



# Perspective on COVID-19 vaccination in patients with immune-mediated kidney diseases: consensus statements from the ERA-IWG and EUVAS

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## ABSTRACT

Patients with immune-mediated kidney diseases are at increased risk of severe coronavirus disease 2019 (COVID-19). The international rollout of COVID-19 vaccines has provided varying degrees of protection and enabled the understanding of vaccine efficacy and safety. The immune response to COVID-19 vaccines is lower in most patients with immune-mediated kidney diseases; either related to immunosuppression or

comorbidities and complications caused by the underlying disease. Humoral vaccine response, measured by the presence of antibodies, is impaired or absent in patients receiving rituximab, mycophenolate mofetil (MMF), higher doses of glucocorticoids and likely other immunosuppressants, such as cyclophosphamide. The timing between the use of these agents and administration of vaccines is associated with the level of immune response: with rituximab, vaccine response can only be expected once B cells start to recover and patients with transient discontinuation of MMF mount a humoral response more frequently. The emergence of new COVID-19 variants and waning of vaccine-induced immunity highlight the value of a booster dose and the need to develop mutant-proof vaccines. COVID-19 vaccines are safe, exhibiting a very

low risk of *de novo* or relapsing immune-mediated kidney disease. Population-based studies will determine whether this is causal or coincidental. Such cases respond to standard management, including the use of immunosuppression. The Immunonephrology Working Group and European Vasculitis Society recommend that patients with immune-mediated kidney diseases follow national guidance on vaccination. Booster doses based on antibody measurements could be considered.

**Keywords:** IgA nephropathy, immunology, immunosuppression, rituximab, vasculitis

## INTRODUCTION

The ongoing coronavirus disease 2019 (COVID-19) pandemic has particularly impacted the lives of patients with immune-mediated kidney diseases. COVID-19 vaccination programmes have been transformative. However, new COVID-19 variants such as delta and omicron, waning immunity post-vaccination leading to the occurrence of breakthrough infections and a lower/absent humoral response in those on immunosuppression are of major concern for those with immune-mediated diseases.

Last year the Immunonephrology Working Group (IWG) of the European Renal Association (ERA) published guidance regarding COVID-19 vaccination in patients with immune-mediated kidney diseases. These recommendations were derived from an understanding of the use of other vaccines in this population and the experience of COVID-19 vaccines in the general population [1]. Patients with immune-mediated diseases, particularly with active disease and/or those receiving cyclophosphamide, rituximab or higher-dose steroid, are at greatly increased risk of severe COVID-19 and fatal outcomes [2–4].

This consensus statement provides an updated overview of vaccine efficacy in patients with immune-mediated kidney diseases. The importance of prioritization for vaccination, booster doses, COVID-19 vaccine safety concerns and equity of vaccine access are discussed.

### Vaccine immunogenicity, efficacy and effectiveness

Immunogenicity refers to the ability of a vaccine to induce an immune response in a vaccinated individual. It is possible to establish the immune response to vaccination in two ways: measurement of the humoral response [spike 1/2 (S1/S2) severe acute respiratory syndrome coronavirus (SARS-CoV-2)/neutralizing antibody titres] and/or the cellular response. The latter is not established in routine assessment and

the former may be associated with a considerable financial cost, precluding routine use for most hospitals. Increasing evidence demonstrates that factors related to comorbidities or immunosuppressive therapy impair the protective immunity of COVID-19 vaccines.

Vaccine efficacy is tested in randomized controlled trials and defined as the percentage reduction in individuals who develop a disease (in this case COVID-19) in a vaccinated cohort compared with those who are unvaccinated. In COVID-19, vaccine efficacy incorporates a measure of the reduction of cases with severe (requiring hospitalization)/fatal COVID-19 disease, an outcome measure of particular importance in vulnerable populations.

The effectiveness of a vaccine boils down to how well it works in the ‘real world’, i.e. does it protect against infection or reduce the severity of infection. Although vaccine effectiveness is extensively studied in immunocompromised patients, large trials in patients with immune-mediated kidney diseases are lacking.

### How do we measure whether the COVID vaccines are ‘working’ in the general population?

Neutralizing SARS-CoV-2 antibodies remain the leading correlate of protective immunity. The subset of antibody generated, i.e. immunoglobulin A (IgA), IgM and IgG, is of importance and the distribution and variation may associate with factors that influence disease severity [5]. It is noteworthy that the evolution towards more virulent SARS-CoV-2 variants precludes guaranteed immunity, even in individuals who are known to have mounted a vaccine response. The currently available vaccines have been developed against the redundant alpha variant of SARS-CoV-2 (Table 1).

In individuals receiving the BioNTech/Pfizer vaccine (BNT162b2), neutralizing antibodies against all variants of COVID-19 were reduced over time. This was more marked against emerging variants of concern, like delta (5.8-fold) and beta (4.9-fold) [6]. Further analyses among haemodialysis patients revealed suboptimal neutralizing antibody levels among infection-naïve individuals receiving a viral-vector vaccine compared with BNT162b2, while two doses of either vaccine could consolidate the response following infection [7–12].

The threshold of neutralizing antibodies to predict protection from infection or severe COVID-19 is unknown. Follow-up data of individuals receiving the Moderna vaccine (mRNA-1273)—the vaccine eliciting the strongest response—indicated that half-life estimates of live-virus neutralization range between 68 and 202 days [13]. Using data from pivotal

Table 1. Vaccine platforms and intended use (for mRNA vaccines according to EMA and FDA)

| Vaccine name            | Vaccine type             | Manufacturer              | Intended use      |
|-------------------------|--------------------------|---------------------------|-------------------|
| BNT162B2                | mRNA                     | Pfizer/BioNTech           | ≥5 years          |
| mRNA-1273               | mRNA                     | Moderna                   | ≥18 years         |
| ChaAdOx1 nCoV-19        | Vectored                 | Oxford-AstraZeneca        | ≥18 years         |
| Ad26.COVS.2.S           | Vectored                 | Janssen/Johnson & Johnson | ≥18 years         |
| Gam-COVID-Vac/Sputnik V | Vectored                 | Gamaleya                  | Not WHO certified |
| NVX-CoV2373             | Recombinant nanoparticle | Novavax                   | ≥18 years         |
| CoronaVac               | Inactivated              | Sinovac Biotech           | ≥18 years         |
| BBIBP-CoV               | Inactivated              | Sinopharm                 | ≥18 years         |
| BBV152 COVAXIN          | Inactivated              | Bharat Biotech            | ≥18 years         |

vaccination trials (prior to the emergence of the delta variant) and convalescent cohorts, prediction models suggest that the neutralization level for 50% protection against COVID-19 is 20% of the mean convalescent level. Fifty percent protection from severe disease is predicted at 3% [14].

Waning immunity has increased the number of breakthrough infections, leading to an increase in COVID-19 cases. An Israeli study serially investigated IgG antibody levels and neutralizing antibody titres after two doses of BNT162b2. Both decreased over time; the antibody levels by a factor of 18.3 and the neutralizing titre by 3.9 from the peak (observed between day 4 and 30 after the second dose). Factors associated with lower neutralizing antibody titres were male sex, older age and immunosuppression. Immunosuppression was the factor with the greatest impact [15].

Over a 20-day period in July 2021, a population-based analysis from the Israeli Ministry of Health database was carried out. It included 4 791 398 individuals from the general population who were double-vaccinated with BNT162b2 between January and June 2021. A consistently increased risk of contracting COVID-19 (rate ratio 1.6–1.7) was reported among all age groups in those vaccinated at an earlier time point. Furthermore, the proportion of severe disease increased in those undergoing earlier vaccination (rate ratio 1.8–2.2). Most reported infections involved the delta variant [16]. Administering a third ‘booster’ dose of BNT162b2 resulted in a lower rate of confirmed COVID-19 in the booster group (reduced by a factor of 11.3) from 12 days after vaccination. Severe COVID-19 was reduced by almost 20-fold [17].

### What about the omicron variant and vaccination?

Preliminary reports investigating neutralizing antibody levels against the omicron variant indicate a reduction in neutralization efficacy following two doses of the BNT162b2 COVID-19 vaccine, measured 165 days after administration of the second dose. Additionally, a third dose is required to achieve significant neutralizing antibodies against this variant in the general population [18, 19]. It is unclear whether a third dose will provide longer-term immunity. There is evidence of a marked reduction in vaccine effectiveness. Immunity from natural infection with omicron, i.e. without vaccination, seems to offer superior protection than two vaccine doses but is inferior to three doses [20, 21].

### What do we know about vaccine immunogenicity and effectiveness in immune-mediated kidney diseases?

Despite being at higher risk of severe COVID-19, patients with chronic kidney disease (CKD) and patients on immunosuppressive drugs were excluded from most trials, thus the efficacy of vaccines in this vulnerable population has remained uncertain [22]. Currently only observational studies measure immunogenicity of vaccination in these patients as humoral response and/or cellular immunity [23].

Patients with immune-mediated glomerular diseases and vasculitis on therapy showed a poor immune response to the first dose of either the BNT162b2 or Oxford/AstraZeneca vaccine (ChAdOx1), with only 28.6% of patients demonstrating

detectable humoral or T cell responses. Seroconversion and T cell response rates increased to 59.4 and 82.6%, respectively, after the second dose [24]. In agreement with data demonstrating that rituximab severely reduces antibody response to H1N1 influenza vaccine [25], rituximab-treated patients with no measurable peripheral B cells did not develop antibodies after two doses of either mRNA-1273 or BNT162b2 vaccine. Antibody responses were induced once B cells repopulated, and furthermore, a robust T cell response could be mounted even in the absence of circulating B cells, measured at a median of 3 weeks from the second vaccination [26].

What if patients have an inadequate or low humoral response? Among 140 patients receiving immunosuppression for rheumatic and glomerular diseases and following two vaccine doses, T cell and humoral responses were found in 82.6 and 59.3%, respectively [24]. It is unclear why, in spite of immunosuppression, a T cell immune response was more common. Uncertainty still exists regarding protection against severe disease forms in those mounting a cellular immune response; both humoral and cellular immune responses contribute to viral clearance and might be necessary to overcome infection, but protection against developing COVID-19 seems to be largely mediated by an antibody response rather than via cellular immunity [27]. Further studies are needed to define the amount of protection afforded by T cell responses to COVID-19 vaccines.

Little is known about COVID-19 severity in those with immune-mediated kidney diseases after vaccination because this has not been studied in detail [28]. We can draw from experience in other cohorts. Symptomatic COVID-19 was reported among 15 of 16 breakthrough infections in patients with systemic rheumatic diseases. Among these, two with interstitial lung disease who were treated with rituximab died and six were hospitalized [29]. Despite impaired humoral vaccine responses, initial evidence based on 65 cases among 2151 solid organ transplant recipients found an 80% reduction in symptomatic COVID-19 following vaccination [30]. A larger investigation from the UK found only a 20% mortality reduction among 4147 COVID-19 cases following vaccination in transplanted patients and a protective effect was only observed after ChAdOx1 (31% reduction) and not after BNT162b2 (3%). Lung transplant recipients and age >50 years were the strongest predictors of mortality. Several caveats need to be considered, as no baseline information about recipients of ChAdOx1 and BNT162b2 was given, including the degree of kidney function impairment, age, transplant type and density of immunosuppression [31]. Following vaccination, the risk of contracting COVID-19 in transplant recipients is ~80-fold higher than for the general population and associated with a 485-fold higher risk of hospitalization and death [32]. Limited evidence exists focussing on kidney transplant recipients. The risk of SARS-CoV-2 infections in vaccinated individuals seems to be lower, while the disease course was reported to be comparable to the pre-vaccine era [33].

Post hoc analysis of the coronavirus efficacy phase 3 mRNA-1273 vaccine trial found that patients with a 50% post-vaccination neutralization titre of 10, 100 or 1000 exhibited 78, 91 or 96% vaccine efficacy, respectively [34]. The higher the

**Table 2. Risk factors for developing severe COVID-19 disease**

| Variables                                     | Low risk  | Intermediate risk  | High risk   |
|---|---|--|---|
| Age (years)                                   | ≤65   | 65–≤75   | ≥75   |
| CKD   | eGFR ≥60 mL/min/1.73 m <sup>2</sup> and/or no/low-grade proteinuria | eGFR ≥30 mL/min/1.73 m <sup>2</sup> and <60 mL/min/1.73 m <sup>2</sup> and/or proteinuria <3.5 g/day | eGFR <30 mL/min/1.73 m <sup>2</sup> and/or proteinuria ≥3.5 g/day |
| Chronic lung disease                          | No  | No   | Yes   |
| Hypertension/CVD                              | No  | Yes  | Yes   |
| Diabetes mellitus                             | No  | No   | Yes   |
| Disease activity                              | Remission/low activity  | -  | Moderate/high/severe  |
| Immunosuppression                             | Monotherapy (non-glucocorticoid-based IS and no RTX, CYC or MMF)    | -  | Any use of glucocorticoids, RTX, or CYC, multiple IS therapies    |
| Vaccine response (humoral)                    | Yes (with high antibody titres)                                     | Yes (with low antibody titres)   | No  |
| Previous COVID-19 severity                    | Mild  | Moderate   | Severe  |
| Previous severe infections (especially viral) | No  | No   | Yes   |

Risk stratification might help prioritize the need for booster vaccinations. Some of these are based on no/very limited evidence, mainly due to a lack of good studies focusing on patients with immune-mediated kidney diseases. For example, we don't know if patients with nephrotic-range proteinuria have a higher risk of contracting severe COVID-19. Similarly, a severe disease course might protect from future severe COVID-19, but it seems plausible that these patients will not mount very effective protection (i.e. antibodies) because they usually have more comorbidities and might have received medication impairing immune response. CVD, cardiovascular disease; CYC, cyclophosphamide; IS, immunosuppression; RTX, rituximab

antibody response, the better the protection against contracting COVID-19. Thus if patients with immune-mediated kidney diseases mount any humoral response, they should be afforded a degree of protection.

The efficacy of vaccines in patients with immune-mediated kidney diseases remains unclear. A suboptimal strategy to better define vaccine efficacy in vulnerable populations could be the enrolment of fewer participants in a study that sets a primary endpoint at a higher risk. In addition to vaccine rollout, we also suggest the prioritization of vulnerable populations in future studies. Reduced protection for many patients with immune-mediated kidney diseases is expected, but vaccination is strongly recommended and patients should be prioritized, according to national guidance, for the administration of primary and booster doses.

Notably, due to the time lag of medical publishing, current data mostly relate to previous SARS-CoV-2 variants, so relevance to the currently highly prevalent omicron variant remains uncertain. Thus, shielding and distancing remain the most important means of protection, especially in vulnerable patients with doubtful vaccine responses.

### Outcomes in those with immune-mediated kidney diseases and COVID-19 infection

Information about COVID-19-related outcomes in patients with immune-mediated kidney diseases remains limited to small reports, thus necessitating extrapolation from other, similar populations.

Patients on maintenance haemodialysis or with CKD, mainly due to diabetes or hypertension, exhibit high mortality rates of up to 30% [35, 36]. Proposed risk factors associated with severe COVID-19 outcomes are summarized in Table 2. A first analysis of the International Registry of COVID Infection in Glomerulonephritis (IRoc-GN) focussing on immune-mediated kidney diseases found 6 fatalities among 40 patients (15%); these patients were older, had more severe kidney impairment and received immunosuppression more

frequently than the survivors [37]. A follow-up was recruited until April 2021 and analysed 125 patients (63 hospitalized, 62 outpatients). After adjustment for confounders [e.g. pre-COVID-19 estimated glomerular filtration rate (eGFR)], the rates of mortality and acute kidney injury (AKI) were similar to those in the earlier analysis, highlighting the impact of comorbidities in patients with immune-mediated diseases [38].

High mortality rates were observed in a UK cohort including 65 patients with vasculitis, 55 of which had a diagnosis of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Overall, 91% were hospitalized and 28% died. Severe COVID-19 disease was more common among patients on background glucocorticoid therapy and with concurrent respiratory diseases [39]. Analysis of the COVID-19 Global Rheumatology Alliance Registry included 1157 patients with connective tissue diseases or vasculitis and reported a 13% mortality rate. Independent predictors of death were age, CKD, higher disease activity and the use of rituximab and glucocorticoids [2]. Glucocorticoid use at higher doses (≥ 10 mg/day) was not only associated with severe disease and COVID-19-related death, but also with increased likelihood of a positive SARS-CoV-2 test. Table 3 illustrates the risks of different immunosuppressants [2–4, 40–44].

The mortality differences seen between the IRoc-GN (15%), the Global Rheumatology Alliance Registry (13%) and those with AAV from the UK cohort (28%) might be explained by a number of factors, including the age of the populations, the incidence of kidney involvement, immunosuppressive therapy and duration. Disease-specific effects are also likely and no information is available about immunosuppression dosing, which may also be relevant.

### Medication, timing and importance of vaccination in those with immune-mediated kidney diseases

Despite the need to extrapolate from other populations, there is little doubt that these data point towards disease- and treatment-related associations with severe

**Table 3. Immunosuppressants and the risk of severe COVID-19 outcomes in patients with either immune-mediated diseases or transplantation**

| Drugs                                     | Risk of severe COVID-19 (including death) outcomes  |
|---|---|
| Steroids                                  | ≥10 mg/day [OR 1.76 (95% CI 1.06–2.96)] [4]   |
|   | 1–10 mg/day [OR 1.69 (95% CI 1.11–2.57)] [2]  |
|   | ≥10 mg/day [OR 1.93 (95% CI 1.11–3.36)] (international registry/CTD and vasculitis) [2]   |
|   | ≥10 mg/day [OR 2.8 (95% CI 1.36–5.79)] [international registry (AAV)] [3]   |
|   | Chronic corticosteroids [OR 1.89 (95% CI 1.43–2.49)] (transplant/autoimmunity) [41]<br>corticosteroids [OR 1.97 (95% CI 1.09–3.54)] (rheumatic diseases) [42] |
| Mycophenolic acid                         | RR 3.94 (95% CI 1.59–9.74) (liver transplantation) [43]   |
|   | OR 6.6 (95% CI 1.47–29.62) (rheumatic diseases) [42]  |
| Azathioprine                              | OR 1.10 (95% CI 0.54–2.24) [international registry (AAV)] [3]   |
| Calcineurin inhibitors                    | HR 0.55 (95% CI 0.31–0.99) (tacrolimus, liver transplant) [44]  |
|   | OR 1.19 (95% CI 0.65–2.20) (CNIs, transplant/autoimmunity) [41]   |
| CD20-depleting agents                     | OR 3.72 (95% CI 1.21–11.48) (international registry/CTD and vasculitis) [2]   |
|   | OR 2.15 (95% CI 1.15–4.01) [international registry (AAV)] [3]   |
|   | OR 4.21 (95% CI 1.61–10.98) (rheumatic diseases) [42]   |
|   | Effect size 3.26 (95% CI 1.66–6.40) (rheumatic diseases) [40]   |
| Belimumab                                 | OR 1.07 (95% CI 0.21–5.37) (international registry/CTD and vasculitis) [2]  |
| Alkylating agents (i.e. cyclophosphamide) | OR 4.30 (95% CI 1.10–16.75) [international registry (AAV)] [3]  |
| Complement inhibitors                     | No data   |

All information provided here is based on observational and retrospective data. The association between higher doses of steroids and risk to develop severe COVID-19 was confirmed not only in autoimmunity or transplantation, but most investigations found only a modest and non-significant increased risk when patients received a steroid dose <10 mg/day. Multiple independent investigations found an association between rituximab use and severe COVID-19. In addition, a combination of different strategies might also portend a higher risk (as seen in transplantation). Notably, the ‘international registry’ [2] included a similar set of patients. For specific references see the Supplementary data, online Appendix. CNI, calcineurin inhibitor; CTD, connective tissue disease; OR, odds ratio; CI, confidence interval; RR, relative risk.

COVID-19 and emphasize the increased risk of patients on immunosuppressive drugs contracting COVID-19. Vaccinating this vulnerable patient cohort is extremely important. Moreover, treatment of severe COVID-19 with higher glucocorticoid doses might not lead to the same benefit seen in the general population with severe COVID-19 [45]. Dedicated trials specifically focussing on patients with immune-mediated diseases are essential.

Different factors also impact the measured COVID-19 vaccine response. Patients on immunosuppression, especially those receiving B cell-depleting agents, glucocorticoids and MMF have impaired humoral response rates. Furthermore, treatment-related impacts, specific disease-associated factors, demographics and comorbidities might influence not only the initial humoral vaccine response rate, but also the longevity of antibody response.

Patients with heavy proteinuria and urinary immunoglobulin loss may exhibit substantial loss of anti-spike protein antibodies in the urine, increasing their risk of infection [46]. Additionally, there may be an impact of immunosuppression (induction or maintenance) on antibody titres. A series of four patients with AAV found that 1 month after rituximab administration (two patients also received cyclophosphamide), SARS-CoV-2 antibody titre levels decreased by 42–78% [47]. More data will provide better guidance, but it seems that in patients with immune-mediated kidney diseases, additional booster doses might be considered. This is likely to be based on SARS-CoV-2 antibody kinetics data from trials, because measurement of neutralizing antibodies is not routine in clinical practice.

The timing of vaccination relative to treatment of the underlying condition creates a dilemma. Control of immune-

mediated kidney disease usually takes priority. Adaptive strategies for maintenance therapy might be employed, especially if the number of cases with COVID-19 is high and patients are at particular risk of contracting severe COVID-19. Weighing the risks and benefits in this scenario is important and rituximab might be postponed or replaced by other immunosuppressive agents to allow for vaccine response.

Several independent investigations have indicated that despite the blunted humoral response to vaccination following rituximab [48], the cellular response might be intact [24, 26, 49–51]. This has been challenged by the RituxiVac study [52], which reported a weaker cellular than humoral response following B cell depletion. Notably, in the RituxiVac study, a whole-blood interferon (IFN) release assay was used, whereas most other studies have used peripheral blood mononuclear cells and spot count assays. Important independent predictors of humoral vaccine response were time elapsed since the last infusion, the presence of circulating CD19<sup>+</sup> B cells [48, 52] and a CD4<sup>+</sup> lymphocyte count >653 cells/μL [52]. Specifically, a minimum of 10 B cells/μL in peripheral circulation were required to mount a humoral response [53]. A third homologous vaccine administration did not induce a humoral response (in 15/16 patients) except in 1 patient who had a recurrence of B cells and detectable antibodies following a third dose [54].

In patients with AAV with a low risk of relapse, maintenance therapy with rituximab might be postponed, allowing reconstitution of CD19<sup>+</sup> B cells, or therapy might be switched to other immunosuppressants. The American College of Rheumatology guidance on COVID-19 vaccination recommends withholding MMF for 1 week when the disease is stable [55]. This strategy was tested in a prospective

**Table 4. Different drugs and the impact on humoral and cellular immune vaccine response: a summary of the level of evidence and factors influencing it**

| Drugs                                     | Humoral-immune vaccine response  | Cellular-immune vaccine response             | Clinical perspective   | Factors influencing response  |
|---|--|--|--|---|
| Steroids                                  | S1/S2 SARS-CoV-2/ neutralizing antibody response ↓/↓                               | →/↓ (limited evidence)                       | T cell response might be impaired with higher doses; overall low evidence                            | Dose-dependent reduced antibody response; impaired cellular response might be dose dependent                        |
| Mycophenolic acid                         | S1/S2 SARS-CoV-2/ neutralizing antibody response ↓/↓                               | → (limited evidence)                         | Antibody response significantly reduced by MMF; unclear evidence related to cellular immune response | Reduced doses associated with response in KTR; transient hold of MMF after vaccine administration (1 week)          |
| Azathioprine                              | S1/S2 SARS-CoV-2/ neutralizing antibody response →/→                               | → (limited evidence)                         | Humoral response seems to be preserved; no information on cellular response                          | –   |
| Calcineurin inhibitors                    | S1/S2 SARS-CoV-2/ neutralizing antibody response ↓/↓, in IMKD limited evidence (→) | T cell response impaired (limited evidence)  | Humoral response in KTR significantly reduced and cellular response in IMKD                          | Presumably a dose-dependent weakened antibody response (time from transplantation to vaccination improves response) |
| CD20-depleting agents                     | S1/S2 SARS-CoV-2/ neutralizing antibody response ↓/↓                               | Controversial evidence, T cell response →, ↓ | No or only marginal humoral response when rituximab is administered 6 months before vaccination      | Presence of CD19 cells, timing (>6 months) and higher CD4 T lymphocytes predict response                            |
| Belimumab                                 | S1/S2 SARS-CoV-2/ neutralizing antibody response →↓/→↓                             | –  | A reduced antibody response and lower seroconversion rate should be expected                         | –   |
| Alkylating agents (i.e. cyclophosphamide) | S1/S2 SARS-CoV-2/ neutralizing antibody response (probably ↓/↓)                    | (probably impaired)                          | No concrete recommendation possible based on current evidence  | –   |
| Complement inhibitors                     | S1/S2 SARS-CoV-2/ neutralizing antibody response (probably →/→)                    | (probably unaffected)                        | No concrete recommendation possible based on current evidence  | –   |

IMKD, immune-mediated kidney disease; KTR, kidney transplant recipient.

single-centre study where peri-vaccination, 24 patients withheld MMF and 171 continued therapy. A higher proportion of patients in the group that withheld MMF developed a humoral response [56]. There are insufficient data on other treatments, but for most agents, a reduced response can be expected (Table 4).

### Vaccine strategy: primary multiple dose or two plus booster doses?

With the emergence of the omicron variant, a two primary dose regimen of either COVID-19 vaccine was deemed insufficient to prevent infection [57]. Thus everybody should receive three doses (‘primary’ vaccination strategy) of a COVID-19 vaccine. Evidence supports this approach for mRNA vaccines [18, 58] and a recent press release also reported effectiveness for ChAdOx1. A fourth vaccine dose for the immunosuppressed patient population is suggested in most countries and for those >60 years of age in Israel. In patients with an ongoing immunosuppression burden and a high likelihood of impaired vaccine response (Table 4), the administration of a fourth vaccine appears important.

The choice of vaccine to boost the immune system is mostly limited by national recommendations. The Evaluating

COVID-19 Vaccine Boosters trial in the UK randomized patients to seven different vaccines after an initial regimen of ChAdOx1 and BNT162b2 (two administrations each). The strongest reactivity was reported for a booster dose with mRNA-1273 after both primary strategies and for the viral-vectored vaccines [ChAdOx1 or Johnson & Johnson/Janssen (Ad26.COV2.S)] after BNT162b2 [59], the latter highlighting the potential role of heterologous vaccine administration.

In solid organ transplant patients, a fourth dose was offered to patients with a weak ( $n = 5$ ) or no humoral response ( $n = 31$ ). BNT162b2 was administered at a median time of 65 days after the third vaccine dose. The number of participants with detectable antibodies increased from 5 to 18 1 month after administration of the fourth dose. Notably, in those with a weak response after three doses, the antibody concentration increased 100-fold following the fourth vaccine dose, but with only a modest increase of the neutralizing antibody titres [60].

In immune-mediated inflammatory disease patients, 66 patients with no response to two vaccine doses received a third dose. A humoral and cellular response was reported in half of the patients. Importantly, there was a significant difference between patients not receiving rituximab and rituximab users

(78.8% versus 18.2% and 80% versus 21.9%) [61]. This was confirmed in a small study that focussed on patients with AAV. Rituximab users had significantly lower anti-S1 IgG antibody and delta variant neutralization levels in comparison to non-users [62].

In a clinical trial, kidney transplant recipients with no humoral response after two doses of mRNA vaccine were randomized to receive BNT162b2/mRNA-1273 or Ad26.COV2.S as their third dose. The number of participants with a humoral vaccine response appeared higher in the Ad26.COV2.S group (42% versus 35%, not significant). Subanalysis of the group receiving another mRNA vaccine after the failure of two initial doses of either mRNA-1273 or BNT162b2 was not provided [63].

What about the timing between infection and administration of booster doses? With the ongoing omicron surge, we suggest booster administration is important because protection from prior infections seems incomplete. Notably, a significantly lower risk of breakthrough infections after prior infection and COVID-19 vaccination was reported from Qatar [64]. The risk of a severe or fatal disease course in reinfected individuals was reduced by 90% in a small population-based analysis [65]. Prior infection might convey some protection from severe disease in healthy individuals; it is not clear if this translates to immunocompromised individuals. Regardless, emerging variants of concern with a high potential of re-infection mean booster vaccination is advised even after a recent SARS-CoV-2 infection.

### What do we know about paediatric patients and vaccination?

Information regarding vaccine efficacy in children with immune-mediated kidney disease is limited. The clinical course of COVID-19 in most children with/without CKD is mild [66], but severe cases and children with a life-threatening multisystem inflammatory syndrome (MIS-C) have been reported [67]. However, an international survey among 113 children receiving immunosuppression (47% kidney transplant recipients) indicated mortality in 4 (3.5%) and ventilatory support in 6 (5%) [68]. Risk factors associated with a more severe illness in adults; active disease, higher doses of glucocorticoids, use of MMF or rituximab are also evident in the paediatric population [69]. This emphasizes that vaccination in children with immune-mediated kidney diseases must also be prioritized. Thus far the only vaccine approved by the Centers for Disease Control and European Medicines Agency (EMA) for use in children (ages 5–17 years) is BNT162b2. Two doses of 30 µg BNT162b2 21 days apart in 12 to 15-year-old participants elicited higher neutralizing antibody titres relative to 16 to 25-year-old participants, with a vaccine efficacy of 100% and an acceptable safety profile [70]. In a dose-finding study, a dose of 10 µg BNT162b2 was found to elicit similar neutralizing antibody titres compared with 30 µg BNT162b2 in 16 to 25-year-old participants. Vaccine efficacy of 90.7% was reported, with no serious adverse events identified [71]. Information about booster doses is not currently available.

### Safety of COVID-19 vaccines in immune-mediated kidney diseases

Systemic and localized adverse events have been assessed by questionnaires in most studies involving patients with autoimmune diseases. Side-effect profiles appear similar between patients with autoimmune diseases and healthy controls. This was observed for different vaccine platforms [72].

Another concern for patients and physicians is the risk of *de novo* and relapsing/flare glomerulonephritis following COVID-19 vaccination. Cases of temporal association of glomerular diseases with vaccination have been reported, but it is unclear if the administration of vaccines has provoked the onset of autoimmunity as a 'second hit' or whether there is a true association. Large population-based investigations are necessary to prove causation. A single-centre study focused on IgA nephropathy found that among 89 patients with a pre-existing disease no disease flare was recorded [73]. The EMA is closely monitoring the occurrence of glomerulonephritis and nephrotic syndrome. A total of 89 cases were reported by 31 July 2021 after the administration of 918 million doses of BNT162b2 worldwide. Reporting bias may underestimate the risk. Table 5 summarizes cases reported in the medical literature. IgA nephropathy and minimal change disease (MCD) are the leading disease entities occurring *de novo* or relapsing/flare after vaccination. Notably the onset or relapse of MCD following certain vaccination has been described prior to the COVID-19 era [74]. Table 5 includes cases reported until the end of December 2021 and includes 45 cases of IgA nephropathy, 36 cases of MCD, 20 of AAV, 11 of membranous nephropathy, 7 of anti-GBM-disease and acute interstitial nephritis, 5 of focal segmental glomerulosclerosis, 3 with lupus nephritis, 2 of IgA vasculitis and 1 each of proliferative GN, IgG4-related disease and scleroderma renal crisis.

Most immune-mediated kidney diseases relapsed/flare or were diagnosed after the second dose of the COVID-19 vaccine, with the exception of MCD, which was usually found after the first dose. An analysis of the World Health Organization (WHO) VigiBase revealed that BNT162b2 might be associated with MCD, while IgA nephropathy was more frequently reported after vaccination with mRNA-1273 [75]. These findings warrant confirmation in independent cohorts, but the benefits of vaccination far outweigh this small, theoretical risk.

Another important question is the re-administration of a COVID-19 vaccine after provoking the onset or relapse/flare of immune-mediated kidney disease. Three case reports indicate that a rechallenge with either the same vaccine (mRNA-1273 or CoronaVac) or a switch from BNT162b2 to mRNA-1273 induced worsening proteinuria and led to the occurrence of AKI in one case with MCD [76–78]. Data on heterologous vaccine strategies are not available.

With the initiation of appropriate management, most disease onset or relapse/flare of immune-mediated kidney disease can be successfully treated in a standard manner. However, outcome data are, short-term, based on the limited follow-up duration.

Table 5. Summary of reported cases of *de novo* glomerulonephritis or a relapse/flare of the established disease. Additional cases can be entered in the IRoC-GN 2 registry (<https://redcapsurvey.niddk.nih.gov/surveys/?s=LCDAMFD9JA>)

| Disease                    | Vaccine platform   | Cases reported | <i>De novo</i> or relapse/flare  | After 1st or 2nd dose of vaccine            | Immunosuppression during vaccination  | Management of active disease after vaccination   | Outcome (creatinine)                                     |
|----------------------------|--|----------------|----------------------------------|---|---|--|--|
| MCD                        | mRNA [27], viral-vectored [7], inactivated whole virus [2]     | 36             | <i>De novo</i> [27], relapse [9] | 1st [18], 2nd [11], unknown [7]             | Not reported [9], no IS [22], corticosteroids [5], tacrolimus [2]             | Corticosteroids [27], rituximab [1], MMF [1], tacrolimus [1], CSA [2] not reported [9]                   | Unknown [15], worsening [2], stable [5], improving [14]  |
| MN                         | mRNA [9], viral-vectored [1], inactivated whole virus [1]      | 11             | <i>De novo</i> [7], relapse [4]  | 1st [2] <sup>c</sup> , 2nd [6], unknown [3] | Not reported [7], no IS [4]   | Conservative [2], corticosteroids [1], tacrolimus [1], obinituzumab [1], rituximab [2], not reported [3] | Unknown [6], stable [1], improving [4]                   |
| FSGS <sup>a</sup>          | mRNA [2], viral-vectored [3]                                   | 5              | <i>De novo</i> [3], relapse [2]  | 1st [3], 2nd [2]                            | Not reported [2], no IS [3]   | Conservative [2], corticosteroids [3], rituximab [1], plasma exchange [1], tacrolimus [1]                | Worsening [2], stable [1], improving [2]                 |
| IgAN                       | mRNA [43], viral-vectored [1], inactivated viral particles [1] | 45             | <i>De novo</i> [26], flare [19]  | 1st [9], 2nd [26], unknown [10]             | Not reported [15], no IS [29], corticosteroids [1]                            | Conservative [11], corticosteroids [18], cyclophosphamide [5], tonsillectomy [1], unknown [7]            | Unknown [12], worsening [2], stable [15], improving [16] |
| IgAV                       | mRNA [2]   | 2              | <i>De novo</i> [1], flare [1]    | 1st [1], 2nd [1]                            | No IS [2]   | Corticosteroids [2]  | Improving [2]  |
| AAV                        | mRNA [16], viral-vectored [4]                                  | 20             | <i>De novo</i> [17], relapse [3] | 1st [6], 2nd [9], unknown [5]               | Not reported [3], no IS [13], corticosteroids [2], rituximab [1] <sup>d</sup> | Corticosteroids [18], rituximab [12], cyclophosphamide [9], PLEX [2]                                     | Unknown [3], worsening [4], improving [13]               |
| Anti-GBM <sup>b</sup> [85] | mRNA [4], inactivated whole virus [2], unknown                 | 7              | <i>De novo</i> [7]               | 1st [1], 2nd [6]                            | Not reported [2], no IS [1]   | Corticosteroids [1], MMF [1], cyclophosphamide [5], PLEX [5]   | Unknown [2], worsening [2], stable [1], improving [2]    |
| LN                         | mRNA [2], viral-vectored [1]                                   | 3              | <i>De novo</i> [2], relapse [1]  | 1st [2], unknown [1]                        | No IS [3]   | Corticosteroids [3], MMF [2]   | Unknown [1], stable [1], improving [1]                   |
| Focal proliferative GN     | Viral-vectored [1]   | 1              | <i>De novo</i> [1]               | 1st [1]                                     | No IS [1]   | Corticosteroids [1]  | Improving [1]  |
| AIN                        | mRNA [7]   | 7              | <i>De novo</i> [7]               | 1st [1], 2nd [6]                            | No IS [7]   | Corticosteroids [7]  | Improving [7]  |
| IgG4-RD                    | mRNA [1]   | 1              | Relapse [1]                      | 2nd [1]                                     | No IS [1]   | Corticosteroids [1], rituximab [1]   | Improving [1]  |
| SRC                        | mRNA [1]   | 1              | <i>De novo</i> [1]               | 1st [1]                                     | No IS [1]   | Conservative [1]   | Stable [1]   |

AIN, acute interstitial nephritis; GBM, glomerular basement membrane; IgAN, IgA nephropathy; IgG4-RD, IgG4-related disease; IS, immunosuppression; LN, lupus nephritis; MN, membranous nephropathy; SRC, scleroderma renal crisis.

<sup>a</sup>Two patients after kidney transplantation; one with a *de novo* case in the allograft.

<sup>b</sup>Including cases with atypical anti-GBM disease [85] and double-positive cases (AAV and anti-GBM disease) [86, 87].

<sup>c</sup>Worsening proteinuria occurred after administration of the second vaccine dose (switch from BNT162b2 to mRNA-1273).

<sup>d</sup>Last rituximab as part of maintenance therapy was given 9 months before vaccination.

### Equity of access to vaccination

The impact of the COVID-19 pandemic has provided harsh lessons about societal inequalities disproportionately affecting the most vulnerable individuals and groups by interacting with and exacerbating every existing social inequality in chronic disease and the social determinants for health. These side effects are greater in low- and middle-income countries. In nephrology, we have seen amplification of inequity of access to trials, treatments and vaccinations.

Equity of access includes children. Vaccination of children was only seriously considered when it became evident that they may spread COVID-19 to the adult workforce. The presumption of a milder COVID-19 illness in children only partially applies to those with immune-mediated kidney diseases and/or CKD. We strongly recommend that access to COVID-19 vaccines be prioritized for children with (immune-mediated) kidney disease.

Equitable global access to and fair distribution of vaccination poses a challenge. Political and economic constraints may limit access to the country that produces it or can afford to pay. Several initiatives are in progress to overcome this, including the COVID-19 Vaccines Global Access (COVAX) Facility, which aims to accelerate the development of COVID-19 vaccines and ensure equitable distribution/availability in low- and middle-income countries (<https://www.gavi.org/vaccineswork/gavi-ceo-dr-seth-berkeley-explains-covax-pillar>). While it is evident that equitable access is paramount, it is less clear whether these or similar schemes will succeed in achieving this ambition [79].

### CONCLUSION AND OUTLOOK

The systematic rollout of COVID-19 vaccines has in real-time enhanced our understanding of vaccine response in healthy individuals and those with comorbidities, especially those receiving immunosuppression. Several immunosuppressants impair vaccine response and the absence of humoral immunity following rituximab is particularly concerning. Maintenance therapy strategies are adopted to provide a 'window of potential' to mount an antibody response. A transient withdrawal of MMF has increased vaccine response rates in patients with autoimmune diseases [56] and might be an option when a short-term suspension of immunosuppression is considered safe.

Patients with immune-mediated kidney diseases should be prioritized to receive booster doses according to national implementation as early as possible, as reduced vaccine response is anticipated in many cases. Reported side effects (including recurrence of disease or *de novo* glomerulonephritis) are rare and large population-based investigations are necessary to provide evidence of a true association [80]. The benefits of COVID-19 vaccines clearly outweigh the potential risks.

Vaccines need to be 'updated' based on the emergence of variants of concern and mutations in the spike protein. Monoclonal antibody treatment has shown high efficacy in preventing severe diseases and patients who do not mount a vaccine response might become eligible to receive a prophylactic dose. As a caveat, the efficacy of these treatments may differ with omicron and newer variants. Such strategies are currently

under investigation [i.e. sotrovimab arm of PROphylaxis for paTiEnts at Risk of COVID-19 infecTion - V (NCT04870333)]. Limited experience using monoclonal antibodies in patients with immune-mediated diseases exists, but efficacy is apparent in the case series [81].

In a single-centre study, monthly casirivimab plus imdevimab (REGEN-COV) was offered to kidney transplant recipients who did not mount an antibody response after three vaccine doses. A total of 88 of 119 patients received at least two infusions and none of these patients contracted COVID-19. Of the 31 patients without monoclonal antibody therapy, 5 were diagnosed with COVID-19 (delta variant) and 2 required intensive care unit management [82]. With the emergence of omicron, preliminary reports suggest that only sotrovimab exerts adequate potency compared with other variants [83].

Concerted efforts must be made to fully vaccinate household relations and close contacts (such as care givers) of patients with immune-mediated kidney disease. BNT162b2 and to a lesser degree ChAdOx1 nCoV-19 reduce transmission with protection waning over time [84], and booster dose administrations are necessary. Almost 2 years into the pandemic, vaccine apathy is evident. People should be encouraged to have all three vaccinations, not least because there is an increasing likelihood that return to pre-pandemic levels of social activity is imminent.

### SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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