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GUIDELINE

Vaccination of adult patients living with chronic kidney disease against SARS-CoV-2: a position statement by the South African Nephrology Society

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ABSTRACT

Safe and effective vaccination of patients living with chronic kidney disease requires an understanding of the unique immunological milieu of this population and of their potential for disease-specific side effects. This Position Statement, issued on behalf of the South African Nephrology Society, provides recommendations for local policy development and for individual practice administration and monitoring of SARS-CoV-2 vaccinations in patients living with chronic kidney disease.

Keywords: SARS-CoV-2; vaccination; kidney disease; immunosuppression; transplantation.

INTRODUCTION

Patients living with chronic kidney disease (CKD) are at increased risk of severe COVID-19 and subsequent mortality [1]; moreover, dependence upon frequent visits to healthcare facilities for the management of CKD increases the risk of acquiring SARS-CoV-2 infection [2]. Although a fully effective treatment for COVID-19 has yet to be discovered, vaccination offers the potential to reduce the risk of infection and disease severity. The utility of this strategy in patients living with CKD remains, however, untested, since vaccine trials have largely excluded this group [3]. Furthermore, there is concern as to the efficacy of vaccination in these patients due to the immunoparesis induced by CKD [4], and the use of immunosuppressant drugs in patients with immune-mediated kidney disease or renal transplants. At present there is little guidance for clinicians on the vaccination of patients affected by CKD against SARS-CoV-2. This statement was compiled by the guidelines committee of the South African Nephrology Society through review of the available literature and consultation between nephrology and infectious disease specialists working in South Africa. The document was reviewed and authorised by the executive committee of the Society for use by its members in the counselling and management of patients undergoing vaccination for SARS-CoV-2.

DISCUSSION

Vaccination of patients living with chronic kidney disease

Although the majority of SARS-CoV-2 vaccine safety and efficacy trials have not used renal function as an exclusion criterion, the number of patients with CKD enrolled in these studies is low [5], and no report exists of chronic dialysis patients having been included in any of these

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studies [3]. As a result, the safety profile and efficacy of SARS-CoV-2 vaccines in these patients has yet to be fully established.

Of particular concern, given the hypercoagulable state that often accompanies CKD [6], is the risk of vaccine-induced thrombotic thrombocytopaenia (VITT). VITT has been predominantly described as a rare complication of the Oxford–AstraZeneca AZD1222/ChAdOx1 nCov-19 vaccine, but has also occurred in association with the Johnson & Johnson/Janssen Ad26.COV2.S vaccine, and most commonly affects women younger than 55 years of age [7]. It is thought that endothelial injury, induced by vaccine-derived spike protein, results in platelet factor (PF4) release; complexing of PF4 with endogenous heparan sulphate leads to a hapten-driven autoantibody response with a clinical presentation similar to that of type II heparin-induced thrombotic thrombocytopenia (HITT) [7]. Although the risk of VITT in patients living with CKD is unknown, some reassurance may be drawn from the low prevalence of VITT in the general population, and the lack of apparent association of VITT with traditional venous or arterial thrombosis risk factors [7]. Considering the low probability of VITT and other potential side effects of vaccination against the disproportionate risk posed to such patients by COVID-19, the Centers for Disease Control and Prevention (CDC) advocates for the vaccination of patients on long-term outpatient dialysis [8].

The recommendation of vaccination based on this risk–benefit analysis assumes efficacy of the vaccines in preventing infection with SARS-CoV-2 or ameliorating the probability of severe COVID-19 in such an event. Progression of CKD is associated with progressive immunoparesis, featuring downgraded dendritic cell activation of lymphocytes [9] and reductions in CD4+ T-helper, CD8+ cytotoxic [10], and B-cell [4] populations. These aberrations impair the induction of immunological memory and may underlie the rapid decline in SARS-CoV-2 antibodies within 3 months in CKD patients surviving infection by the virus [11].

The choice of vaccine may compensate for immunoparesis. The ability of viral vectored and mRNA vaccines to induce humoral and T-cell immunity [12] offers theoretical benefit for their use in preference to whole killed virus in such patients. Comparison of phase 3 trial reports suggests that mRNA vaccines may induce humoral immunity more reliably than replication-defective viral vector carrying pathogen gene vaccines, and the former may therefore be more effective in CKD patients [12]. In addition, limited data suggest an enhanced immune response may be elicited by administration of a third dose of mRNA vaccine [13].

Vaccination in patients living with immune-mediated kidney disease

Patients living with immune-mediated kidney disease face additional vaccine safety and efficacy concerns beyond those arising from renal dysfunction as discussed previously.

Immunological pathways important in vaccine response are known to be involved in the generation of autoimmunity and immunological disorders have been reported as rare complications of SARS-CoV-2 vaccination [14]; such observations raise the possibility of vaccine-mediated flares of pre-existing autoimmune disease. Since initial vaccine safety trials mostly excluded patients with autoimmune disease [14], the clinical validity of this theoretical concern remains largely untested. Nevertheless, because the diagnosis of COVID-19 in the setting of immune-mediated kidney disease is associated with an increased risk of both acute kidney injury and mortality [15], the ERA Immunonephrology Working Group recommends the vaccination of patients living with autoimmune kidney disease [14].

Where possible, the CDC recommends delaying initiation of immunosuppressive treatment until at least 2 weeks have elapsed from completion of the selected vaccination regimen [16]. In patients already receiving immunosuppression, or in those in whom initiation cannot be delayed, timing of vaccination should take into consideration the proposed immunosuppression protocol. Although limited data are available, vaccination of patients on high-dose corticosteroid therapy (20 mg prednisone equivalent or greater) is less likely to be effective [14]. Dose-dependent reductions in the response rate to influenza vaccination have been described in patients receiving mycophenolate mofetil (MMF) [17]; the threshold MMF dosage for effective vaccination against SARS-CoV-2 is, however, not known. Calcineurin inhibitors may also attenuate vaccine response [18], although protective immunisation has been demonstrated in transplant recipients receiving these agents [19]; data from influenza vaccines suggest that azathioprine does not significantly affect seroconversion [17].

Murine models suggest a dose-dependent temporal effect for cyclophosphamide on lymphocyte populations, with CD4+ T-helper and B-cell lineages decreasing from day 1 following pulse administration to a nadir at day 4, followed by gradual repopulation until day 10, when counts again begin to decline [20]. Accordingly, it has been suggested that administration of intravenous cyclophosphamide should be delayed by at least 1 week after vaccination, to increase the probability of successful seroconversion [21].

Rituximab, which inhibits the induction of the humoral response, is of particular concern in reducing the efficacy of vaccination. Previous experience with influenza vaccination

suggests that delaying immunisation until 6 months have elapsed since the last rituximab dose improves vaccine responsiveness [22]. However, prolonged deferment of SARS-CoV-2 immunisation in anticipation of optimising immunological reactivity during the ongoing pandemic may be undesirable in this vulnerable patient group. Where possible, SARS-CoV-2 vaccination should be administered 4 weeks prior to initiation of rituximab to allow for induction of humoral immunity [21]; for patients already receiving rituximab, a reasonable stratagem may be to proceed with immunisation with a booster dose administered 3–6 months after completion of rituximab therapy [21,23]. Additional confidence as to the probability of immunisation success in these patients may be obtained through the cytometric confirmation of B-cell repopulation prior to inoculation [23].

Table 1 outlines recommendations for the timing of vaccination in patients receiving immunosuppression. The CDC recommends that patients on active treatment with high-dose corticosteroids, alkylating agents, antimetabolites, or immunosuppressive biological agents who have received either the Pfizer–BioNTech BNT162b2 or the Moderna mRNA-1273 vaccine be considered for a third dose at least 28 days after completion of the 2-dose regime; it is not yet known whether booster immunisation is indicated for patients receiving the Johnson & Johnson/Janssen Ad26.COV2.5 vaccine [16].

Patients living with autoimmune kidney disease may require cyclical high-dose immunosuppression, which could reduce the anamnestic response in those previously successfully vaccinated against SARS-CoV-2. Whereas serial serological assay for persistence of immunity to the virus has been suggested in such cases [21], the utility of these tests in the clinical setting has yet to be established [16].

Table 1. Recommendations for the timing of vaccination in patients receiving immunosuppression [21].

Immunosuppressant	Timing of vaccine
Azathioprine	No delay indicated
Calcineurin inhibitors	No delay indicated
Cyclophosphamide (oral)	No delay indicated
Hydroxychloroquine	No delay indicated
Low-dose corticosteroid (<20 mg/d prednisone equivalent)	No delay indicated
Mycophenolate mofetil	No delay indicated
High-dose corticosteroid (>20 mg/d prednisone equivalent)	Preferably delay vaccination until weaned to low dose
Cyclophosphamide (intravenous)	Delay cyclophosphamide dose until 1 week after vaccination
Rituximab	Delay rituximab dose until 4 weeks after vaccination

Vaccination in renal transplant recipients

Maintenance of operational tolerance in transplant recipients requires the inhibition of T-cell and B-cell activation pathways, which are central to the generation of immunity by vaccination. Suppression of antigen-dependent T-cell expansion and differentiation by calcineurin inhibitors, restriction of lymphocyte proliferation by antimetabolites, T-cell independent loss of antibody production by B cells due to MMF, and reduction in the expression of pro-inflammatory cytokines by corticosteroids exert an additive effect in patients on combination immunosuppression following transplantation [19]. Depleting agents, such as antithymocyte globulin (ATG), which directly reduce dendritic and T-helper cell populations, and rituximab, which targets immature B cells, inhibit multiple stages in the acquisition of immunity [19]. Reflecting these effects of long-term immunosuppressant use, reduced humoral responses to both the Pfizer–BNT162b2 [24] and the Moderna mRNA-1273 vaccines [25] have been reported in renal transplant recipients. Of concern, T-cell directed therapies may impair the anamnestic effector response even in those patients with documented antibody elucidation in response to vaccination [10].

Because recipients require ongoing immunosuppression, vaccination is most likely to be successful if undertaken before transplantation [26]. Temporal kinetics in the dosing of immunosuppressants results in reduced vaccination success rates in the first 3–6 months after engraftment [27]; for similar reasons, vaccination is best deferred following periods of augmented immunosuppression for the treatment of rejection, particularly if the prescribed protocol includes high-dose MMF [28]. Improved seroconversion rates have been reported in recipients on stable immunosuppression therapy who received a third dose of the Pfizer–BNT162b2 vaccine administered 61 days after the standard second dose [29]; the CDC recommends administration of a third dose of mRNA vaccine at least 28 days after completion of the 2-dose regime [16]

Vaccination has theoretically been associated with an increased risk of rejection [28]. Although rare, isolated cases of rejection following SARS-CoV-2 vaccination have been reported, and consideration should be given to monitoring graft function for signs of rejection after immunisation [30].

In general, SARS-CoV-2 vaccines are well tolerated by transplant recipients with a similar side-effect profile to that reported for non-immunosuppressed individuals [31]. Despite concerns regarding the efficacy of these vaccines in such patients, the significant risk of severe COVID-19 disease and subsequent mortality in transplant recipients [32] favours the use of this intervention.

Vaccines

A summary of available anti-SARS-CoV-2 vaccines currently approved for use in African jurisdictions is presented in Table 2 [33].

Killed whole virus

Killed whole virus vaccines in use on the African continent include Sinovac's CoronaVac, Bharat Biotech's COVAXIN (BBV152), and Sinopharm's BBIBP-CorV [33]. Limited data from small size phase 2 trials indicate seroconversion rates of 96–100% with mainly mild side effects reported (Table 2); in general, trials support a two-dose schedule [34-37]. All vaccines in this group can be stored at 2–8°C, which facilitates their use in regions with poor healthcare infrastructure [12].

Replication-defective viral vector carrying pathogen genes

Replication-defective viral vectors are a novel vaccination strategy in which the cellular machinery of the vaccine recipient is induced to temporarily express specific pathogen antigens by RNA introduced by a viral vector, which has itself been rendered incapable of replication by gene deletion. Subsequent presentation of antigen via the major histocompatibility complexes (MHC) of the affected cell facilitates the development of an adaptive immune response [38]. The use of a replication-defective viral vector renders this technique safe for use in immunocompromised patients. Vaccines of this type in use on the African continent include AZD1222/ChAdOx1nCoV-19 (Oxford–AstraZeneca), Sputnik V (Gamaleya Research), and the Johnson & Johnson/Janssen Ad26.COV2.5 (in use only in South Africa) (Table 2). Large-scale phase 3 studies indicate an efficacy of 70–91% for these vaccines with generally good tolerability [39-41]; all are storable at 2–8°C [12].

mRNA vaccines

mRNA vaccines are an innovative vaccine technology in which mRNA for a target antigen is introduced to cells using a lipid nanoparticle (LNP) delivery vehicle. Once endocytosed, LNP facilitates release of mRNA, which is then translated into antigen that is presented by the cell to the immune system using MHC complexes [42]. mRNA vaccines offer several advantages over conventional vaccination strategies, including improved cellular immunogenicity (via antigen presentation on MHC class I), absolute reduction in risk of both vaccine infection (due to independence from a viral vector) and insertional mutagenesis (due to use of non-replicating mRNA), and increased potential for rapid development and manufacture [42]. Both the Pfizer–BioNT162b2 and the Moderna mRNA-1273 mRNA vaccines are in use in the African context (Table 2). Large-scale phase 3 studies indicate an efficacy of 95% with mainly mild adverse effects [43,44]. Although the vaccines are stable at 2–8°C for a limited period, long-term storage requires low temperature refrigeration (–20°C to –70°C), limiting the widespread use of these vaccines [12].

Immunological monitoring

Immunity against future infection by a pathogen requires the acquisition of both humoral and cellular response arms. Since the relative contribution of either response to protection against SARS-COV-2 is unknown, assessment of immunity following vaccination should ideally measure both [45].

Cellular uptake of the SARS-CoV-2 virion in preparation for replication is accomplished by binding of the receptor binding domain (RBD) of the S1 subunit of the spike glycoprotein to surface expressed angiotensin-converting enzyme 2, followed by S2-mediated fusion of the viral and host cell membranes [46]. Whereas the S2 subunit is highly conserved in coronaviruses, the S1 unit is relatively specific for SARS-CoV-2 and forms the antigenic target for the majority of available vaccines [45]. Available serological tests for humoral response to SARS-CoV-2 are able to detect IgA, IgM, IgG or total immunoglobulin level against nucleocapsid (N) or spike glycoprotein (S) specificities [45]; only those that are specific for anti-S1 IgG antibody are suitable for determining vaccine humoral effect.

Although anti-RBD IgG titres remain elevated for at least 6 months in survivors of SARS-CoV-2 infection [47], the total duration of detectable persistence of antibody in either natural or post-vaccination immunity is not known, and the threshold titre for humoral protection against infection has not been determined [46]. It is therefore unclear whether the natural history of IgG expression in COVID-19 survivors can be extrapolated to post-vaccination immunological monitoring.

Up to 40% of SARS-CoV-2 infected patients may fail to mount a detectable antibody response to the virus [45]; significantly, memory T cells have been extracted from convalescent antibody-negative patients [48], suggesting

Table 2. SARS-CoV-2 vaccines in use in Africa.

Vaccine	Reported efficacy	Reported adverse effect profile	Number of doses	Countries authorising use [33]
Killed whole virus				
BBIBP-CorV (Sinopharm) [34]	Patients <60 yr: 100% at 28 days (independent of dose)* Patients >60 yr: 92% 4 mg dose 96% 8 mg dose* Phase 2 trial (n = 448)	Nil severe 23% mild: fever, local pain, fatigue, loss of appetite, nausea	1 (8 mg) or 2 (4 mg) (d0, d28)	Algeria, Angola, Cameroon, Chad, Comoros, Congo Republic, Egypt, Equatorial Guinea, Ethiopia, Gabon, Guinea, Libya, Mauritania, Morocco, Mozambique, Namibia, Niger, Senegal, Sierra Leone, Seychelles, Somalia, Sudan, Tunisia, Zambia, Zimbabwe
Coronavac (Sinovac) [35,36]	Patients <60 yr: 100% at 56 days* (6 mg dose) Phase 2 trial (n = 118) Patients >60 yr: 99% at 56 days* Phase 2 trial (n = 98)	Nil severe 23% mild: Local pain Nil severe 22% mild: Local pain	2 (d0, d28)	Benin, Botswana, Djibouti, Egypt, Guinea, Togo, Tunisia, South Africa, Zimbabwe
Covaxin (BBV152) (Bharat Biotech) [37]	96.6% at 56 days (6 mg dose)* Phase 2 trial (n = 177)	1 patient with grade 3 fever 21.1% mild: local pain, headache, fever, nausea, vomiting	2 (d0, d28)	Mauritius, Zimbabwe
Replication-defective viral vector carrying pathogen genes				
Ad26.COV2.5 (Janssen, Johnson & Johnson) [39]	Moderate to severe COVID-19: 66.9% at 28 days** Severe COVID-19: 85.4% at 28 days** Phase 3 trial (n = 39,321) 20H/501Y.V2 (beta) variant: Moderate to severe COVID-19: 64% at 28 days** Severe COVID-19: 81.7% at 28 days**	0.4% severe: Thromboembolic (n = 11), seizure (n = 4), Guillain-Barre (n = 1) Mild: Local pain (48.6%), headache (38.9%), fatigue (38.2%), myalgia (33.2%), nausea (14.2%)	1	South Africa
ChAdOx1nCoV-19 (AZD1222) (Oxford–Astra-Zeneca) [40]	70.4% at 2 months** Pooled interim analysis of 4 phase 2/3 studies (n = 23,848)	Generally well-tolerated. 2 cases of transverse myelitis in the vaccine group: 1 possibly vaccine-related (d10), 1 probably due to underlying, previously undiagnosed multiple sclerosis	2 (d0, d28)	Algeria, Angola, Benin, Botswana, Burkina Faso, Cabo Verde, Cameroon, CAR, Comoros, Cote d'Ivoire, Djibouti, DRC, Egypt, Eswatini, Ethiopia, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Libya, Madagascar, Malawi, Mali, Mauritania, Mauritius, Morocco, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Somalia, South Sudan, Sudan, Togo, Tunisia, Uganda, Zambia
Sputnik V (Gam-COVID-Vac) (Gamaleya Research) [41]	91.6% at 21 days** Interim analysis of phase 3 trial (n = 21,977)	0.4% severe (all considered unrelated to vaccine by IDMC) 45% mild: Flu-like illness, injection site reactions, headache, asthenia	2 (d0, d21)	Algeria, Angola, Congo Republic, Guinea, Libya, Mauritius, Seychelles, Tunisia, Zimbabwe
mRNA vaccines				
BNT162b2 (Pfizer–BioNTech) [43]	95% at median 2 months** of follow-up Phase 3 trial (n = 43,548)	0.02% severe: Shoulder injury due to local reaction, lymphadenopathy, paroxysmal ventricular arrythmia, paraesthesia. 2 deaths – cardiac arrest (4 in placebo) Mild: Local pain (83%), fatigue (59%), headache (52%), fever (16%)	2 (d0, d21)	Cabo Verde, Mauritania, Rwanda, Togo, Tunisia, South Africa
mRNA-1273 (Moderna) [44]	94.1% at median 63 days** of follow-up Phase 3 trial (n = 30420)	1.3% severe hypersensitivity reaction in 1.5%. Mild: Local pain (84%), 63.6% fatigue, myalgia, headache, arthralgia, nausea or vomiting	2 (d0, d28)	Rwanda

*Vaccine efficacy determined by demonstration of neutralising antibodies.
**Vaccine efficacy determined by prevention of COVID-19.

that the cellular arm of the immune response may provide protection against subsequent infection. Thus, evaluation of antibody titre alone after administration of vaccines capable of inducing a T-cell response (Oxford–AstraZeneca ChAdOx1nCoV-19, Pfizer–BioNT162b2 and Moderna mRNA-1273) [45] may not accurately reflect the potency of immunisation achieved.

In view of these limitations, neither the US Federal Drug Administration [49] nor the CDC [50] currently recommends existing serological tests for the evaluation of post-vaccination immunity.

RECOMMENDATIONS

Consideration of the available literature suggests the following approaches to the vaccination of patients living with CKD against SARS-CoV-2:

1. All patients living with CKD, including those with immune-mediated kidney disease and renal transplant recipients, constitute a high-risk group for the develop-ment of severe COVID-19 [1,2] and should be offered vaccination for SARS-CoV-2, including those with documented antecedent infection with SARS-CoV-2.
    - 1.1 All such patients should therefore receive the first available vaccine with documented efficacy in preference to waiting for vaccine with perceived higher efficacy.
    - 1.2 However, if available, all such patients should preferably be offered vaccination with mRNA vaccines, in view of apparent enhanced reliability of reactogenicity [12].
2. Steps should be taken in all such patients receiving vaccination against SARS-CoV-2 to limit and to monitor for potential side effects.
    - 2.1 Patients with a known allergy to PEG (LNP stabiliser) should not be offered vaccination with either mRNA-1273 or BNT162b2 but should be offered vaccination with either a replication-deficient viral vector vaccine or a killed whole-virus vaccine. Similarly, patients with a known allergy to polysorbate 80 (stabiliser in replication-deficient viral vector vaccines) should be offered vaccination with either an mRNA or a whole killed virus vaccine and should not receive either the ChAdOx1nCoV-19 (AZD1222) or the Ad26.COV2.5 vaccine [14].
    - 2.2 A low threshold for investigation for VITT should be maintained in female patients under the age of 55 immunised with the Ad26.COV2.5 vaccine, who report symptoms suggestive of cerebral venous sinus thrombosis, deep vein thrombosis, or pulmonary thromboembolism [7].
    - 2.3 The possibility of acute rejection should be considered in any transplant recipient manifesting a sudden deterioration in graft function after recent vaccination.
3. The timing of vaccination in patients living with immune-mediated kidney disease and in renal transplant recipients should be individualised in the context of prescribed or planned immunosuppression.
    - 3.1 Where possible, initiation of immunosuppression should be delayed by two to four weeks to allow for adequate immunisation [16,21].
        - 3.1.1 In cases requiring emergent therapy, intravenous pulse cyclophosphamide infusion should, where possible, be delayed by at least one week following vaccination [21].
    - 3.2 In patients already receiving corticosteroids, vaccination should, where possible, be delayed until the prescribed dose is less than 20 mg/day prednisone or equivalent [21].
    - 3.3 Where local policy allows, all patients on high-dose immunosuppression regimes or regimes which include biologics, who receive an mRNA vaccine, should be offered a third vaccine dose administered at least 28 days after the scheduled second dose [13,16,29].
        - 3.3.1 In patients receiving rituximab who receive an mRNA vaccine, booster vaccination should be administered 3–6 months after completion of treatment course, or once B-cell repopulation is confirmed by peripheral blood flow cytometry [21,23].
4. Routine monitoring for immunological response to vaccination is not currently indicated in the clinical setting, regardless of the perceived immunological competency of the individual patient [16,49,50].
5. All patients living with CKD should continue to practise masking, hand hygiene, and social distancing regardless of vaccination status.

CONCLUSIONS

Patients living with CKD are at high risk of severe COVID-19, and dependence on hospital-based specialist care for treatment of CKD increases individual risk of contracting SARS-CoV-2. No satisfactory treatment protocol for COVID-19 is currently available; however, hope

of relief from the pandemic is now at hand in the form of novel vaccines. To optimise the success of immunisation of this vulnerable patient population, nephrologists are urged to acquaint themselves with all aspects of SARS-CoV-2 vaccination.

Conflicts of interest

The authors have no conflicts of interest to declare.

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