for COVID-19

HVKPs who are infected with COVID-19 should be offered the full range of treatments shown to be effective. As soon as neutralising antibody therapies become available in the UK, we recommend that HVKPs who develop COVID-19 infection and are antibody negative should be prioritised for neutralising antibody therapy. Note: implementing this recommendation will require further guidance on antibody testing to be developed and, if antibody status testing is unavailable, we would suggest that HVKPs requiring hospitalisation are considered for neutralising antibody therapy.

Research

We recommend continued urgent research on how best to protect HVKPs from COVID-19 infection, including studies of vaccine dose, additional doses, combinations of different vaccines, and studies of drug prophylaxis: and we recommend that all clinicians ensure that the widest possible range of HVKPs are given access to these studies as soon as possible.

The available evidence

The phase 3 trials of the Pfizer/BioNTech, Moderna, Astra-Zeneca and Janssen vaccines included too few people with advanced kidney disease or people on immunosuppression therapy to provide any useful information for this guidance. To date, 35 small studies of the effects of COVID-19 vaccination on various aspects of immunity have been reported; these are summarised in a narrative review in press[3]. Most studies reported on the effects of the Pfizer/BioNTech mRNA vaccine. Development of anti-spike IgG antibodies after two doses of vaccine was reported in 70-96% of dialysis patients and in 3-59% of kidney transplant patients. There are case reports of relapse of glomerulonephritis, *de novo* glomerulonephritis, and acute transplant rejection following vaccination, but causation has not been established. A regularly updated summary of the evidence is available at http://www.nephjc.com/news/covid-vaccine.

A graphical representation of the development of anti-spike IgG antibodies following vaccination in HVKPs is shown in Figure 1.

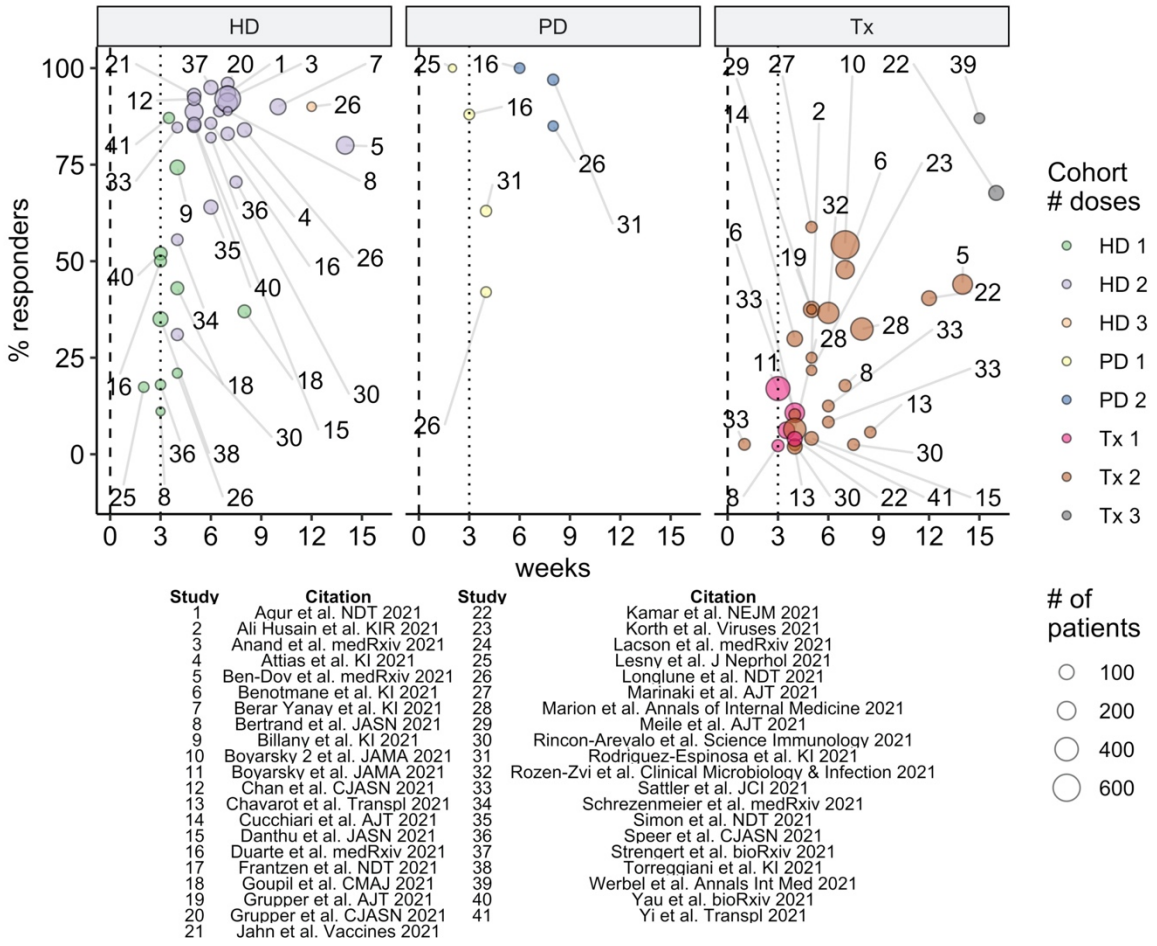

FIGURE 1: Percentage sero-response as reported in published or pre-printed studies in haemodialysis, peritoneal dialysis, and renal transplantation patient groups. Data after one, two or three doses are indicated by the colour of the point. The size of each point reflects the number of patients tested at that timepoint. Each point is labelled with a number, with first author, journal (or pre-print server) and year listed in the table. Studies used a variety of different measures of antibody responses and where immunoglobulin isotypes were reported separately, we have retained IgG data alone. Where baseline serology is known we have used sero-naive vaccine recipient data. For some studies, for example, Yi et al. more than one modality was included and, where possible from the data available, we show these separately.

Antibody response to vaccination in research studies

As discussed in detail in the review, a wide range of antibody tests were used in these studies. There are no reliable data on the relationship between an antibody titre using a given assay and the degree of protection that titre confers. While it is reasonable to assume that higher titres, in any given assay, indicate a higher degree of protection, it is currently impossible to give, for any assay, a 'cut-off' level at which HVKPs can assume similar degrees of protection to that seen in the general population. Importantly, vaccination may give substantially less protection against new strains of the SARS-COV-2, such as the Delta variant. *In vitro* neutralisation assays, which test the ability of a patient's serum to inactivate live virus (and therefore allows testing of multiple different viral strains) are the most reliable way of assessing protection but are not yet widely available[4].

The guideline group carefully considered this evidence to inform advice on how to advise patients wishing to have an antibody test following 2-dose vaccination. Many patients are keen to undergo testing in the hope of understanding their risk level post vaccination. However, the absence of reliable evidence, for each available assay in the UK, of what would constitute a 'protective' antibody level – and how long such protection would last – unfortunately means that it is currently impossible to define a 'positive test'. Conversely, patients with 'negative' tests may still have T-cell mediated immunity and therefore may be more protected than the antibody test result suggests.

The RECOVERY platform recently reported that infusion of neutralising monoclonal antibodies, in addition to standard therapy, improved outcomes in the subset of patients with COVID-19 infection who were sero-negative (using an indirect ELISA for anti-spike IgG) on admission[5]. If, as seems likely, this trial results in a change to clinical practice guidelines for the treatment of COVID-19 infection in the UK, then rapid determination of antibody status (or routine testing of all patients at risk) will be necessary in order to ensure that this expensive treatment is offered only to seronegative patients.

Studies to date have identified a number of predictors of a poor antibody response to vaccination, many of which (e.g. age) are not modifiable.

Risk factors for poor response in haemodialysis patients:

- Older age
- Concomitant use of immunosuppression

The following risk factors for poor response in kidney transplant recipients have been identified:

- Older age
- Triple immunosuppression
- Use of mycophenolate
- High-dose steroids
- Belatacept
- Vaccinated within the first year post-transplant

Effects of vaccination in non-transplant immunosuppression

There are no published data on COVID-19 vaccine immunogenicity/efficacy specifically in patients with immune-mediated kidney diseases[6]. However, there are a small number of studies examining immunogenicity in rheumatology cohorts. The largest of these, a multi-centre study from Israel, examined almost 700 patients, including some with lupus and vasculitis, who received two doses of the Pfizer mRNA vaccine, reporting an overall seroconversion rate of 86%[7]. Patient factors associated with non-seroconversion included increasing age and an underlying diagnosis of ANCA-associated vasculitis (AAV) or inflammatory myositis. Treatments associated with non-seroconversion included rituximab, glucocorticoids and mycophenolate mofetil (MMF).

The significant impact of rituximab on serological responses to mRNA vaccines has been confirmed in a few additional studies in rheumatology populations and is not unexpected[8-10].

Unpublished data from Imperial College indicate that B-cell depletion at time of vaccination (and by association, time since rituximab treatment) had a significant impact on serological response to vaccination (e.g. 41% seroconversion if treated <6m ago versus 71% seroconversion if treated >6m ago). Most patients who were B cell deplete did have detectable T cell

responses. Although there are no available data for cyclophosphamide, we might expect the effect on serological responses to be comparable given the depleting effect of cyclophosphamide on circulating B cells.

We therefore continue to advise vaccination in all immunosuppressed patients, including those recently treated with B-cell depleting therapies, as current vaccines appear to have some immunogenicity and thus may confer some protection from infection or severe disease. However, since the serological response is severely blunted, we recommend that patients vaccinated under recent (<6 month) treatment with B-cell depleting therapies (including cyclophosphamide) should continue to use enhanced precautions.

We recommend that vaccination is completed (i.e. 2 doses) prior to receiving further doses of rituximab and that there is a four week interval between vaccination and subsequent rituximab treatment, where it is safe to do so (e.g. patients with stable disease at low risk of relapse). This is consistent with both UK Arthritis and Musculoskeletal Alliance (ARMA) and American College of Rheumatology (ACR) guidance[11,12]. There are no data yet on the impact of rituximab treatment after vaccination (i.e. all published data relates to vaccination after previous rituximab treatment), but it is expected that vaccination in rituximab-naive patients will induce long-lived S-specific plasma cells which should not be directly impacted by rituximab treatment (bone marrow resident plasma cells are demonstrated after natural SARS-CoV-2 infection).

There is some evidence (with non-COVID vaccines, in rheumatology populations) that withholding immunosuppression for 1-2 weeks following vaccination may improve immunologic responses. Indeed, ACR guidelines advise withholding MMF or methotrexate (MTX) for 1-2 weeks post-vaccination in patients with stable, well-controlled disease[12]. However, these recommendations may not be applicable to patients with immune-mediated kidney disease, in whom the risks and consequences of disease flare are likely greater than in rheumatic diseases. **We therefore do not recommend routinely withholding maintenance immunosuppression around the time of vaccination in our patient group**. This is analogous to routinely withholding MTX from rheumatoid arthritis patients when admitted to hospital; we would not do the same with MMF in renal transplant patients.

There are case reports of glomerular disease flare temporally associated vaccination (including IgA nephropathy, nephrotic syndrome, AAV, anti-GBM disease) though it is not possible to prove these are causal[13]. We believe the benefits of vaccination outweigh the small risk of relapse, and that vaccination is recommended to all patients.

Registry studies and evidence awaited

A large study using *in vitro* neutralisation assays (at the Crick Institute) is examining the effects of COVID-19 vaccination in HVKPs. Preliminary results are expected within weeks: when these are available, this guideline will be critically reviewed, and if necessary, revised.

The Scottish Renal Registry (with data on just over 5000 renal replacement patients in Scotland) and the Registry at NHS Blood and Transplant (NHSBT, with data on all patients either on the waiting list for or in receipt of a solid organ transplant throughout the UK) are already performing linkage studies that will give epidemiological data on the incidence and outcomes of PCR-proven COVID-19 infection, linked to vaccination status, in large cohorts of dialysis patients and kidney transplant recipients. The UK Renal Registry (which holds data on all renal replacement patients throughout the UK) is urgently seeking linkage to this data in order to enhance understanding of vaccine efficacy and will therefore add further understanding in haemodialysis and peritoneal dialysis patients when available.

Early data from the period December 2020 to 24th June 2021 from NHSBT, shows that of 6724 solid organ transplant recipients who have received neither vaccine, 466 (7%) had a PCR-confirmed COVID infection of which 189 (40%) died. In 41,258 patients who had received a single vaccine, 316 (0.8%) had a PCR-confirmed COVID infection later than 14 days after the vaccine dose, of whom 32 (10%) died. Of 39280 patients who had completed both vaccines, 76 (0.2%) had a PCR COVID-confirmed infection greater than 14 days after the 2nd dose, of whom, 6 (8%) died. These findings have not been adjusted for risk factors[14].

The OCTAVE study is recruiting 5000 patients with suppressed immune systems, including a large cohort of HVKPs, to study the effects of COVID-19 vaccination.

Several single-centre studies are being performed, including a comprehensive assessment of the effects of COVID-19 vaccination in HVKPs at Imperial College, London.

PROTECT-V is a platform trial investigating drug prophylaxis of COVID-19 infection in HVKPs. The first agent under investigation is a nasal formulation of Niclosamide.

Summary

We continue to recommend 2 dose vaccination in everyone with kidney disease, which ever stage they are at.

We recommend that people with kidney disease be offered and receive a booster dose.

We recommend that people with kidney disease who are likely to have a lower response to vaccination continue to use social distancing and protective measures, even after any changes in government guidance in relation to the general population.

We **do not** recommend that patients reduce their immunosuppression during vaccination.

We recommend regular Lateral Flow Tests and vaccination of households where kidney patients live.

We recommend that patients speak with their employers and ask for a risk assessment before returning to the workplace https://www.kidneycareuk.org/news-and-campaigns/news/half-million-people-not-protected-covid-19-vaccines-need-workplace-support/.

Further research

Further work is urgently needed to answer many questions, including:

- Would a third dose of vaccine improve antibody responses in those not developing antibodies after standard 2-dose vaccination? What should the timing of this dose be?
- What are the potentially modifiable predictors of poor response to 2-dose vaccination in dialysis, transplant, and immunosuppressed kidney patients?
- Would combinations of different vaccines generate more protection?
- What is the predictive value of antibody testing following vaccination in HVKPs?

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