



## REVIEW ARTICLE

# SARS-CoV-2 vaccination in solid-organ transplant recipients: What the clinician needs to know

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## SUMMARY

In response to the COVID-19 pandemic, SARS-CoV-2 vaccines have been developed at an unparalleled speed, with 14 SARS-CoV-2 vaccines currently authorized. Solid-organ transplant (SOT) recipients are at risk for developing a higher rate of COVID-19-related complications and therefore they are at priority for immunization against SARS-CoV-2. Preliminary data suggest that although SARS-CoV-2 vaccines are safe in SOT recipients (with similar rate of adverse events than in the general population), the antibody responses are decreased in this population. Risk factors for poor vaccine immunogenicity include older age, shorter time from transplantation, use of mycophenolate and belatacept, and worse allograft function. SOT recipients should continue to be advised to maintain hand hygiene, use of facemasks, and social distancing after SARS-CoV-2 vaccine. Vaccination of household contacts should be also prioritized. Although highly encouraged for research purposes, systematic assessment in clinical practice of humoral and cellular immune responses after SARS-CoV-2 vaccination is controversial, since correlation between immunological findings and clinical protection from severe COVID-19, and cutoffs for protection are currently unknown in SOT recipients. Alternative immunization schemes, including a booster dose, higher doses, and modulation of immunosuppression during vaccination, need to be assessed in the context of well-designed clinical trials.

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## Key words

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## Introduction

Coronavirus-associated disease or COVID-19, caused by the novel coronavirus SARS-CoV-2, has led to more than three million deaths and it is dramatically affecting health care systems all over the world. Solid-organ transplantation has been impacted by COVID-19 causing a decrease in transplant activity during the first wave of the pandemic [1]. In parallel, solid-organ transplant (SOT) recipients seem to be associated with impaired outcomes

of COVID-19, probably related to the number of comorbidities present in these patients rather than the net state of immunosuppression [2,3]. It has not yet been elucidated whether chronic drug-associated immunosuppression may decrease the development of the COVID-19 inflammatory phase [4,5], which is associated with a need for respiratory support for severe lung disease, being the ultimate cause of death.

Vaccination against SARS-CoV-2 efficaciously protects against the development of COVID-19, as shown

in large phase III trials and real life experience [6–9]. Vaccination against SARS-CoV-2 seems to be the most appropriate way to reach herd immunity, and therefore reduce SARS-CoV-2 transmission in the community. Within a record time frame, several vaccines have been developed using different technologies [10], and by May 2021, more than 1.2 billion vaccination doses have been given all over the world.

SOT recipients elicit reduced immunogenicity to a number of vaccines, because of inhibition of lymphocyte activation, interaction with antigen-presenting cells, and decreased B-cell memory responses, depending on the type of immunosuppressive drug [11]. Extensive experience with the use of influenza vaccine in SOT recipients have shown that antibody and cell-mediated immune responses are lower as compared with the general population [12–14]. Despite that, the use of influenza vaccine has been robustly associated with reduction of influenza-associated complications in SOT recipients [15,16]. While data are still being generated, current evidence suggest that the immunogenicity of SARS-CoV-2 vaccine is also suboptimal in SOT recipients [17]. The extent of a potential reduction of SARS-CoV-2 vaccine efficacy is not yet known.

In this review, we will address important issues regarding SARS-CoV-2 vaccination in SOT recipients. We will summarize the existent literature on the immunogenicity and safety of SARS-CoV-2 vaccines in the transplant population, including data on humoral and cell-mediated immune responses after vaccination. We will also assess the identified risk factors for vaccine nonresponse as well as limitations of the current evidence. Finally, we will highlight current recommendations from international societies on SARS-CoV-2 vaccination in the transplant population.

### Are SOT recipients at higher risk for complications of COVID-19?

Several studies have concluded that COVID-19 among SOT recipients are associated with increased severity and high mortality rates. Rates of reported complications were high in most studies: ICU admission ranged from 9% to 61%, respiratory failure requiring intubation from 27% to 39%, and acute kidney failure from 30% to 89% [18]. Age and comorbidities are known risk factors associated with COVID-19 severity and higher mortality in general population [19] as well as among SOT recipients [2,20,21]. SOT recipients with COVID-19 admitted to hospital usually have multiple conditions that put them at high risk for complications

and death. Those patients are predominantly 50 or older (with median age ranging between 49–73.6 years) and have several comorbidities including diabetes, hypertension, cardiovascular disease, chronic kidney disease, and obesity [18,22], which have been associated with worse outcomes after COVID-19. Comorbidities rather than immunosuppression intensity were the main risk factors for impaired outcome in a large cohort [2].

In a recent meta-analysis, the pooled case fatality rate was 24% [23], but they ranged from 10% to 50% depending on study location, prevalence of mortality-associated risk factors, clinical management, and health-care system capacity [18,24]. The mortality rates in liver and heart transplant recipients seem to be lower compared with kidney transplant recipients [18], while some reports have shown higher complication rates in lung transplant recipients [25]. Importantly, some recent studies comparing SOT with comorbidity-matched non-SOT populations using propensity scores have failed to demonstrate transplant status as a risk factor for higher mortality rates [3,26,27].

Data regarding the impact of COVID-19 on graft function are limited. Acute rejection during acute phase of COVID-19 has rarely been reported, despite immune dysfunction associated with severe COVID-19 and routine modulation of immunosuppression during acute infection [1]. Graft loss associated with early COVID-19 has been reported in up to 11% of the cases [28], but data on long-term graft function are currently lacking.

### How can we prevent COVID-19 in SOT recipients through vaccination?

As for many other infectious diseases, particularly in immunocompromised patients, vaccination against SARS-CoV-2 seems to be the most significant measure to protect individuals and household members to decrease the risk of SARS-CoV-2 acquisition and development of clinical disease, as well as to decrease transmission in the community. The next section summarizes main evidence and recommendations regarding SARS-CoV-2 vaccination in SOT recipients (Table 1).

### Which SARS-CoV-2 vaccines are available and which of them are recommended for SOT patients?

Several SARS-CoV-2 vaccines have been approved for administration in various countries and are available for selected populations based on local recommendations and regulations (see supplemental Table). These include

**Table 1.** Key points.

- Antibody levels and seroconversion rates to the SARS-CoV-2 mRNA vaccines are lower in SOT recipients than in the general population.
- Cell-mediated immune response to mRNA SARS-CoV-2 vaccines has been insufficiently assessed in SOT recipients.
- There are no published data on the immunogenicity of other SARS-CoV-2 vaccines in SOT recipients.
- Safety of mRNA SARS-CoV-2 in SOT recipient seems to be very similar to that of the general population.
- At this stage, a particular vaccine cannot be recommended over all available vaccines.
- Immunosuppressive regimens including mycophenolate and/or belatacept seems to be associated with poorer antibody responses.
- Modulation of immunosuppression before vaccination is not currently recommended, outside a clinical trial.
- Additional risk factors for poor immunogenicity response to SARS-CoV-2 vaccine are older age, shorter time from transplantation and worse graft function.
- Potential strategies for increasing the immunogenicity of mRNA vaccines in SOT recipients include to administer a third dose or using higher doses. Preliminary data show that a third dose of mRNA vaccine can partially improve immunogenicity in nonresponders.
- A cocooning strategy of vaccinating household members is highly recommended, if availability of the vaccine is assured.
- Waiting for having more data, vaccinated SOT recipients should continue precaution measures to avoid acquisition of SARS-CoV-2

mRNA-based vaccines (Moderna, Pfizer-BioNTech), those utilizing replication-deficient viral vectors (Oxford-AstraZeneca, Johnson and Johnson, Sputnik V, Cansino), inactivated virus (Sinopharm, Sinovac), and protein subunits (Novavax) [29]. Since none of the currently available vaccines is based on live replicating viral vectors, all are acceptable for transplant recipients. Thus, transplant patients should receive whichever vaccine is available to them based on local regulations and distribution policy. Vaccine prioritization is also recommended for transplant candidates, particularly those accepted on the waitlist, and for the household members and/or caregivers of SOT recipients.

### Are immunogenicity and safety of SARS-CoV-2 vaccines different from the general population?

#### *Are SARS-CoV-2 vaccines immunogenic among SOT recipients?*

As expected, evidence of the efficacy of SARS-CoV-2 vaccines among SOT recipients is only starting to accumulate, as immunosuppressed patients were excluded from all major vaccination trials used for approval processes. Among the general population, current vaccines have been extremely effective compared with placebo, reaching efficacy of 94–95% with the mRNA vaccines for protection of COVID-19 [6,7]. Accordingly, these vaccines elicited strong both antibody and T cell responses [30,31]. Subsequent reported vaccine efficacy in clinical trials have ranged from 50% to 95%, according to study population, background risk of COVID-19 during the study and presence of virus variants [32].

However, all the currently approved SARS-CoV-2 vaccines have shown nearly 100% efficacy to prevent severe disease leading to hospitalization or death (Table S1).

In the first studies published to date among SOT recipients, mRNA vaccines mRNA-1273 (Moderna) or BNT162b2 (Pfizer-BioNTech) elicited much weaker antibody responses compared with controls, measured either in frequency of seroconversion, which remained between 5% and 58.8%, or antibody titers, which remained significantly lower compared with controls [17,33–35]. A summary of the studies assessing immunogenicity and safety of SARS-CoV-2 vaccines can be found in Table 2 and Fig. 1.

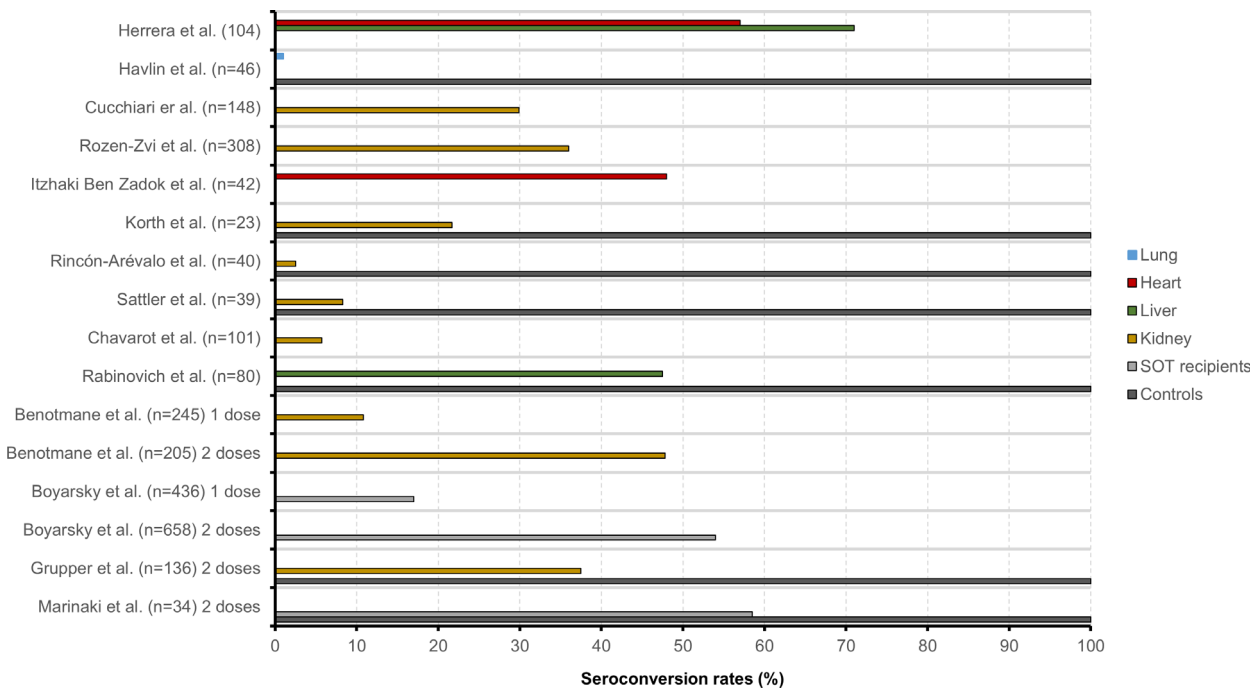
Risk factors for poor response to vaccination in these studies included older age and higher intensity of immunosuppression, especially the use of antimetabolites and belatacept [17,34–37]. Kidney transplant patients treated with belatacept showed an extremely low seroconversion rates (5%) after mRNA-based vaccine, not related with the timing between vaccination and belatacept injections [36,37]. Longer time from transplantation and better kidney function was associated with higher immunogenicity in one study in kidney transplant recipients [38,39]. In the only published study assessing both mRNA-based vaccines, antibody response after mRNA-1273 was higher as compared with BNT162b2 (60% vs. 48%, respectively) [34], although the clinical significance of this observation is not known, so that both vaccines are equally recommended post-transplant. Less data exist on the immunogenicity of the other vaccines, but small studies have reported even lower antibody responses after

**Table 2.** Studies of SARS-CoV-2 vaccine safety and immunogenicity among solid-organ transplant recipients.

Publication	Vaccine	Number of transplant patients and type of transplant	Control	Seroconversion	Side effects
Boyarski BJ, et al. May 6, 2021 [34]	2 doses: BNT162b2 (Pfizer-BioNTech) 51%; OR mRNA-1273 (Moderna) 49%	N = 658; 322 kidney, 129 liver, 97 heart, 71 lung, 5 pancreas, 22 multiorgan	No controls	15% after 1 <sup>st</sup> dose, additional 39% after 2 <sup>nd</sup> dose; 46% remained seronegative after 2 doses	Not reported
Ou MT et al. April 9, 2021 [60]	2 Doses: BNT162b2 (Pfizer-BioNTech) 54%; OR mRNA-1273 (Moderna) 46%;	N = 741; 363 kidney, 141 liver, 111 heart, 82 lung, 7 pancreas, 37 multiorgan	No controls	Not reported	Local reactions: 85% after first dose, 78% after second dose. Systemic reactions: 49% after first dose, 69% after second dose.
Benotmane I, et al. April 20, 2021 [39]	1–2 doses: mRNA-1273 (Moderna)	One dose: N = 245, all kidney Two doses: N = 205, all kidney	No controls	10.8% after 1st dose; 47.8% after 2nd dose	Not reported
Sattler A, et al, June, 2021 [47]	2 doses: BNT162b2 (Pfizer-BioNTech)	N = 39, all kidney	39 healthy controls, 26	hemodialysis patients	2.6% (vs. 100% in healthy controls and 84.6% hemodialysis patients)
Not reported					
Chavarot N. et al. April 8, 2021 [36]	2 Doses: BNT162b2 (Pfizer-BioNTech)	N = 101, all kidney	No controls	2% after 1st dose; 5.7% after 2nd dose	Not reported
Marinaki et al, April 17, 2021 [17]	2 Doses: BNT162b2 (Pfizer-BioNTech)	N = 34; 10 kidney, 24 heart	116 matched health care workers	58.8% (vs 100% in controls), IgG titers significantly lower among SOT	Not reported
Grupper et al, April 18, 2021 [35]	2 Doses: BNT162b2 (Pfizer-BioNTech)	N = 136, all kidney	25 health care workers	37.5% (vs. 100% in controls), IgG titers significantly lower among SOT	Similar between SOT and controls
Rincon-Arevalo H et al., preprint April 20, 2021 [88]	2 Doses: BNT162b2 (Pfizer-BioNTech)	N = 40, all kidney	25 healthy controls, 44 dialysis patients	2.5% (vs. 100% in healthy controls and 70.5% and dialysis patients)	The only one kidney transplant patient who presented positive anti-S1 IgG postvaccine had had prior unrecognized infection
Rabinowich L, et al. April 20, 2021 [33]	2 Doses: BNT162b2 (Pfizer-BioNTech)	N = 80, all liver	25 healthy controls	47.5% (vs. 100% in healthy controls)	Similar between SOT and controls
Korth J et al. April 25, 2021 [38]	2 Doses: BNT162b2 (Pfizer-BioNTech)	N = 23, all kidney	23 health care workers	21.7% (vs. 100% in controls). IgG titers significantly lower among SOT	Not reported

Table 2. Continued.

Publication	Vaccine	Number of transplant patients and type of transplant	Control	Seroconversion	Side effects
Schmidt T, et al., preprint May 14, 2021 [41]	1 Dose: BNT162b2 (Pfizer-BioNTech) 20%; OR mRNA-1273 (Moderna) 5.5%; OR ChAdOx1 74.5%	N = 40; 36 kidney, 1 liver, 1 heart, 2 liver-kidney	70 healthy controls	5.3% (2/38*) (vs 80% in controls) * two patients with evidence of prior infection was excluded.	None adverse events reported more frequently among SOTr compared with controls (32% vs 1%, p-value 0,018).
Cucchiari D, et al, May 26,2021 [48]	2 Doses: mRNA-1273 (Moderna)	N = 148; 133 kidney and 15 pancreas-kidney	No controls	29.9%	75–86% pain at the injection site (1 <sup>st</sup> and 2 <sup>nd</sup> dose), 25–27% fatigue. No serious adverse events.
Itzhaki Ben Zadok et al. April 29, 2021 [89]	2 Doses: BNT162b2 (Pfizer-BioNTech)	N = 42, all heart	No controls	15.4% after 1st dose; 48.6% after 2nd dose 35.7% who were nonresponders to 1 <sup>st</sup> vaccine dose became S-IgG seropositive to 2 <sup>nd</sup> vaccine dose 36.4%	Local reaction: 71% pain at the injection site, 5% redness. Systemic reactions: 14% fatigue, 12% arthralgia, 10% myalgia, 5% headache, 1% fever. No serious adverse events were reported
Rozen-Zvi B et al. May 3, 2021 [90]	2 Doses: BNT162b2 (Pfizer-BioNTech)	N = 308, all kidney	No controls		
Havlin J, et al, May 21, 2021 [91]	2 Doses: BNT162b2 (Pfizer-BioNTech)	N = 46, all lung	10 healthy controls	0% after two doses (vs 100% in healthy controls)	Not reported
Herrera et al, AJT July 22, [92]	2 Doses: mRNA-1273 (Moderna)	N = 104; 58 liver, and 46 heart	No controls	37.9% of the liver and 11% of the heart recipients after 1 <sup>st</sup> dose; 71% of the liver and 57% of the heart recipients after 2 <sup>nd</sup> dose.	80% pain at the injection site, fatigue (15%), swelling (12%), low-grade fever (7%).



**Figure 1** Summary of seroconversion rate of mRNA vaccines in SOT recipients (light grey), liver (green), heart (red), lung (blue) and kidney (yellow) transplant recipients, as compared with a control group (dark grey).

Ad26.COVS.2.S (Janssen) [40] or ChAdOx1 nCoV (Astra-Zeneca) vaccines [41].

At least three studies have reported improved immunogenicity with a third dose of mRNA vaccine, increasing the rate of antibody response to 47–68% and with higher antibody titers [42,43]. For example, among 159 patients who had no humoral response after two doses of mRNA vaccine, a significant antibody response was detectable in 49% after a third dose of mRNA-1273 vaccine [44].

*If antibody responses are suboptimal, what do we know about T cell responses to the vaccines?*

Analysis of cell-mediated immunity against SARS-CoV-2 in SOT recipients who experienced COVID-19 have shown that T cell responses are comparable to nonimmunosuppressed individuals [45,46]. However, not much data are yet available about the T cell responses to SARS-CoV-2 vaccines in the SOT population. In a study including 39 kidney transplant recipients, antibody response to mRNA vaccine remained poor, but >80–90% of SOT recipients mounted CD4+ and CD8+ T cell responses [47]. These T cell responses, however, showed impairment in cytokine production and activation profiles. In another study among 148 kidney or simultaneous pancreas-kidney transplant recipients, 65% of the patients showed either cellular or humoral

responses to the mRNA-1273 vaccine [48]. In the cohort of 101 kidney transplant recipients treated with betalacept, a specific T-cell response for the SARS-CoV-2 S1 pool of peptides was observed only in 2/40 patients (5.0%) on day 28, and in 7/23 patients (30.4%) 1 month after the second injection of BNT162b2 vaccine [36].

Although influenza vaccines are different types of vaccines compared with SARS-CoV-2 vaccines, they may give some insight into vaccine responses among SOT patients. Similarly to SARS-CoV-2 vaccines, the rate of seroconversion with seasonal influenza vaccination among SOT recipients has remained low, between 34% and 52% [49–51]. Despite this, there is strong evidence suggesting that influenza vaccine elicits adequate T cell responses also among SOT recipients [52], and in described influenza outbreaks, vaccination has shown good clinical efficacy in protecting from severe disease [16,53,54]. Therefore, it is essential to know whether the suboptimal immunogenicity of the SARS-CoV-2 vaccine seen in SOT recipients leads to a significant reduction in the protection against severe forms of COVID-19 (see next section).

*What is known about vaccine efficacy among SOT recipients?*

There is an increasing number of published reports about the frequency or severity of COVID-19 in



vaccinated SOT recipients or candidates. A recent registry-based study from the United Kingdom showed that mortality in COVID-19 positive patients was reduced from 12.0%–12.6% to 7.7% among those who had received two doses of vaccine, compared with unvaccinated patients or those who had only received a single dose, respectively [55]. The largest cohort of breakthrough infections to date after two vaccine doses was reported by Qin *et al.*, among 18215 fully vaccinated SOT recipients, breakthrough COVID-19 infection was reported in 151 patients (0.83%), of whom 87 (58%) were hospitalized and 14 (9%) died [56]. When compared with the general population, SOT recipients were estimated to have an 82-fold higher risk for breakthrough infection, and 485-fold higher risk of breakthrough infection with associated hospitalization and death. Another study described 55 SOT patients who developed COVID-19 after receiving two doses of mRNA vaccines. Of these 55 patients, 15 required hospitalization, six were admitted to the ICU, and three patients died [57]. In addition, Wadei *et al.* recently reported seven patients with undetectable or low titer antispikes antibodies who developed COVID-19 infection after receiving 1 or 2 doses of the SARS-CoV-2 mRNA vaccine [58]. Relating this to the total number of vaccinated SOT recipient within their center, the authors estimate a postvaccination infection rate of 0.6%, which is significantly higher compared with the rate 0.05% seen in the general population [59]. Overall, it seems that, although vaccination highly protects SOT recipients from symptomatic SARS-CoV-2 disease, the level of protection is lower than in the general population.

#### *Are COVID-19 vaccines safe in SOT recipients?*

Although the current approved vaccines for COVID-19 represent novel types of vaccines, there are no theoretical concerns that they should not be safe among immunosuppressed individuals, as they contain no live viruses capable of replicating in the vaccinated host. In the first studies assessing safety of SARS-CoV-2 mRNA vaccines among SOT recipients, the type and rate of adverse events have been similar to nonimmunosuppressed individuals (ranging from 70% to 85% of pain at the injection site and 15% to 20% of fatigue), and severe adverse events have been rare or nonexistent [33,35,60]. In the largest study to date, among 741 SOT recipients with two doses of mRNA vaccination, local site reactions were recorded in 78–85% of individuals, and systemic reactions in 49–69% of individuals, with the higher rate of systemic reactions recorded after the

second dose [60]. One episode of acute rejection was recorded after vaccination. As mentioned, very few studies about the safety of other types of SARS-CoV-2 vaccines are currently available. To our knowledge, no cases of life-threatening thrombosis have been reported in SOT recipients receiving the ChAdOx1 vaccine, a serious adverse event rarely reported in the general population with this vaccine.

During the 2009 influenza A(H1N1) pandemic, some studies reported safety concerns, namely stimulation of development of HLA antibodies, with the adjuvanted influenza vaccines [50], whereas other studies have found no evidence of HLA antibody formation after influenza vaccines [61,62], and influenza vaccines are strongly recommended to SOT recipients. Similarly, as no theoretical or real-world concerns have been raised, SARS-CoV-2 vaccines are recommended to SOT recipients by transplant societies [63].

#### **When should SOT candidates and recipients be vaccinated?**

Although there is no evidence to support recommendations, the ideal timing of vaccination in the pretransplantation setting may be at least two weeks prior to transplant [63]. Transplantation should not be delayed because of SARS-CoV-2 vaccine schedule. Patients who are transplanted in between vaccine doses, should delay the second dose until at least 1 month after the transplant surgery if no T-cell/B-cell depleting agent was used for induction, or at least 3–6 months after the transplant surgery if a T-cell/B-cell depleting agent was used for induction [64]. To date, no recommendation supporting the use of a third dose in these cases has been given.

In the post-transplantation setting, the ideal timing of vaccination is uncertain. Transplant Societies recommend delaying vaccination at least 1 month from transplant surgery, and at least 3 months from use of T-cell depleting agents such as anti-thymocyte globulin or specific B-cell depletion agents such as rituximab, which may require a longer deferral period (e.g. 6 months) [64].

For two dose-vaccines, time interval between the first and second doses should follow manufacture indications. For mRNA vaccines, the WHO recommends that countries experiencing exceptional epidemiological circumstances may consider delaying the administration of the second dose up to 42 days based on currently available clinical trial data, as a pragmatic approach to maximizing the number of individuals benefiting from a first

dose while vaccine supply continues to increase. However, evidence for this extension is not strong and it is discouraged in transplant patients.

### Should SOT recipients with prior COVID-19 get the SARS-CoV-2 vaccine?

Transplant recipients with prior COVID-19 should receive vaccination. In general, the protection induced by vaccination is expected to be higher than after natural infection, thus people who had proven COVID-19 (or may have had) can and should receive the COVID-19 vaccine because it will give them additional protection. Testing for antibodies to COVID-19 as a marker of past infection is not recommended or needed prior to vaccination.

The optimal timing to vaccination after infection is unknown. According to data from general population reporting persistence of anti-SARS-CoV2 antibodies over 3 months after COVID-19 diagnosis [65], generally a 3–6-month interval is recommended between infection resolution and vaccination [66]. However, experts recommend administering vaccination in transplant patients as soon as it is available for them after clinical resolution and documenting that the patient is no longer contagious [64]. Vaccination should be delayed by 3 months in patients that received monoclonal antibodies or convalescent plasma for COVID-19.

People with previous infection have been shown to generate strong humoral and cellular responses to one dose of the BNT162b2 vaccine [67]. In addition, a preprint study found that individuals with prior exposure to SARS-CoV-2 demonstrated strong humoral and antigen-specific responses to the first dose but muted responses to the second dose suggesting that one dose of the vaccine may be sufficient for people who have already been infected with SARS-CoV-2 [68]. Recently, a study including 41 patients who were already seropositive at baseline because of previous exposure to SARS-CoV-2, showed marked increases in antibody titers already after a single dose of mRNA vaccine [69]. In another study, prior COVID-19 was associated with a 6.28-fold higher chance of a positive antibody response as compared with naïve patients after one dose of mRNA vaccine [70].

In case of SARS-CoV-2 infection or COVID-19 diagnosis in between doses, current recommendation for SOT recipients is to administer the second dose after the symptoms have completely resolved, and the patient is no longer contagious [64].

### How long will vaccine protection last?

At the time of writing, it is unknown how long someone remains protected from COVID-19 after being vaccinated as well as if the protection length varies between the different vaccine types [71]. A preliminary report, from an ongoing phase 1 trial, included 33 healthy adult participants stratified by age group, which were assessed up to 180 days after the second dose of 100 µg mRNA-1273 vaccine by three distinct serologic assays (enzyme-linked immunosorbent assay, pseudovirus neutralization assay, live-virus focus-reduction neutralization assay). Antibodies persisted through 6 months in the majority of participants [72]. Ongoing studies are monitoring immune responses beyond 6 months as well as determining the effect of a booster dose to extend the duration and breadth of activity against emerging viral variants [71]. In SOT recipients, only 4% of patients with detectable antibody responses one month after the second dose of mRNA vaccine had undetectable levels at 3 months post vaccination, with 43% of patients having an increase in antibody levels [73].

### Should SOT recipient's immune response be tested after being given SARS-CoV-2 vaccine?

Humoral and cellular immunity does not necessarily correlate with vaccine efficacy, which is related to the clinical outcome. All vaccines may theoretically prevent COVID-19-related complications and deaths irrespective of the patient's immunological status. Current published clinical trials with SARS-CoV-2 vaccine in the general population have consistently shown high rates of humoral and cellular response and 100% of clinical efficacy in preventing severe disease (supplemental table). However, real life data have shown lower efficacy because of different factors such as viral mutations promoting immunological escape, the intensity of virus exposure, social distancing practices, and the population's immunological status [32].

There are several commercially available serological testing assays, which detect antibodies against SARS-CoV-2 spike and nucleocapsid antigens. The majority of these methods are not able to distinguish between neutralizing and non-neutralizing antibodies and only detect a subset of the total pool of neutralizing antibodies [74]. The gold-standard method to assess the presence of neutralizing antibodies remains a virus neutralization test requiring live virus and a biosafety level 3 laboratory, a labor- and time-consuming assay



which is not routinely available. Traditional antispikes or anti-RBD antibodies of SARS-CoV-2 have been shown to be related to neutralizing antibodies detected by the traditional standard methods [75,76]. Functional antibody testing using a based competition-binding assay against ACE2 have been proposed to determine the neutralizing antibodies effect on the ACE2-RBD interaction [77]. Although those methods have been used in the clinical practice as a surrogate marker for COVID-19 protection, no correlates of protection have been defined yet. Thus, we invite to keep caution in interpreting current literature data about vaccine immunogenicity as surrogate of clinical efficacy of vaccine in SOT recipients.

Assessment of SARS-CoV-2-specific T cell responses can be done using similar techniques available to assess the immune cellular responses to other pathogens. Those methods are able to measure cellular activation and cytokine responses after either T or B cell stimulation with specific SARS-CoV-2 antigens through enzyme-linked immunosorbent spot assay and enzyme-linked immunosorbent assay, or to evaluate memory B-cell responses through flow cytometry [78,79]. It is worth mentioning that also these tests are laborious, not routinely performed in clinical practice, and there are several platforms for result interpretation.

According to what exposed above, although the researches on the immunogenicity of SARS-CoV-2 vaccines in SOT recipients, its correlation with clinical efficacy and its length are strongly encouraged, the routine use of serological and cellular immunity assays to test response to vaccine are not recommended at this stage.

### **Should immunosuppressive regimens be modified before or after vaccination?**

Transplant Societies [63,64] recommend continuing stable maintenance of immunosuppressive regimens, including antiproliferative agents (such as mycophenolate mofetil) in patients that are receiving SARS-CoV-2 vaccination. Alteration of immunosuppression, outside the setting of a clinical trial, is discouraged because of the potential risk of rejection.

### **Should a different vaccine schedule be applied specifically for SOT recipients?**

Several studies have assessed the immunogenicity and safety of different influenza vaccine preparations specifically in SOT recipients, including high-dose vaccine, intradermal administration, and vaccination with a

booster dose [13, 80, 81]. Although some of these strategies have shown promising results in terms of increase of antibody levels after vaccination, none of them is currently used in the routine clinical practice, and none of them has shown a reduction in clinical influenza-related complications in transplant recipients as compared with the standard vaccine. We do not currently recommend using different amounts of mRNA, or a different way of administration of the SARS-CoV-2 vaccine in SOT recipients in the routine clinical practice. While preliminary studies show that an additional dose of vaccine may help to increase immune responses to the vaccine, more data are needed assessing the clinical benefit of this approach. Such strategy needs to be balanced against the availability of the vaccines and equity with regard to other vulnerable populations. The optimal solutions may be different in different countries, depending on the epidemiological situation.

### **Vaccination among children and adolescents**

Albeit children and adolescents tend to have milder disease compared with adults, pediatric population with underlying conditions are more likely to experience severe COVID-19 and might get benefits of full vaccination against SARS-CoV-2 alongside other priority groups for vaccination [82]. While no published data about SARS-CoV-2 vaccination among the pediatric population are available, several trials including pediatric population and pediatric SOT recipients are underway and should support update in the current recommendations. Extrapolation from the general population would suggest that at least the mRNA vaccines are safe and effective also among the adolescent population [83]. On note, no SARS-CoV-2 vaccine is currently approved for individuals < 12 years of age.

### **Which are the other preventive measures against COVID-19 to be applied in SOT recipients?**

Based on the current recommendations, all vaccinated individuals should continue to take precautions in order to avoid SARS-CoV-2 infection. These strategies need to follow the local recommendations based on the prevalence of active SARS-CoV-2 infection in the local community. Given the lower immunogenicity response by SOT recipients after full SARS-CoV-2 vaccination, the recommendations to maintain hand hygiene, use of facemasks, and social distancing after SARS-CoV-2 vaccine are particularly important among SOT recipients

[63]. Additional measures relevant for this population may be to reduce medical facility visits balancing the need of patient evaluations against the risk of infection, and implementing telemedicine approaches where possible. Recommendations regarding testing for SARS-CoV-2 infection, quarantine/isolation, and proactive monitoring for asymptomatic patients should be followed also for SARS-CoV-2-vaccinated SOT recipients. PCR-based testing in respiratory samples for SARS-CoV-2 is recommended in all patients undergoing invasive procedures, including transplantation, irrespective of vaccination status. In case of positive result, the procedure should be canceled or postponed. Once positive, PCR-based testing can remain positive for several weeks after resolution of symptoms [84]. Repeat SARS-CoV-2 PCR testing to determine the duration of viral shedding should not be recommended, since a positive PCR test does not mean that the patient is infectious, and viral tissue culture is not available to assess for viable virus in clinical laboratories [85]. The CDC currently recommends isolation precautions for 10 days after symptom onset (with fever resolution lasting at least 24 h without the use of fever-reducing medications), with extension to 20 days for immunocompromised patients or those with severe illness [71]. Repeat PCR testing can result in unnecessarily prolonged isolation and anxiety for patients and medical teams.

## Conclusions

SOT recipients are at risk for developing a higher rate of COVID-19-related complications and therefore they are at priority for immunization against SARS-CoV-2. Preliminary data suggest that the immunogenicity of current vaccines is lower than initially expected in SOT recipients. However, there are several unanswered questions that need to yet be addressed through implementation of appropriate studies. First, although research is advancing very fast in this topic, larger studies of SOT recipients need to assess both humoral and cellular immune responses and clinical efficacy to all SARS-

CoV-2 vaccines available. These cohorts should include lung transplant recipients, patients early post-transplantation, and patients receiving different immunosuppressive regimens. More importantly, these studies should assess efficacy of vaccination for preventing COVID-19, hospitalization rates, and death, with the goal to find immune markers for clinical protection against severe disease. Robust data on clinical protection is still lacking. All interventions testing novel schedules for vaccination, including a booster dose and modulation of immunosuppression during vaccination need to be done in the context of well-designed clinical trials. The example of trials including thousands of patients for evaluating therapeutic options for the treatment of COVID-19 [86,87] illustrates how pragmatic research can be successfully performed to rapidly address unmet research needs in the context of an ongoing pandemic.

## Authorship

All authors participated equally in the writing of the manuscript.

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## Conflict of interest

None.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Summary of current SARS-CoV-2 vaccines.

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