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Review

Benefit–risk evaluation of COVID-19 vaccination in special population groups of interest

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ABSTRACT

Several population groups display an increased risk of severe disease and mortality following SARS-CoV-2 infection. These include those who are immunocompromised (IC), have a cancer diagnosis, human immunodeficiency virus (HIV) infection or chronic inflammatory disease including autoimmune disease, primary immunodeficiencies, and those with kidney or liver disease. As such, improved understanding of the course of COVID-19 disease, as well as the efficacy, safety, and benefit-risk profiles of COVID-19 vaccines in these vulnerable groups is paramount in order to inform health policy makers and identify evidence-based vaccination strategies. In this review, we seek to summarize current data, including recommendations by national health authorities, on the impact and benefit-risk profiles of COVID-19 vaccination in these populations. Moving forward, although significant efforts have been made to elucidate and characterize COVID-19 disease course and vaccine responses in these groups, further larger-scale and longer-term evaluation will be instrumental to help further guide management and vaccination strategies, particularly given concerns about waning of vaccine-induced immunity and the recent surge of transmission with SARS-CoV-2 variants of concern.

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1. Introduction

COVID-19 vaccines have proven of great value in controlling severe COVID-19 within the general population; however, vaccination is inherently complex in high-risk populations due to factors such as immune suppression or overactivation, and vaccines elicit differing responses in terms of efficacy and immunogenicity. The reasons behind this are multifactorial and include the type and severity of the disease(s), patient characteristics (e.g., age and comorbidities), and concomitant therapies. Owing to this complexity, approaches to optimise vaccination strategies in these special populations are of paramount importance. In this review, we discuss the risks associated with COVID-19 infection in these populations, including the impact of comorbidities and treatment recommendations. Populations discussed include patients who are immunocompromised (IC), have a cancer diagnosis, human immunodeficiency virus (HIV) infection or chronic inflammatory disease including autoimmune disease, primary immunodeficiencies, and those with kidney or liver disease. Discussion of the pediatric population was excluded from this review as this is a unique group requiring an in-depth discussion beyond the scope of this manuscript. Scientific and clinical evidence on COVID-19 vaccination continues to evolve in these groups and as such we provide a summary of current data to support clinical assessment for the benefit-risk evaluation of vaccination, as well as guidance and recommendations on dosing schedules to aid decision-making. We focus on four of the earliest approved vaccines that have been distributed worldwide in a large proportion of the population, namely Ad26.COV2.S (Johnson & Johnson), AZD1222 (Oxford/AstraZeneca), BNT162b2 (Pfizer/BioNTech), and mRNA-1273 (Moderna). Other more recently approved vaccines, i.e., NVX-CoV2373 (Novavax), will be discussed where data is available in these populations. References for this review were identified through searches of PubMed and pre-print servers *medRxiv* and *bioRxiv* for English language articles published from 1 December 2019 to 04 April 2022. Additional sources of information included healthcare agency websites, ClinicalTrials.gov and pharmaceutical press releases.

2. Immunocompromised patients

2.1. Immune status, mortality, morbidity and clinical presentation

IC patients include those receiving immunosuppressive therapies (e.g., anti-rejection medication for transplant recipients) and those with cancer, chronic inflammatory diseases (including rheumatoid arthritis and systemic lupus erythematosus) and certain chronic infections such as HIV.[1] Although the spectrum of clinical presentation of COVID-19 in patients who are immunosuppressed may not differ markedly to that seen in the general population,[2] the underlying immunosuppression is often associated with increased disease severity.[3] Studies have shown that some patients with cancer have a higher rate of COVID-19-related death [4–7] and a more severe disease course has been reported.[7,5,6]. Chemotherapy within the last 28 days is a risk factor for mortality [8] and metastatic disease is associated with a 2.4-fold mortality increase.[9]

COVID-19 outcomes are particularly poor in patients with haematological malignancies. Indeed, overall survival rates of around 67% were reported in recipients of stem cell transplantation in the pre-vaccine era.[10] Multiple myeloma and chronic lymphocytic leukaemia also markedly increase the risk of severe COVID-19.[5,11] Solid organ transplant (SOT) recipients require prolonged pharmacological immune suppression to prevent graft rejection and, although symptoms of disease are generally similar to those in non-transplant patients,[12,2] rates of COVID-19-related hospitalisation are higher than the general population. [7,12,1] Furthermore, an increased risk of mechanical ventilation or death due to COVID-19 has been reported compared with matched controls.[13]

Medications commonly used to treat chronic inflammatory diseases, including autoimmune diseases, typically target the inflammatory cascade and include agents such as anti-interleukin [IL]-1 or anti-IL-6, as well as glucocorticoids. Of note, dexamethasone and anti-IL-6R therapy are also used to treat severe COVID-19, [14] but do not appear to provide significant protective effect from

chronic use.[14,15,5]. Indeed, patients receiving treatment for chronic inflammatory diseases are at higher risk of infection and poor outcomes.[14,15,5]

COVID-19 incidence is higher in patients with autoimmune rheumatic disease, and this may be associated with ongoing treatment in this population as patients are primarily treated with immunosuppressive medications which can reduce the production of neutralizing antibodies, suppress T cell responses or inhibit cytokines, depending on the mode of action.[16]

Patients receiving glucocorticoids have a higher risk of infection,[17] hospitalization, emergency care, and intensive care unit admission.[18,19] Furthermore, those receiving B cell-depleting agents or certain immunosuppressants are at a markedly increased risk of mortality due to COVID-19 (odds ratio: 4.0 with rituximab and 2.2 with immunosuppressants vs methotrexate monotherapy).[20]

HIV infection is also a significant independent risk factor for both critical COVID-19 infection and in-hospital mortality and is seen even in patients living with HIV with well-controlled disease.[21] Comparable clinical evidence for other clinical conditions is currently unclear but almost all patients with IC might be considered to be at risk of more severe COVID-19 disease.[1]

Patients with inborn errors of immunity (IEI; also referred to as primary immunodeficiencies), although a heterogenous population, are a group of special interest particularly with respect to COVID-19 as they are in general known to be more susceptible to infectious diseases due to their immunocompromised status.[22] With regard to COVID-19, a multicenter, retrospective international study in 94 patients with IEI reported that while the majority have a mild course of disease, younger patients present with more severe symptoms and there are higher rates of intensive care unit admission when compared with the general population.[23] Another single-centre report found the rate of death was higher in patients with IEI vs. the general population (25% vs. 10%).[24] A small study showed that patients with IEI with severe or fatal COVID-19 failed to elicit a specific antibody response to SARS-CoV-2 but robust T cell responses were observed.[25] Some specific immunodeficiencies have been reported to be associated with a higher risk of severe COVID-19, e.g., nuclear factor kappa-B subunit 2 deficiency.[26]

2.2. Potential benefits of COVID-19 vaccination

Given the increased rates of morbidity and mortality for IC patients, there is an urgent need to understand the efficacy of vaccination in this population. This is particularly important as these groups were underrepresented in the initial vaccine trials.

Live-attenuated vaccines are contraindicated in patients with immunodeficiency due to the risk of vaccine-viral replication. However, the currently approved COVID-19 vaccines discussed in this manuscript are not live-attenuated and as such all are appropriate for usage in patients with IC.[27] The immunogenicity of COVID-19 vaccines in patients with IC is a topic of intense investigation. Vaccines appear to induce robust immune responses in patients with solid tumour cancers,[6] but responses in blood cancer are more variable and depend on the nature of the underlying malignancy and intercurrent treatment. Vaccines appear well tolerated in SOT recipients, but more research is required on determinants of vaccine response.[28] Vaccination is recommended for patients living with HIV and immune responses appear comparable to healthy controls for those receiving antiviral therapy who have undetectable viral load and CD4 counts > 200 cell/mm^3.[29–31] For patients who require treatment for COVID-19, evaluation should be given to ensure that there are no potential drug-drug interactions.[32] Importantly, however, although COVID-19 vaccines are somewhat less immunogenic in this population, and might provide a lower level of clinical protection compared with the general population, they still appear likely to offer a considerable degree of protection against severe disease or death.[3334]

2.3. Treatment and immune concerns

The mainstay of treatments used for severe SARS-CoV-2 infection are immunomodulatory or immunosuppressive (e.g., dexamethasone, tocilizumab),[35] and as such this offers an additional clinical challenge in those who are already immunocompromised. Importantly, monoclonal SARS-CoV-2 spike-specific antibody infusions can reduce the mortality rate in patients who are seronegative and require hospitalisation for COVID-19,[36] and IC patients who do not elicit a robust SARS-CoV-2 immune response may shed the virus over an extended period and thus be a source of transmission and driver of new variants.[37]

Novel oral antiviral drugs to treat COVID-19 offer a promising alternative, particularly for vulnerable IC patients where other treatments may exacerbate the disease or where vaccination provides lower efficacy than the general population. Molnupiravir, an orally active RdRp inhibitor, has shown promising results in Phase II [38] and III [39] trials, reducing the risk of hospitalization and death in unvaccinated individuals,[3839]. In a Phase II to III clinical trial, another oral antiviral drug, Nirmatrelvir, reduced the risk of COVID-19 disease progression by 89% vs. placebo in patients with at high risk of severe disease, including those with immunosuppressive disease. Both Molnupiravir and Nirmatrelvir have been approved for emergency use by both the EMA [40] and FDA. [41,42]A recent observational study identified multiple factors which increase the likelihood of vaccine failure in IC patients, such as treatment with anti-metabolites, radiation therapy and lung transplantation, and showed that humoral immune responses are dependent on the type of immunosuppressive condition.[43] As an example, the probability of a vaccine response was reduced in those who had lung transplants within a year of vaccination, potentially due to the high level of immunosuppression. [43]

2.4. Vaccination guidelines and considerations

Clinical trials examining COVID-19 vaccine safety and efficacy largely excluded IC populations and broadly comprised healthy participants or those with stable pre-existing medical conditions, although some chronic inflammatory diseases were included.[44–46] Owing to the lack of evidence in these populations, COVID-19 vaccine labels define risks and warnings for use (including patients with solid organ or blood/marrow transplant, people living with HIV who are not well controlled on therapy, and patients taking immunosuppressive medications), and state that IC patients may have a diminished vaccination response.[47–50] Multiple global organizations have released guidance on vaccination of IC patients, suggesting prioritization of this group. Due to the inadequate immune responses following two vaccine doses in some IC patients, three doses are now considered the primary regimen for mRNA vaccines in this population and additional (fourth) doses are now recommended by major global agencies and authorities in IC patients to boost immunity.[51] Table 1 summarizes key guidance from national public health agencies and associations regarding vaccination and additional dosing.

2.5. Clinical data: immunogenicity, reactogenicity and safety

A US study comparing fully vaccinated (98% with BNT162b2 or mRNA-1273) healthy healthcare workers (n = 107) and IC patients (n = 489) found seropositivity was reduced in IC patients, particularly those with SOT (37%) and haematological malignancies (55%),

Table 1
Summary of recommendations from national guidelines/public health bodies*.

Population	General COVID-19 vaccination guidance/considerations	COVID-19 additional dose/booster guidance/considerations	Regulatory approvals
Immunocompromised	• CDC and WHO state individuals may choose to be vaccinated if they are part of a group that is recommended for vaccination [1,130] *Active cancer and those on treatment* NCCN guidance recommends that patients should be prioritized for vaccination, but vaccination should be delayed by ≥ 3 months following HSCT or engineered cellular therapy (e.g., CART) to maximize therapy [131] NIH states that COVID-19 vaccination of patients receiving aggressive CT may need to be delayed until neutrophil cell counts recover [132] *Patients undergoing transplant surgery* NIH states vaccination should be completed ≥ 2 weeks prior to SOT or started 1 month after a SOT [132] *Patients with autoimmune and inflammatory rheumatic diseases* ACR states the benefits of COVID-19 vaccination outweigh the risks of new-onset autoimmunity, flares or disease worsening. Patients should receive both vaccine doses of multidose vaccines, even if there are non-serious adverse events associated with the first dose.[126] EULAR guidance states that vaccinations should preferably be given when the disease is in a quiet phase; it is also preferable to vaccinate before planned immunosuppression if feasible. A decrease in medication is not advised [127]	• CDC recommends patients who are moderately to severely immunocompromised (cancer, stem cell or organ transplant, rheumatology on immunosuppressive or immunomodulators, advanced or untreated HIV, moderate or severe primary immunodeficiency) should receive an additional dose at ≥ 28 days after the second dose [122] UK JCVI recommends a third booster dose in severely immunocompromised patients with leukaemia, advanced HIV and recent organ transplants [133]	• EMA has approved a third primary dose of BNT162b2 or mRNA-1273 for severely IC patients ≥ 12 years of age (administered ≥ 28 days after the second dose) [39,37] FDA has approved a third primary dose of BNT162b2 or mRNA-1273 for individuals ≥ 12 years of age who have undergone SOT, or are diagnosed with conditions that are considered to have an equivalent level of immunocompromise (administered ≥ 28 days after the second dose)[127,128]
Kidney disease	• ERA–EDTA states that the benefits of COVID-19 vaccines outweigh any theoretical risk in patients with kidney disease and recommended immediate prioritisation of COVID-19 vaccine distribution for patients undergoing dialysis [135] CDC states that vaccination at the dialysis clinic is recommended, owing to risks associated with seeking out separate venues [136] UK joint renal societies state that patients with stage 5 CKD not receiving replacement therapy, and patients with kidney disease receiving immunosuppressive treatment, are considered clinically extremely vulnerable and are therefore a priority for COVID-19 vaccination [137]	• See above for recommendations regarding IC patients.	
Liver disease	• EASL guidelines on COVID-19 vaccination in patients with liver disease note that although vaccines may be less effective in individuals with decompensated cirrhosis, there is no evidence that the vaccines are harmful in these patients; thus, they should be prioritised for vaccination [138] The American Association for the Study of Liver Diseases recommends prioritising patients with cirrhosis, liver cancer, patients receiving immunosuppression such as liver transplant recipients and living liver donors for COVID-19 vaccination [139]	• See above for recommendations regarding IC patients.	

*Guidance, recommendations, and regulatory approvals are updated regularly. Please refer to the relevant sources for the most up-to-date information.

compared to healthy controls (98%). Seropositivity among patients with solid neoplasms and autoimmune disease was also lower (82% and 84% respectively) although patients with well-controlled HIV had good responses (95%).[43] Data from a cohort study in 604,035 individuals showed that patients with IC have a higher rate of COVID-19 breakthrough infection following a two-dose vaccine regimen when compared to immunocompetent individuals, although this was still substantially less when compared with those who were unvaccinated. [52] The same trend was also observed in a study conducted specifically in patients with cancer. [53] As such, vaccine response rates in patients with IC are variable and more studies are required to clearly determine the degree to which immunity is diminished (refer to Galmiche et al. 2021 for a recent systematic review).[54] Immune responses to COVID-19 vaccines differ between individuals depending on underlying IC conditions and the degree of immune impairment. The following sections describe studies examining these specific populations and include safety data where available.

2.5.1. Patients with cancer

Vaccine-induced immune responses are reduced in patients with solid tumours who are undergoing current chemotherapy but appear well maintained during disease remission. In 102 patients undergoing systemic treatment for cancer who received BNT162b2 vaccination, 90% were seropositive for anti-SARS-CoV-2 spike protein antibodies ≥ 12 days following the second dose compared with 100% of healthy control subjects (n = 78). Chemotherapy combined with immunotherapy was the only factor associated with low IgG titres.[55] In certain circumstances, vaccination may be recommended to be delayed for patients undergoing intercurrent therapy with immunosuppressive drugs such as cytotoxic chemotherapy (e.g., those receiving cytotoxic CT).[56]

A prospective, longitudinal observational study (SOAP-02, n = 151) of patients with cancer showed that after the second dose of BNT162b2, vaccine-elicited antibodies were present in 18/19 (95%) of patients with solid cancers.[57] Patients with haematological cancers had a lower antibody response (8/44 [18%] patients

after a single dose and 3/5 [60%] of patient after a second dose) but larger studies are required to elucidate immunogenicity in this group further.[57,54] The OCTAVE (Observational Cohort Trial-T-cells Antibodies and Vaccine Efficacy in SARS-CoV-2) trial is one of the largest trials to date to investigate vaccination in immune vulnerable patients and reported that all patients with cancer (breast and lung, n = 139) had anti-spike seroconversion following the second vaccine dose.[58] A major unanswered question for patients with cancer is whether the use of specific drugs impacts vaccine immunogenicity. Findings from the VOICE trial, a prospective, multicentre, non-inferiority trial carried out in three centres (n = 791) enrolling participants without cancer and those with cancer receiving different treatments, showed that the majority of patients with cancer develop an adequate antibody response. However, 9/131 (7%) of the patients treated with immunotherapy, 37/229 (16%) of the patients treated with chemotherapy, and 16/143 (11%) of the patients treated with chemoimmunotherapy had suboptimal response or did not respond compared with 1/240 (<1%) participants without cancer, which gives a justification for a third vaccine dose in this group.[59] In the CAPTURE study, after the first vaccine dose only 39% of patients developed SARS-CoV-2 neutralising antibodies and 44% had detectable specific T cells, while after full vaccination 83% of patients with cancer developed neutralising antibodies and 79 % T-cell responses. Importantly, only 53% of patients developed specific neutralising antibodies against the delta variant, suggesting a lower efficacy towards this variant of concern.[60] Patients with a hematological malignancy are at particular risk of a suboptimal vaccine response. This is particularly true for patients with B cell chronic lymphoid leukemia, where 33% fail to sero-covert after dual vaccination. [61] Another study showed that 46% of haematological cancer patients failed to produce antibodies following two doses of a COVID-19 mRNA vaccine.[62] Immune responses are also poor in patients with acute leukaemia whilst in contrast, conditions such as chronic myeloid leukaemia do not appear to impair vaccine responses.[63] Vaccines are recommended as early as 3 months after stem cell transplantation in these groups, but response rates remain poor.[64]

Omicron (B.1.1.529), which has a higher transmissibility than the wild-type and other variants,[65] currently accounts for the majority of COVID-19 cases worldwide.[66] Vaccination with the primary (two dose) course is known to be less robust against Omicron (B.1.1.529) than for the wild-type in the general/immunocompetent population,[67] and additional (booster) doses are required to improve immunity. Data characterizing immune responses following vaccination in immunocompromised and other special populations is lacking, but some data is emerging to further support a third dose in these populations. One study examined the impact of booster vaccination on immune responses in patients with cancer with different types of solid tumours (n = 50) and reported that those who received a booster mRNA dose had a significantly greater neutralizing capacity against the Omicron (B.1.1.529) variant in comparison to those who received two doses where neutralizing antibody titres were reduced by 21.3-fold ($p < 0.01$).[68] A study in patients with monoclonal gammopathies at different stages of disease, including multiple myeloma (n = 40), showed that neutralizing antibody responses against Omicron (B.1.1.529) were reduced compared to the wild-type strain following the primary vaccine regimen, but were improved following a booster dose. [69]

2.5.2. Solid organ transplant recipients

Studies over several years have shown that immune responses are impaired in SOT recipients [70] and, as such, it is not unexpected that poor antibody responses to COVID-19 mRNA vaccination have been observed among SOT recipients. In the COVID-19 Antibody Testing of Recipients of Solid Organ Transplants study (N = 436), only 17% of participants developed a measurable anti-spike protein antibody response to a single dose of COVID-19 mRNA vaccine; younger participants, those not receiving anti-metabolite maintenance immunosuppression, and those who received mRNA-1273, were more likely to mount an antibody response.[71] Studies conducted in specific SOT populations including liver [72,73], kidney, [74–76], heart [77], and lung [78] transplant recipients have shown impaired vaccine responses. A study conducted in Israel in patients undergoing liver transplantation (n = 80) showed dampened vaccine responses; only 48% developed neutralizing antibodies post-vaccination, with immunogenicity negatively impacted by older age, poorer renal function, and mycophenolate mofetil/high-dose steroid treatment.[72] In heart and lung transplant recipients (n = 34), both anti-spike antibody and T cell responses were significantly blunted following the first and second doses of mRNA vaccination (at 21 and 28 days, respectively) and after a longer time period of observation (120 days).[79]

A major risk factor for poor antibody responses in kidney transplant patients is the number and type of immunosuppressive therapies.[74] As such, vaccination prior to transplantation may result in a more sustained humoral vaccination response.[80] Consistent with findings in liver and kidney transplant recipients, patients receiving a lung transplant also had a substantially diminished humoral response following two doses of BNT162b2, with age and concomitant therapies (such as antimetabolites) being associated with poorer responses.[78] Improved immunogenicity has been shown in SOT patients in response to incremental vaccine delivery. Kamar et al. reported that seroprevalence increased from 0%, 4%, and 40% before the first, second, and third doses, respectively, and reached 68% 4 weeks after the third dose.[81] Antibody titres were significantly higher after the third dose, increasing from 36 to 2,676 [$P < 0.001$]), and there were no reports of SARS-CoV-2 infection or acute rejection episodes following receipt of three doses.[81,82] Similarly, a randomized control trial with mRNA-1273 in SOT patients demonstrated high immunogenicity (median viral neutralisation: 71% vs. 13%; mRNA-1273 vs placebo, respectively). Local and systemic events were more frequent in those receiving mRNA-1273, but these were mild-to-moderate, and acute transplant rejection was not reported.[83] Similar findings have been shown in patients who have undergone kidney transplantation and there is hope that this approach may go some way to negate the impact of antimetabolite and steroid treatment on immunogenicity.[84,85] A third vaccine dose in liver transplant recipients was able to increase immune responses by 44%, although mycophenolate mofetil treatment still predisposes patients to poorer responses.[86] The tolerability of repeated vaccine dosage is also an important consideration. A prospective study in SOT patients (n = 741) reported that reactogenicity of mRNA vaccines in this population was similar to that in the initial clinical trials, with injection site pain, fatigue, and headaches being the most commonly described symptoms.[87]

As mentioned previously, variants of concern have become a topic of significant importance, particularly with the emergence of Omicron (B.1.1.529), and the efficacy afforded by the vaccines against such variants currently remains unclear. One study in kidney transplant recipients has shown that none of the patients included had neutralizing antibodies against Omicron (B.1.1.529) after the second vaccine dose, and this increased to only 12% of patients after the third dose.[87]

2.5.3. Patients living with HIV

Immune response to vaccines in persons living with HIV have been shown to be dependent on the level of CD4 + T cells. With advances in anti-retroviral therapy, the majority of persons living

with HIV achieve normalization of CD4 counts; however, even in these patients, subtle defects in immune function may persist and impair vaccine response. In a study examining HIV + individuals (n = 121) who had received the first dose of an mRNA vaccine (mRNA-1273 in the HIV + subgroups, BNT162b2 in the HIV- control group), those with CD4 counts > 250 cells/mm^3 had an anti-receptor binding domain IgG response similar to the general population, although HIV + individuals with the lowest CD4 + counts (<250 cells/mm^3) had a significantly blunted response.[88] In a prospective cohort study which enrolled patients living with HIV (with or without anti-retroviral therapy) with stable viral suppression and robust CD4 + T cell counts, two doses of mRNA-1273 (4 weeks apart) gave rise to humoral immune response at the same level as those without HIV infection.[89] HIV + individuals with CD4 counts > 350 cells/mm^3 also demonstrate humoral and cellular responses similar to control groups after ChAdOx1 nCoV-19 vaccination, with no increase in adverse events frequency.[31] The NVX-CoV2373 COVID-19 vaccine, which in late 2021 and early 2022 was granted emergency use authorization for use in the general population by multiple regulatory authorities including the EMA,[90] is a protein subunit vaccine which could offer an alternative in certain populations. Data is still limited in special populations, but the pivotal Phase 2a/b randomized control trial of NVX-CoV2373 (n = 2,684) included both individuals who were HIV-negative (94%) and a small number of individuals living with medically stable HIV (6%).[91] The trial was not powered to assess efficacy in the HIV population; however, vaccine efficacy estimates (against confirmed symptomatic mild, moderate, or severe COVID-19) was lower when the analysis was conducted on HIV-negative and HIV-positive individuals (49.4%, 95% CI 6.1–72.8) when compared to HIV-negative individuals only (60.1%, 95% CI 19.9–80.1).[91]

2.5.4. Patients with chronic inflammatory diseases (including autoimmune diseases)

Concerns associated with vaccination in chronic inflammatory diseases (including autoimmune diseases) include reduced vaccine efficacy and exacerbation/flare of disease. Current data suggests that patients with inflammatory disorders typically do elicit humoral immune responses but these are often reduced in those undergoing B-cell depletion therapy.[92–96] A prospective study in adults with chronic inflammatory diseases (COVaRiPAD) showed that glucocorticoids and B-cell-depleting therapies impaired COVID-19 mRNA vaccine immunogenicity, with 10-fold and 36-fold reductions in humoral response versus controls, respectively.[92] Similarly, the RituxiVac open-label trial, which examined mRNA COVID-19 vaccination in IC patients (including those with vasculitis, B-cell lymphoma and rheumatoid arthritis), mirrored these results and recommended that a personalized approach to vaccination, e.g., based on peripheral B-cell count, may be appropriate especially those who are undergoing intensive treatment.[95] In two cohorts of patients with chronic inflammatory disease, treatment with B-cell depleting agents or non-biological agents (particularly methotrexate) were associated with lower immune responses to BNT162b2.[93] Evidence from a small study (n = 13) showed that, although humoral antibody responses may be blunted, T cell-mediated immune responses are mounted in rituximab-treated inflammatory rheumatic diseases who have B cell depletion and further illustrates the importance of vaccination in this group, even when humoral responses are impaired.[96] Similarly, abatacept moderately impairs vaccine immunogenicity and thus timing of treatment, particularly if combined with methotrexate, so should be considered on a case-by-case basis to improve vaccine responses.[97] Inflammatory bowel disease (IBD), which usually requires immunosuppression with immunomodulators (e.g., azathioprine) or anti-tumour necrosis factor drugs (e.g., infliximab), is associated with attenuated antibody responses following vaccination with a single dose of either BNT162b2 or AZD1222 vaccines; however, a second dose may lead to higher humoral immune responses.[94] Results from the OCTAVE trial showed that only 8/29 (27.6%) of ANCA-associated vasculitis patients seroconverted following a second vaccine dose, below that of healthy controls (100%).[58] A nationwide study (MAJIK-SFR Registry) assessed the impact of targeted disease modifying anti-rheumatic drugs (DMARDs) on immune response to vaccination in 113 patients with rheumatoid arthritis (87%) or psoriatic arthritis (27%). The proportion of patients with detectable anti-spike antibodies following vaccination remained high (88%). Lack of response was associated with older age, suggesting that these patients should undergo serological assessments to ascertain if a third dose is required.[98] Data on safety of COVID-19 vaccines in the autoimmune setting are limited; however, a questionnaire assessing adverse events in autoimmune vs control patients (n = 2,440) reported that these were comparable to controls after the first vaccination, which was independent of the type of vaccine, and that COVID-19 vaccination does not trigger disease flares in this group.[99]

2.5.5. Patients with inborn errors of immunity

Given the heterogeneity of patients with IEIs, vaccine responses against infectious diseases in general are known to differ but, whilst caution should be given for live-attenuated vaccines, vaccination in this group is often recommended other than in cases where they are unlikely to have benefit such as in patients with severe antibody deficiency.[100] With respect to COVID-19, patients with IEI represent an important group of interest due to the possible increased risk of severe disease [23] and, although it is not possible to provide general recommendations due to the heterogeneity of this group, understanding the benefit-risk profile of COVID-19 vaccination is needed to formulate the most appropriate treatment and vaccine strategies. A small study investigating the cellular and humoral responses following two mRNA vaccine doses showed that the majority of patients (18/22; 82%) were positive for neutralizing anti-spike antibodies and a tolerable safety profile was observed.[101] The same study also reported that older patients with common variable immunodeficiency mounted lower antibody responses, suggesting additional booster doses may be relevant for this population.[101] Another study in patients with IEIs with functional B-cell defects showed stimulation of receptor binding domain-specific IgG responses following mRNA vaccination (16/33; 48%), but only 2 of these patients had neutralizing antibodies. However, the majority of patients elicited vaccine-induced T cell responses (24/31; 77%), which may lead to reduced COVID-19 severity in this group, and the vaccines had a tolerable safety profile.[102] Additional studies are required to further define the recommendations of COVID-19 therapies and vaccination in this group.

3. Patients with kidney disease

3.1. Mortality, morbidity and clinical presentation

SARS-CoV-2 infection is primarily known to cause respiratory complications, but other organs, including the kidney, are also known to be severely impacted. Correspondingly, patients with kidney disease and those requiring dialysis are an extremely vulnerable group with additional clinical challenges.[103] As shown by several large meta-analyses, the clinical evolution of COVID-19 in patients with kidney impairment is more severe than compared to the general population and has higher mortality rates.[104,105] In patients on haemodialysis and kidney transplant

recipients, the case-fatality/mortality rates are around 15% and 19 to 23%, respectively.[106,107]. When compared to patients without chronic kidney disease (CKD), patients with pre-existing CKD have an increased risk of severe COVID-19 disease and death [108,109], and mortality rates correlate with worsening renal injury.[110]

3.2. Impact of comorbidities and high-risk groups

The majority of end-stage renal disease (ESRD) patients, who are on chronic dialysis treatments, have comorbid conditions associated with a higher risk of COVID-19 risk (e.g., obesity, diabetes and cardiac disease [111]); however, kidney disease is also classed as an independent risk factor for severe outcomes of COVID-19 when data is adjusted for comorbid conditions.[111] Dialysis treatment necessitates frequent hospital and health centre visits thus patients undergoing this treatment have limited ability to self-isolate and are at particularly high risk of SARS-CoV-2 infection (5 to 20-fold vs. the general population).[112] Furthermore, patients undergoing dialysis have an increased risk of death (30–130% more likely vs. hospitalised patients without CKD) [112] and longer hospital stays.[113,112] Diabetic nephropathy also puts patients in the higher risk category, having a higher probability of hospitalization and death vs patients with CKD alone.[114] Immunosuppressive therapies make recipients of kidney transplants more vulnerable to a severe course of disease *[see section on IC]*.[115]

3.3. Potential benefits of vaccination

Although immune dysregulation in patients with kidney disease may lead to reduced protection from COVID-19 vaccination compared with the general population, it is likely that vaccination will provide some level of protection, with potential to reduce mortality, disease severity and risk of infection.

3.4. Treatment and immune concerns

CKD patients commonly have an increased risk of infectious complications as they are routinely managed with immunosuppressive therapies.[116] In CKD patients who are hospitalized with severe COVID-19, reports have shown that they have disruptions in cellular immunity such as an elevated monocyte-to-lymphocyte ratio.[117] Key considerations for treating patients with kidney disease who have COVID-19 include drug–drug interactions and nephrotoxicity of drug combinations, as well as dialytic clearance in those undergoing dialysis which will lead to excessive clearance of drugs and possibly dampened efficacy.[116,118] A potential underlying cause of the susceptibility of ESRD patients to SARS-CoV-2 infection is an impaired adaptive and innate immune system; it has been reported that the function of immune cells, such as T lymphocytes and natural killer cells, is altered in ESRD patients leading to dysregulated immunity.[111]

3.5. Vaccination guidelines and considerations

Vaccination, including a third booster does, is recommended to be prioritized in patients with kidney disease. Refer to Table 1 for a summary of current recommendations.

3.6. Clinical data: immunogenicity, reactogenicity and safety

In a prospective study (n = 154), humoral immune responses at 4 weeks after a single dose of BNT162b2 were induced in only 43% of COVID-19-naïve patients receiving haemodialysis. The patients who did not respond initially continued without a response at 8 weeks. A delayed immune response was seen in those with previous COVID-19 infection.[119] However, in an observational study in SARS-CoV-2-seronegative haemodialysis patients who received both doses of BNT162b2, the proportion of seropositive patients increased after the second dose to 97.9% compared to 42.0% after the first dose.[120] Consistent with trials in the general population, adverse events were mild-to-moderate, with injection site pain being the most frequent local reaction.[120] In line with this, interim results from the OCTAVE trial showed that immunogenicity following a second dose was comparable to heathy controls; 94.6% and 83.3% of patients with ESRD requiring haemodialysis without or with immunosuppression, respectively, mounted an antibody response.[58] In a study which included a large population of patients receiving dialysis (n = 2,099), a third of patients receiving dialysis and fully vaccinated with Ad26.COV2.S demonstrated lower immune responses.[121] With regard to vaccine effectiveness against variants of concern, namely Omicron, data is scarce in this population. One recent study showed that three doses is necessary to provide protection against infection; vaccine effectiveness against Omicron infection in patients who had received a booster vaccine was 47% with AZD1222 and 66% with BNT162b2. No protection against infection was observed in those individuals who had received the two dose regimen.[122] Safety data remains limited in patients with kidney disease and inclusion of patients in COVID-19 clinical trials was low, and many excluded patients with CKD.[123] The COViNEPH project, a prospective cohort study, examined 190 dialysis patients in comparison to matched controls and reported that reactogenicity and safety following vaccination with BNT162b2 was similar.[124] The REnal Patients COVID-19 VACcination Immune Response (RECOVAC IR) study is a prospective, controlled, multicenter study which is ongoing and will assess safety of mRNA-1273 in CKD patients.[125]

4. Patients with liver disease

4.1. Mortality, morbidity and clinical presentation

A meta-analysis showed that acute liver injury is common in COVID-19 and associated with poor outcomes. Elevated alanine aminotransferase and aspartate aminotransferase, which is a characteristic of hepatocyte damage, is also associated with extended hospitalization and may be predictors of poor outcomes in this population.[126] Pre-existing chronic liver disease (CLD) in patients who have SARS-CoV-2 infection relates to higher incidence of liver injury, hospitalisation and mortality rates than the general population.[127–130] In patients hospitalized for COVID-19, a notable 20% have CLD and their mortality risk is markedly increased (approximately 3-fold) compared to patients without CLD.[129] An international registry study (n = 745) comparing CLD patients with non-CLD patients reported that SARS-CoV-2 infection can cause complications of liver disease; patients with cirrhosis may have a substantial reduction of liver function and elevated rates of acute hepatic decompensation (46%).[131] Of note, patients presenting with acute hepatic decompensation did not always have respiratory symptoms at COVID-19 diagnosis which underlines that high rates of SARS-CoV-2 testing should be carried out in this setting.[131]

4.2. Impact of comorbidities

The clinical consequences and pathogenesis of COVID-19 disease in patients with acute liver injury and liver function has been an important concern particularly due to the risk factors associated with these conditions such as obesity, diabetes, malnutrition, and older age. In a multicentre study comparing cirrhosis patients with

matched controls, the Charlson Comorbidity Index was the only reported independent mortality predictor, which points to a central role of multiple comorbidities in determining COVID-19 severity in patients with liver disease.[132] However, CLD and non-alcoholic fatty liver disease appeared to be independent risk factors for intensive care unit admission and mechanical ventilation in a study which controlled for comorbidities.[128]

4.3. High-risk groups

Pre-existing cirrhosis corresponds to more pronounced rates of severe disease and mortality when compared to patients without cirrhosis.[131,132] Additionally, clinical complications and disease deterioration are more common in patients with cirrhosis as compared to those with CLD without cirrhosis.[127] There have been studies showing that non-alcoholic fatty liver disease is linked to progressive COVID-19 disease, increased risk of hospitalisation and prolonged SARS-CoV-2 shedding.[133,134] Further, immunosuppressive medications in liver transplant recipients may cause an increased risk of SARS-CoV-2 infection and COVID-19 severity *[see section on IC patients].*[135] Other possible risk groups include patients with chronic hepatitis B or C disease (adjusted odds ratios for COVID-19 infection vs patients without CLD of 4.37 and 8.93, respectively [both $P < 0.001$]).[130] Some reports have shown that patients with well-controlled chronic viral hepatitis or autoimmune liver disease do not have an increased risk of poorer COVID-19 outcomes.

4.4. Potential benefits of COVID-19 vaccination

Immune impairment in cirrhosis patients is known to cause hyporesponsiveness to other types of vaccines (e.g., hepatitis B vaccine [136]). Despite this, the potential benefits of COVID-19 vaccination likely outweigh the risks given the serious health sequalae from COVID-19 in this setting.[137,138] Evidence to date does not suggest that COVID-19 vaccines will be have detrimental impacts on patients with CLD with decompensated cirrhosis and those on immunosuppressive medications.[139]

4.5. Treatment and immune concerns

Drug-related multiorgan damage, including liver damage, is a concern in all patients with COVID-19 [135] and surveillance of drug-induced liver injury is paramount in those with existing liver damage. CLD, especially if associated with cirrhosis, results in diminished innate and humoral immunity which may result in higher vulnerability to SARS-CoV-2 infection. [135,131] The SARS-CoV-2-induced inflammatory storm may be heightened in patients with non-alcoholic fatty liver disease who are known to have perturbed immune systems, such as high neutrophil-to-lymphocyte ratios.[140]

4.6. Vaccination guidelines

Refer to Table 1 for a summary of current recommendations.

4.7. Clinical data: immunogenicity, reactogenicity and safety

Preliminary data from OCTAVE has shown that 51% of patients with liver disease (including patients with liver cirrhosis, undergoing liver transplant and those with autoimmune liver disease on immune suppressive therapy) have lower levels of antibody reactivity compared to healthy controls.[58] However, despite this reduced antibody response, reports have shown that patients with liver cirrhosis who are fully vaccinated with mRNA or adenoviral vaccines have reduced rates of COVID-19 infection, hospitalization, or death.[141,142] Although these rates may be lower than reported in trials in the general population, these preliminary data warrant vaccination in this population. In a study in Israel among healthcare professionals (n = 719), BNT162b2 was shown to be effective in patients with non-alcoholic fatty liver disease, with antibody responses in 98.5% of participants; however, overall effectiveness reduced with older age. This may warrant a third dose of BNT162b2 in this population.[143] Long-term safety data is not yet available for COVID-19 vaccination in liver disease patients but emerging reports demonstrate that vaccines may be both effective and tolerable.[138] The known benefits of robust immunogenicity mounted by vaccination, the safety data available from the randomized control trials and real-world evidence, and to protect against COVID-19 infection should be weighed against the risks and patients should be assessed for suitability on an individual basis.[138] Prospective registries should be utilized in future to further understand the safety profiles of currently available vaccines in this population.[138]

5. Conclusions

The special populations described in this review are at high risk of SARS-CoV-2 infection, and initial data from immunogenicity and safety studies support the use of COVID-19 vaccines in virtually all groups, with the benefits generally outweighing the risks. Emerging ongoing clinical trial data will provide further information on the immune response to vaccination and safety data in these special populations and inform on the most optimal vaccine strategies. Real-world evidence studies carried out in countries where vaccines are widely available will further help with understanding vaccination in these groups. Additionally, a deeper understanding of the immunological responses is needed; some studies to date report only on seropositivity or negativity as opposed to neutralizing anti-spike IgG antibodies levels post-vaccination, and the latter may provide a more accurate reflection of duration of protective immune response.

5.1. Vaccine suitability/eligibility

Healthcare professionals should carefully assess the benefits and risks of COVID-19 vaccination on a case-by-case basis and prioritize suitable patients without contraindications. Consideration should also be given in terms of the incidence of infection in the community at the time of vaccination, and persons (e.g., health workers and relatives) who have frequent contact with vulnerable patients should be vaccinated where possible.[144] In those who are vaccinated, adjustment of current medications in terms of dose and timing with vaccination may be appropriate for some patients and should be considered alongside relevant guidance (see previous sections). Disease control following vaccination should be closely observed and delay in vaccination due to current immunosuppressive treatments to avoid an attenuated response should be carefully assessed; if incidence in the population is high, protection with vaccination earlier could still be more beneficial than a delay to allow a more robust immune response.[144]

5.2. Choice of vaccine platform and additional dosing

The mRNA and replication-deficient adenoviral platforms, as well as the protein-based NVX-CoV2373 vaccine (although data is more limited), are all known to have a tolerable safety profile and give rise to potent immune responses among the general population.[44–46,145,91] They have differing mode-of-actions and immunological properties, but all give rise to balanced humoral and cellular immunity.[44–46,145,91]

Due to the blunted immune responses to vaccines in some special populations, such as kidney disease, and the emergence of highly transmissible SARS-CoV-2 variants, vaccines with a higher potency may be preferable. The ability of each vaccine to protect against infection is likely influenced by multiple factors including age, disease type and stage, performance status, and current therapies. In patients where a robust immune response fails to be mounted, strategies include homogenous (same vaccine) or may include heterogeneous (different platform) boosting.[146] Additional doses of mRNA vaccines as part of the primary series are recommended in moderate-to-severely immunocompromised patients by the CDC (which recommends four doses)[27]. The EMA has approved a third primary dose of BNT162b2 or mRNA-1273 for severely immunocompromised patients $\geq$ 12 years of age,[49,47] and, similarly, the FDA's approval states that those eligible for a third primary dose of BNT162b2 or mRNA-1273 are individuals $\geq$ 12 years of age who have undergone SOT, or are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.[147,148] Heterologous boosting could result in longer-lasting stimulation of cellular responses by stimulating different immune pathways in the general population and such a strategy has been shown to be tolerable and immunogenic in randomized trials conducted in the general population [149] and regulatory bodies and public health bodies, including the CDC, recommend heterologous booster dosing in IC individuals.[27]

5.3. Timing of vaccination

Most vaccination plans for patients in the special populations discussed here will require a personalized approach, and the optimal time window may heavily depend on concomitant therapies. As described above, immunosuppressive therapies, such as rituximab, have been shown to dampen vaccine effectiveness. Temporary cessation of such therapies or use of other therapies could be considered, with the possibility to return to the standard therapy following vaccination. Alternatively, COVID-19 vaccination could occur prior to or at the end of a rituximab treatment cycle. In SOT patients, completion of vaccination prior to transplantation may avoid the decrease in vaccine immune response caused by immunosuppressive therapies.[150] Temporary reduction or cessation of mycophenolate mofetil could be considered on a case-by-case basis and with evaluation of risk of graft rejection.

5.4. Other topics/considerations

The possibility of simultaneous infection with influenza and SARS-CoV-2, which can exacerbate disease complications, particularly in high-risk groups, could be avoided by administering the influenza vaccine to IC patients.[151] There is currently limited data available for paediatric patients within these special populations, who may also be more prone to more severe COVID-19 disease vs. the general paediatric population.[152] The data is continually evolving on vaccination strategies in special populations, and there are still currently inconsistencies and lack of consensus among health organizations with regard best management practices. For example, in the US, methotrexate is not administered one week following vaccination [153] whereas in Europe, EULAR do not recommend withholding vaccination at this time.[154] In patients with haematological diseases, there is a paucity of data on humoral immune responses, particularly those who are receiving rituximab where antibody responses are drastically diminished 6 months following vaccination.

5.5. Future outlook

Although multiple studies have begun to elucidate the efficacy and safety of COVID-19 vaccines among the special populations described in this manuscript, there are persistent gaps in our understanding of vaccination in these groups. More detailed characterization of both cellular and humoral immunity, particularly in those populations where immunogenicity is particularly low and/or where concomitant therapy impacts responses, such as SOT recipients, will help further inform on the most optimal vaccine strategies for these patients. Indeed, in some patient groups, such as those with IEIs, whilst lower vaccine-induced neutralizing antibody responses are observed when compared with healthy controls, robust antigen-specific T cell response are mounted.[155] Memory T and B cells have recently been shown to contribute to the neutralizing breadth of antibodies against the Omicron (B.1.1.529) variant,[156] and antigen-specific T cells are known to be a correlate of mRNA-based vaccine efficacy, particularly against severe disease,[157] highlighting that data on the immune dynamics and mechanisms of protection following vaccination is important to enable further development of vaccines and to guide their use. With waning immunity among the general population following vaccination and the emergence of SARS-CoV-2 variants, additional dosing has become paramount in both the general population and particularly these special populations. Additional dosing or an extended primary series is particularly pertinent in IC patients, where viral loads can remain high over a longer time period, prolonging the window of opportunity for the emergence of SARS-CoV-2 variants.[158] Protection against some variants, such as Omicron (B.1.1.529), may wane faster [159], and additional booster doses beyond the primary regimen have become a key vaccination strategy with the emergence of this partial immune escape variant to improve immune protection given by the primary regimens which is insufficient against Omicron. [160,161] Variant-adapted vaccines to target virus evolution, including Omicron-specific vaccines, are being investigated in clinical trials. [162,163] Furthermore, additional data investigating adenoviral vector vaccines, which is currently lacking, will help to further characterize the efficacy and safety vaccines in vulnerable groups.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: TB has received honoraria from Abbvie, Gilead, GSK, Janssen, MSD/Merck, Novartis, and Roche. GC has received honoraria from BMS, Pfizer, Novartis, Lilly, Roche, Astra Zeneca, Daichii Sankyo, Exact Sciences, Seagen, Gilead, Celcuity for taking part in advisory boards. FB reports fees from AstraZeneca, Boehringer, Bone Therapeutics, CellProthera, Expanscience, Galapagos, Gilead, Grunenthal, GSK, Eli Lilly, Merck Sereno, MSD, Nordic, Nordic Bioscience, Novartis, Pfizer, Roche, Sandoz, Sanofi, Servier, UCB, Peptinov, 4P Pharma, 4Moving Biotech, grants from TRB Chemedica, outside the submitted work. SP receives a salary from BioNTech SE. PM and AG have nothing to disclose.

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