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REVIEW

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Vaccination and their importance for lung transplant recipients in a COVID-19 world

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ABSTRACT

Introduction: Lung transplant patients are immunocompromised because of the medication they receive to prevent rejection, and as a consequence are susceptible to (respiratory) infections. Adequate vaccination strategies, including COVID-19 vaccination, are therefore needed to minimize infection risks.

Areas covered: The international vaccination guidelines for lung transplant patients are reviewed, including the data on immunogenicity and effectivity of the vaccines. The impact on response to vaccination of the various categories of immunosuppressive drugs, used in the posttransplant period, on response to vaccination is described. A number of immunosuppressive and/or anti-inflammatory drugs also is used for controlling the immunopathology of severe COVID-19. Current available COVID-19 vaccines, both mRNA or adenovirus based are recommended for lung transplant patients.

Expert opinion: In order to improve survival and quality of life, infections of lung transplant patients should be prevented by vaccination. When possible, vaccination should start already during the pre-transplantation period when the patient is on the waiting list. Booster vaccinations should be given post-transplantation, but only when immunosuppression has been tapered. Vaccine design based on mRNA technology could allow the design of an array of vaccines against other respiratory viruses, offering a better protection for lung transplant patients.

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1. Introduction

Coronavirus disease 2019 (COVID-19) caused by an infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first described in Wuhan, China in December 2019 [1]. The virus has since then spread around the globe, and in March 2020 was declared a pandemic by the World Health Organization (WHO) [2]. COVID-19 can manifest itself as asymptomatic, a mild viral illness, or moderate or severe respiratory disease. Furthermore, it may also lead to a severe cytokine storm and associated severe respiratory syndromes. Case fatality rates vary per country from 0.1% to as high as 9.1% [3]. Rarely, children may develop a severe inflammatory syndrome within a few weeks after infection.

As compared to recipients of other transplanted organs, lung transplant patients deserve special attention as the lung is the main target of COVID-19 [4]. Furthermore, lung transplant recipients could be more vulnerable because levels of immunosuppression are generally higher than other solid organ transplant recipients, and viral infections are thought to be able to provoke chronic rejection of the lung allograft. In this paper, the various immunosuppressive drugs used in the post-transplantation period will be discussed with respect to their effects on the immune system. Immunosuppressive drugs with a strong anti-inflammatory effect are also being used to control inflammation in COVID-19, and this aspect is included. Because immunosuppression increases the risk for (respiratory) infections, transplant recipients are also recommended to be vaccinated against vaccine-preventable diseases post-transplant. The current literature on the immunogenicity and effectivity of vaccines recommended for lung transplant recipients will be reviewed in order to highlight the importance of vaccination during the COVID-19 pandemic.

2. Immunosuppression after transplantation and its effects on the immune system

To prevent organ rejection, transplant patients are treated with heavy doses of immunosuppressants in the first six months post-transplantation [5]. Although the dose and type of immunosuppressant(s) are decided on a case-by-case basis, there exist recommendations or guidelines on vaccinations for lung transplant candidates and recipients [6]. Here we will discuss some of the most commonly prescribed immunosuppressants for lung transplant patients and review their potential influence on vaccine response (Table 1). In addition, we will also describe how these immunosuppressants could, because of their anti-inflammatory potential, play a role in the clinical course of COVID-19 by analyzing the observed effectivity and reported patient outcomes.

2.1. Corticosteroids

Corticosteroids are a group of compounds that mimic the endogenous steroid hormones produced in the adrenal cortex. Corticosteroids are divided into two classes:

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Article highlights

- Lung transplant patients are a special risk group for COVID-19 as lungs are the primary target for SARS-CoV-2
- The various immunosuppressants can have a negative impact on the response to recommended vaccinations.
- Immunosuppression, especially corticosteroids, can have a positive effect on COVID-19 outcome
- Most vaccines, including SARS-CoV-2 vaccines are well tolerated by lung transplant patients
- Emerging data indicate a poor antibody response to mRNA vaccines in lung transplant patients. (Long term) efficacy is unknown and therefore it is recommended that patients will be monitored and additional vaccine doses and/or types could be needed.

mineralocorticoids which regulate electrolyte and fluid homeostasis, and glucocorticoids which have anti-inflammatory properties [7]. Some of the most commonly prescribed glucocorticoids are prednisone and dexamethasone. Although dexamethasone has been found to be seven times more potent than prednisone on a weight for weight basis, it also has more side effects. Due to this fact, dexamethasone has been reserved for patients who do not respond to prednisone or whose symptoms cannot be controlled by prednisone [8]. In transplant medicine, corticosteroids are used to prevent organ rejection by starting at high doses after surgery and slowly tapering to a reach a maintenance dose.

2.1.1. Response to vaccination

Corticosteroids have a long history of use for numerous diseases because of their well-known anti-inflammatory properties. With this background it is surprising that relatively little attention has been paid to its potential influence on vaccine responses. The United States Centers for Disease Control and Prevention (CDC) recommends the use of prednisone to be tapered and ultimately stopped 1–3 months before the administration of live (attenuated) vaccines in patients taking high daily doses [9]. High doses are defined as > 20 mg/day and doses below that threshold are not considered immunosuppressive to a degree that would preclude the use of live vaccines. With regards to the tetanus toxoid vaccine, combination therapy using prednisone inhibited cellular and humoral immune responses toward the vaccine; though it is unclear whether this effect is primarily caused by prednisone or by the second combination medication [10]. Conflicting results were also found with the 23-valent pneumococcal polysaccharide vaccine (Pneumovax®) [11–13]. Studies in rheumatoid arthritis patients showed that combined prednisone or prednisolone use did not influence vaccine response [12], whereas a study on lung transplant candidates treated with prednisone states that it severely impairs the response [13]. Moreover, a longitudinal study on patients with inflammatory diseases reported that poor serological responses were only observed in those taking prednisone doses of ≥10 mg/day [14]. The impaired response could be due to the severity of the disease or the dosage of prednisone, however, caution is recommended when giving them to lung transplant patients. The effect of prednisone on the antibody response to influenza vaccination is also variable, with evidence of normal responses for the H1N1 monovalent vaccine and normal-to-lower lower antibody responses for the trivalent seasonal influenza vaccine [15,16]. Lastly, prednisolone was associated with a lower anti-HPV antibody response when measured 7 months post vaccination [17].

Limited literature is available regarding the relationship between dexamethasone use and vaccine response, however, combination therapy including dexamethasone has been reported to severely impair response to the 23-valent pneumococcal polysaccharide vaccine [13]. For corticosteroids as a whole, its use has been linked to poorer response toward the hepatitis B vaccine but was linked to improved seroprotection rates against H3N2 influenza [18,19]. With regards to the effects of corticosteroids on vaccine response, the available data presented are difficult to interpret given that a proportion of the studied populations often receive a combination of immunosuppressive medications, which may also include corticosteroids. Moreover, the studies mentioned often include non-lung transplant patients, making it difficult to generalize these results.

2.1.2. Potential effect on COVID-19

Because of its anti-inflammatory properties, prednisone also has been considered for treatment of COVID-19 with the objective to dampen the cytokine release storm. A review on the effectivity of prednisone in the treatment of COVID-19 however was inconclusive [20]. Patient outcomes also varied greatly, with studies claiming that the early use of short-course methylprednisolone might be beneficial for moderate-to-severe patients or those who develop acute respiratory distress syndrome, but at the same time, doses ≥10 mg/day may increase mortality rates [21–23]. On the other hand, the corticosteroid dexamethasone has been widely studied in hospitalized COVID-19 patients, and it was found that dexamethasone is effective in moderate-to-severe patients receiving respiratory support [24,25]. Dexamethasone by now has become one of the standard drugs for treatment of COVID-19, especially in moderate to severe patients [26–28]. This conclusion was supported by the Infectious Diseases Society of America and is published in their guideline on the treatment and management of patients with COVID-19 [29].

Similar studies on corticosteroids as a whole also observed significant reduction in mortality, ICU admission, and risk of intubation among patients requiring respiratory support [30–33]. Results stemming from single center retrospective studies found that every 10 mg increase in corticosteroids is associated with an additional 4% mortality risk and that systemic corticosteroid treatment does not show significant benefits [34,35]. Currently, a phase 3 clinical trial (NCT04341038) is underway to evaluate the efficacy and safety of methylprednisolone pulses in patients with severe pneumonia, hypothesizing that the pulses would better control hyperinflammation [36]. It should be noted that a clear distinction may exist both in context as well as clinical outcomes between chronic corticosteroid use as part of an immunosuppressive regimen and the use of corticosteroids in the acute setting of a SARS-COV-2 infection.

Table 1. Overview of immunosuppressive drug used in lung transplantation recipients: effect on COVID-19 and on response to vaccination.

Compound	Category Immunosuppressant Severity	Effective in COVID-19	COVID-19 Outcome in Patients on Immunosupressant	Potential effect on response to vaccination	Reference
Prednisone/ Prednisolone	Light	Inconclusive, but recommend limiting oral prednisone to the most severe clinical scenarios where its use is well established and cannot be substituted with other medications	more deaths if dose >10 mg/day No difference (> 7.5 mg/day)	Combination therapy severely impairs response to 23vPPV Recommended to stop 1–3 months before live vaccinations in patients with high daily doses Doses <20 mg/day is not immunosuppressive of the use of live vaccines Inhibited cellular response against tetanus toxoid	11–19,22-25
		Methylprednisolone pulses might be beneficial in severe patients	Early short-course methylprednisolone reduced escalation of care and improved clinical outcomes in moderate to severe covid Methylprednisolone may be beneficial for patients who develop ARDS	Significantly lower anti-HPV 16 titers at month 7 ≥10 mg/day had poorer serological responses toward 23vPPV No association found in humoral response toward H1N1 vaccine Associated with lower anti-body responses to trivalent influenza vaccine Prednisolone treatment did not influence response to Pneumovax®(23 valent pneumococcal vacc.) Doses ≤10 mg/day no effect on the response rate toward 23-valent pneumococcal vaccine and trivalent subvirion influenza virus vaccine	
Dexametha-sone	Light	Yes, on patients needing respiratory support Yes, in severe and critically ill patients No, in patients without hypoxemia	Lower 28-day mortality rate in hospitalized patients receiving respiratory support Early administration could reduce duration of ventilation and overall mortality in moderate-to-severe ARDS	Combination therapy severely impairs response to 23vPPV	15,26–30
Cortico-steroids	Light	Yes, on patients requiring high-flow oxygen Systemic corticosteroids increased risk for hospitalization Maintanence corticosteroids no risk of severe covid Systemic corticosteroid treatment did not show significant benefits	Prevents in-hospital mortality when used with tocilizumab No association between therapy and outcomes in patients without ARDS Every 10 mg increase was associated with additional 4% mortality risk Lowered the risk of intubation in patient with severe pneumonia	Poorer response to HBV Increased seroprotection against H3N2	20,21,31–37
Tacrolimus	Moderate	May be beneficial Inhibits the growth of human coronaviruses at low micromolar, non-cytotoxic concentrations in cell culture Might be beneficial in severe patients	Better survival in patients >70 y/o Increased risk for hospitalization No difference No risk for severe covid	reduces immunogenecity No significant difference Monotherapy does not impair PPSV23 immunogenecity	37–50

(*Continued*)

Table 1. (Continued).

Compound	Category Immunosuppressant Severity	Effective in COVID-19	COVID-19 Outcome in Patients on Immunosupressant	Potential effect on response to vaccination	Reference
Mycophenolate mofetil	Moderate	Inconclusive, but recommended to stop	No difference	No significant difference Significantly reduces protection rate and seroconversion for H1N1 & H3N2 vaccines Reduces response to HepA No significant difference toward flu vaccine	12,19,22,39,51–55
			More severe (doses >1000 mg/day)	No influence toward H1N1 vaccine Significant reduction toward H1N1 vaccine if dose ≥2 g per day Completely disturbed primary and secondary humoral responses toward tetanus toxoid and pneumococcal polysaccharide Significantly lower seroconversion rates of HPV 6 and 8 at month 12, and lower anti-HPV 16 titers at month 7	
Sirolimus/ Rapamycin/ mTOR inhibitors	Moderate	Promising: The mTOR signaling pathway significantly inhibits MERS-CoV replication in vitro Promising: sirolimus may inhibit mTOR signaling and RNA synthesis pathway and DNA topoisomerase 2-beta in HCoV-infected cells Sirolimus + dactinomycin synergistically targets HCoV-associated host protein subnetwork by 'Complementary Exposure' pattern, offering potential combination regimen for HCoV treatment	N/A	Lower H1N1 antibody titer postvaccination in patients taking mTOR inhibitors	56–68
Basiliximab	Severe	N/A	N/A	Improves response	39
Azathioprine	Severe	N/A	No effect	No significant difference toward flu vaccine Doses ≤3 mg/kg is not immunosuppressive toward live vaccines Decreased seroprotection against H1N1 & H3N2	11,21,53,59

2.2. Calcineurin inhibitors

2.2.1. Response to vaccination

With regard to vaccine response, tacrolimus monotherapy does not impair the antibody response toward the 23-valent pneumococcal polysaccharide vaccine, nor does it negatively affect the response to influenza vaccine [37,38]. High doses of tacrolimus (9.4 µg/mL) however, did reduce the response to human papillomavirus (HPV) vaccine [39]. While cyclosporine also does not negatively affect responses toward the influenza vaccine, it has been shown to partially inhibit the ability to mount a primary humoral response toward the tetanus toxoid and pneumococcal polysaccharide vaccines [10,38]. Interestingly, the boosting of secondary humoral responses was not affected. The latter observation has important consequences for the design of vaccination schedules of lung transplantation patients as will be discussed below (expert commentary).

2.2.2. Potential effect on COVID-19

Research regarding cyclosporine and tacrolimus use in the context of COVID-19 are limited to in vitro laboratory experiments and one ongoing phase 3 clinical trial (NCT04341038) [36]. The mechanism of action involves the interaction between SARS-CoV non-structural protein Nsp1 and host cyclophilins or immunophilins (FK506-binding proteins) that modulate the Calcineurin/NFAT pathway. This pathway plays a role in immune system activation and regulates immune processes such as apoptosis, anergy, and T-cell development. In order to be activated, NFAT must first be dephosphorylated by calcineurin A and it is this step which can be inhibited by Cyclosporin A [40]. Multiple in vitro studies using other human coronaviruses have shown promising results with cyclosporin A and tacrolimus, because both drugs appear to be able to inhibit viral growth and replication [40–43]. Yet, preliminary reports on COVID-19 patient outcomes are inconclusive [44,45]. The use of calcineurin inhibitors has been associated with decreased mortality [46,47], better survival in patients older than 70 years [48], better survival in patients with severe pneumonia [46], but with an increased risk for hospitalization [49].

2.3. Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a reversible inhibitor of inosine monophosphate dehydrogenase and its interactions with the immune response to vaccination have been well documented. MMF completely disturbs primary and secondary humoral responses toward tetanus toxoid and pneumococcal polysaccharide vaccines, reduces response toward the hepatitis A vaccine, significantly lowers seroconversion rates of HPV-6 and −8 after 12 months, and lowers anti-HPV-16 antibody titers after 7 months [10,17,50]. For the response to influenza vaccination, variable and contradictory results have been obtained (Table 1) [38,51–54]. Temporary cessation of MMF is recommended should the patient become infected with SARS-CoV-2 [20].

2.4. mTOR inhibitors

Similar to calcineurin inhibitors, mammalian target of rapamycin (mTOR) inhibitors have shown promising results in vitro against the replication, signaling, and RNA synthesis pathways of human coronaviruses [55,56]. In one kidney-pancreas transplant recipient, the use of everolimus contributed to a relatively mild disease course and complete recovery from COVID-19; supporting previous research that shows that mTOR inhibitors can have anti-viral effects [57]. Little is known regarding the effect of mTOR inhibitors on vaccination response, yet it has been shown that these drugs impair H1N1 antibody titers after influenza vaccination [58].

2.5. Basiliximab and azathioprine

Literature of the use of basiliximab (a chimeric mouse-human monoclonal antibody to the IL-2 receptor α chain) and azathioprine in the context of COVID-19 and vaccination response is very limited. A small number of COVID-19 positive solid organ transplant recipients receiving azathioprine therapy behaved like other recipients on other immunosuppressive medication [59]. Furthermore, the CDC states that for azathioprine doses ≤3 mg/kg is not immunosuppressive toward live vaccines, and conflicting information was found regarding the flu vaccine [9,19,52]. Less is known about basiliximab, but a study showed that it improves the antibody response to influenza vaccine [37].

3. Vaccination responses in lung transplant recipients

While life expectancy has increased over time, infections remain the second leading cause of mortality in transplant recipients [60,61]. Due to the lifelong immunosuppressive therapy that lung transplantation recipients receive, they are at risk for potentially life-threatening infections. Furthermore, since the response toward vaccinations are also diminished in organ failure, lung transplant candidates should also be immunized prior to transplantation. The American Society of Transplantation (AST) have published guidelines for the recommended vaccinations and travel vaccinations for adult lung transplant candidates, shown in Tables 2 and 3 respectively [6].

Most inactivated vaccines are safe to administer after transplantation, but live vaccines should only be administered prior to transplantation. The AST further recommends vaccinations to be completed by 2 weeks for inactivated vaccines and 4 weeks for live vaccines prior to transplantation, if possible. If the series has been started but was not completed prior to transplantation, it may be continued approximately 3–6 months after transplantation when baseline immunosuppression levels are attained.

In healthy adults, vaccination will induce a humoral immune response (as measured by an increase in antibody titers) as well as a cellular T cell mediated immune response and will offer clinical protection against the pathogen. However, in lung transplant candidates and recipients, the ability to mount adequate immune responses might be

Table 2. Recommended vaccines for lung transplant recipients.

Vaccination	Type of Vaccine	Recommended for Lung Transplantation		Immunogenicity Data Availability	Clinical Protection
		Before	After		
Influenza	Inactivated	✓	✓	Yes	Variable*
Hepatitis B	Subunit	✓	✓	Yes	Yes
Hepatitis A	Inactivated	✓	✓	Yes	Yes#
Tetanus	Toxoid	✓	✓	Yes	Yes#
Pertussis (Tdap)	Subunit	✓	✓	Yes	Yes#
Polio	Inactivated	✓	✓	No	Unknown
Haemophilus influenza type B	Conjugate	✓	✓	No	Unknown
Streptococcus pneumoniae (conjugate vaccine)	Conjugate	✓	✓	Yes	Unknown
Streptococcus pneumoniae (polysaccharide vaccine)	Polysaccharide	✓	✓	Yes	Yes
Meningococcal	Conjugate	✓	✓	No	Unknown
Rabies	Inactivated	✓	✓	No	Unknown
Human papillomavirus (HPV)	Recombinant	✓	✓	Yes	Unknown
Measles/Mumps/Rubella	Live attenuated	✓	×	Yes	Yes#
Rotavirus	Live attenuated	✓	×	No	Unknown
Varicella	Live attenuated	✓	×	Yes	Some protection
BCG	Live attenuated	✓	×	No	Unknown
Anthrax	Inactivated	×	×	No	Unknown
Smallpox	Live attenuated	×	×	No	Unknown

* = some strains may be more immunogenic
# = based on seroprotective Ab levels obtained
Adapted from reference 6.

Table 3. Recommended travel vaccines for lung transplant recipients.

Travel Vaccination	Type of Vaccine	Recommendation		Immunogenicity Data Availability	Clinical Protection
		Before	After		
Yellow fever	Live attenuated	✓	×	No	Unknown
Japanese encephalitis	Inactivated	✓	✓	No	Unknown
Salmonella typhi (Intramuscular)	Polysaccharide	✓	✓	No	Unknown
Salmonella typhi (oral)	Live attenuated	✓	×	No	Unknown
Cholera	Live attenuated, Inactivated, Subunit	✓	×	No	Unknown

Adapted from reference 6.

impaired; and if they were to reach satisfactory levels, it is still uncertain if they offer clinical protection. Gangappa et al. [62] hypothesized that polysaccharide vaccines may be more effective in transplant recipients in comparison to peptide and protein vaccines because the antibody response to polysaccharide antigens is not dependent on T-cell help. We have analyzed the literature on immunogenicity and clinical efficacy of recommended vaccines and included a summary of the outcomes in Tables 2 and 3. Many recommended vaccines have limited available data on immunogenicity and clinical protection, suggesting that recommendations were made based on solid organ transplant recipients in general and not specifically for lung transplantations, highlighting the areas for potential future research.

3.1. Influenza

The international consensus of protective antibody levels for the influenza vaccine is set as a 1:40 serum dilution for hemagglutination inhibition titer [63]. This threshold on average is only reached by approximately 30% of lung transplant recipients 4 weeks postvaccination [64]. For the cellular immune response to influenza vaccination, as well as for other vaccines for that matter, no international consensus criteria have been defined. In terms of cell-mediated immune response, lung transplant recipients failed to demonstrate responses 4 weeks postvaccination as measured by their IL-2, IL-10, IFN-gamma, and granzyme B levels [65]. Studies using trivalent seasonal influenza vaccines showed variable results among different strains, indicating that some strains may be more immunogenic than others and that clinical protection may vary [66,67]. Furthermore, a 5-year longitudinal study showed that post lung transplant patients have significantly lower seroconversion rates compared to pre-transplant levels, indicating that patients have a stronger response before transplantation and that yearly seasonal vaccination should start prior to transplantation [68].

3.2. Hepatitis A and B

Whilst relatively little research has been performed on the hepatitis A vaccine and lung transplant patients, the clinical protection offered by the hepatitis A vaccine is a well-known example of absolute correlation toward clinical protection where >10 IU/L IgG anti-Hepatitis B almost always guarantees protection against the disease [63]. A vaccine catch-up plan constructed by Blanchard-Rohner et al. [69] demonstrated that the hepatitis A vaccine is well accepted among lung transplant candidates. Their study found that only 57% of candidates at listing were seroprotected but this was increased to 87% after the catch-up vaccination. Seroprotection was maintained for at least one year (average time before transplantation). To our knowledge, no data have been published on the antibody

response to Hepatitis A vaccination of lung transplant recipients.

Hepatitis B antibody concentrations in lung transplant recipients have been shown to decrease rapidly after transplantation, possibly resulting from the high doses of immunosuppressive therapy. But at the same time, it has also been noted that recipients who were vaccine responders at any point before transplant maintained a T-cell response to HBsAg that is comparable with healthy subjects albeit their rapidly decreasing antibody concentrations; revealing that recipients retain functional lymphocytes that are responsive to HBsAg [70]. This is in line with the fact that HBsAg memory B cells are directly correlated to clinical protection, despite diminished antibody levels [71].

3.3. Tetanus, pertussis, Tdap

Current recommendations for the tetanus, tetanus and diphtheria (Td), or tetanus, diphtheria, and pertussis (Tdap) booster vaccines are the same for healthy individuals and lung transplant patients, implying repeat vaccinations every 10 years. It should be kept in mind that the repeated vaccination for healthy adults is not implemented in every country. Although it has not been established whether the 10-year interval should be revised for transplant patients, it has been observed that their antibody concentrations were significantly lower than healthy individuals in as early as 0–5 years post-vaccination [72]. This suggests that their ability to mount and maintain a protective response postvaccination may be impaired. Considering that antibody seroprotection almost guarantees clinical protection, it is recommended to monitor antibody levels in lung transplants patients at regular intervals to ensure patient safety.

3.4. Streptococcus pneumoniae

The *Streptococcus pneumoniae* vaccines come in two forms: a 23-valent polysaccharide vaccine (PPSV23) and a 7- or 13-valent conjugate vaccine (PCV7 or PCV13). Conjugate vaccines induce a T-cell dependent response which may produce antibodies with higher affinity and may also lead to the formation of memory B cells, whereas the polysaccharide vaccine induces a T-cell independent response.

Prior to the introduction of conjugate vaccines, transplant patients received only the PPSV23 vaccine. Pre-vaccination immune status assessment of lung transplant candidates revealed that more than half of the candidates had serum concentrations below the normal range for IgM, IgA, IgG, IgG1 and/or IgG2 immunoglobulin isotype and/or subclass levels. Serotype specific pneumococcal antibodies also were found to be decreased as compared to age matched controls [73]. Post-vaccination assessment resulted in a higher fraction of candidates with protective antibody levels, but a majority had titers that did not reach protective levels (>1.3 μg/L) for at least 70% of the serotypes tested. Humoral immune status studies on lung transplant recipients found that most patients became humoral immunodeficient after transplantation which is noticeable within the first-year post-transplant [13]. Partial recovery of all immunoglobulins and subclasses have been documented after several years, possible owing to the tapering of immunosuppressive therapies. However, the humoral immune status is still significantly lower than that before transplant and was never found to return even after several years. Fortunately, despite their impaired immune status, most patients were able to produce at least a partial antibody response.

Due to the suboptimal immune response of lung transplant patients toward the pneumococcal polysaccharide vaccine, current recommendations include an initial dose of a conjugate vaccine (PCV7 or PCV13, depending on country) and a subsequent PPSV23 dose at least 8 weeks later [74]. Studies performed to investigate the efficiency of the recommended dual administration have so far failed to show the value of the additional PPSV23 for the overlapping serotypes. The standalone administration of the pneumococcal conjugate vaccine proved to be immunogenic pre- and post-transplant as well as being well tolerated in lung transplant patients, but no significant enhancement of antibody levels was observed when followed-up by the PPSV23 [75]. Furthermore, 1-year follow up serological testing in lung transplant recipients who had the combined vaccine administration showed a decrease in antibody levels that are comparable to recipients who previously only received the PPSV23 [76].

3.5. Human papilloma virus

The quadrivalent Human Papilloma Virus (HPV) vaccine is recommended for all individuals between the ages of 9 and 26 to prevent cervical cancer, anal cancer and anogenital warts [77]. The utilization of this vaccine in the context of organ transplantation may vary between countries but are administered to transplant candidates in the age group who have not received the HPV vaccine or have not completed the 3-dose series [6]. Immunogenicity studies are limited, but Kumar et al. [39] concluded that the HPV vaccine is safe and well tolerated in lung transplant recipients, but compared to other transplanted organs, lung transplantation was associated with lower antibody responses.

3.6. Measles, mumps, and rubella

Studies on the measles, mumps, and rubella vaccination in lung transplant recipients are very limited. However, antibody seroprotection toward measles and rubella have been identified as examples of absolute correlation toward clinical protection (i.e. seroprotection almost guarantees protection) [63]. In line with this, a study in Denmark has included lung transplant patients and analyzed serostatus prior to transplantation and one-year post-transplant [78]. Approximately 13% of lung transplant patients were seronegative to at least one of the MMR viruses prior to transplantation. Unfortunately, the data was not reported per organ. Assuming that lung transplant recipients behave like other solid organ transplant recipients, 21% seroconverted for measles, 62% for mumps, and 15% for rubella. Among the recipients that remained seronegative for at least one year, 43% remained seronegative and 57% seroconverted during follow up. Additionally, lung transplant recipients were found to be more likely to seroconvert, which was hypothesized

due to the transfer of antibody-producing long-lived plasma cells from a seropositive donor lung [78]. It should be kept in mind that measles and mumps vaccines are live-attenuated and are therefore contra-indicated after lung transplantation

3.7. Varicella

Based on the studies reported in the literature, the varicella vaccine would offer some clinical protection as patients who were seropositive may still develop some form of herpes zoster.

Live attenuated Herpes Zoster vaccine was found to induce a strong humoral and cellular immune response in lung transplantation candidates [79], irrespective of underlying condition. The cell mediated response, assessed by in vitro induction of γ-interferon secreting T cells, was decreased after lung transplantation during the period of highest immunosuppression but returned in the period afterward [79].

3.8. Importance of other vaccines

Whilst waiting for the development and distribution of the COVID-19 vaccine, the possible protective properties of other vaccines toward SARS-CoV-2 was explored, following the rationale of 'trained immunity.' The trained immunity hypothesis suggests that live attenuated viruses such as those used in the MMR and BCG vaccines induce nonspecific innate memory immune cells that also function against non-related pathogens. Multiple published reviews on this matter have demonstrated a correlation between the administration of the BCG vaccine and (1) enhanced H1N1 antibody titers, (2) increased responsiveness toward hepatitis B vaccine, and (3) enhanced nonspecific T-helper 1 and T-helper 17 responses [80]. Furthermore, it has also been suggested that BCG vaccine may protect against respiratory syncytial virus, HPV, and herpes simplex virus [81]. Despite extensive research being done on the BCG vaccine, it is not included in the national vaccination program of most westernized countries. Hence, the use of an MMR vaccine was proposed to offer a form of protection against (severe) COVID-19. Currently, there are a number of ongoing clinical trials to study the potential benefit of the BCG vaccine against COVID-19 (registered as NCT04327206, NCT04414267, NCT04369794, NCT04350931 in clincialtrials.gov) [82–85].

In a preprint article by Pawlowski et al. [86], immunization records among 137,037 COVID-19 positive individuals were explored to analyze the association between past immunizations and infection rates. The results show statistically significant correlations between history of vaccination against poliomyelitis, *Haemophilus influenzae* type b, MMR, varicella, 13-valent pneumococcal conjugate, influenza, hepatitis A, and hepatitis B vaccines administered in the past 1, 2, and 5 years and decreased SARS-CoV-2 infection rates. In addition, recipients of the polio and *Haemophilus influenzae* type b vaccines generally demonstrate the lowest risk for SARS-CoV-2 infection. When matched by race, the 13-valent pneumococcal conjugate vaccine significantly decreases infection rates among the Afro American population. While these data may point toward a role of non-COVID-19 vaccines in offering some level of protection, potential biases should be considered, such as differences in socioeconomic status in vaccinated and nonvaccinated individuals, as well as the 'healthy user' selection bias.

4. COVID-19 vaccination for lung transplant recipients

When the first vaccines against COVID-19 were approved by the end of 2020, all countries were quick to develop vaccination schedules and setting priorities for specific groups because of limiting availability of vaccines. Most countries started with vaccinating the (vulnerable) elderly and essential health workers, followed by those with underlying medical problems or belonging to specific risk groups, and finally healthy adults. Recently, transplant patients have also been vaccinated, as many international societies and bodies recommend transplant patients to get the vaccine [87–92]. A COVID-19 Vaccine FAQ Sheet published by the American Society of Transplantation (AST) indicate that based on their expert opinion, the vaccines are unlikely to trigger rejection episodes and are unlikely to induce more severe side effects than in other at-risk groups [88]. In the Emergency Use Application for the Moderna, Pfizer/BioNTech, and Janssen/Johnson & Johnson vaccines, no transplant patients were included in the phase 3 trials with any of these vaccines. However, the data on vaccination of immunocompetent participants showed 94.1–95% and 66% efficacy in preventing COVID-19 infection by the Pfizer/BioNTech & Moderna and Janssen vaccine respectively. Based on previous vaccination guidelines, the AST advices to complete the vaccine series at least 2 weeks before transplantation or to start at least 1 month thereafter. Should patients receive a transplant only after one dose (of a two-dose series), the second dose should be administered at least 4 weeks after transplantation or until immunosuppressive therapy has been decreased.

Lung transplant patients have an impaired immune system due to their immunosuppressive medication. As described above, in a number of cases it has also been shown that lung transplant candidates and/or recipients may have impaired vaccination response, also marked by their rapidly decreasing antibody concentrations. In a small study, antibody response to SARS-CoV-2 was assessed by measuring IgG antibodies to the spike protein (anti-S1-IgG). The 2 lung transplant recipients in this study were hospitalized and received COVID-19 convalescent plasma. At a median of 98 days after their COVID-19 diagnosis, the two lung recipients and two other solid organ recipients failed to show an increase in IgG antibody levels, compared to the 14 other who did respond and had higher antibody levels. The authors conclude that solid organ transplant recipients may be able to produce a durable immune response toward SARS-CoV-2, but the administration of convalescent plasma (passive immunization) might mask or diminish the natural antibody response [93]. It should be noted that it was impossible to determine whether the lowered antibody response was due to impaired production or due to a more rapid turnover of produced antibodies. Currently, a clinical trial (NCT04852276) is in progress to analyze the immune response to COVID-19 vaccination in

individuals with and without immune deficiencies or dysregulations [94].

After the approval for the emergency use of the Pfizer/BioNTech and Moderna vaccines, 187 solid organ transplant recipients, of which 14% were lung transplantation patients, in the United States were recruited to undergo early vaccination in a first study of its kind [95]. Vaccination of solid organ transplant recipients with mRNA vaccines did not result in extraordinary adverse effects were found, however, a slightly higher frequency of fatigue, headache, and myalgias were reported in comparison to the general population [95]. No accelerated transplant rejection was seen during early follow up. During the H1N1 influenza pandemic, solid organ transplant recipients were vaccinated with H1N1 vaccine and tolerated it well [96]. Furthermore, a study analyzing the risk of organ rejection following seasonal trivalent inactivated influenza vaccines was not increased, as observed over three consecutive influenza seasons [97]. Inactivated viral vaccines (e.g. hepatitis A virus), live attenuated virus vaccines (e.g. MMR), subunit vaccines (e.g. *Streptococcus pneumoniae*), and viral-like particle vaccines (e.g. hepatitis B) have also been tolerated well in lung transplant patients [98].

As many more patients received their vaccination, it was soon evident that the majority of solid organ transplant recipients, including lung transplants, have impaired immune responses [99–108]. In a small study by Havlin et al. [99], none of the 12 lung transplant patients tested after two doses of the mRNA BNT162b2 vaccine developed anti-SARS-CoV-2 IgG. However, 4 out of the 12 did show a specific T cell response. In a larger study from Israel in 168 lung transplant recipients, just 18% had positive S-IgG titers within 3 weeks after the second vaccine dose [100]. Differences among vaccine types were also observed. Boyarsky et al. [107] observed that patients that received the Moderna vaccine were more likely to develop an antibody response as compared to those that received the Pfizer/BioNTech vaccine. This was confirmed by Narasimhan et al. [108], where they concluded that the Moderna vaccine evoked a 23-fold higher seropositivity rate than the Pfizer/BioNTech vaccine in lung transplant patients. Despite receiving both doses of the BNT162b2 mRNA vaccine, Basic-Jukic and Ivo [109] reported two cases of SARS-CoV-2 infection in renal transplant recipients; highlighting the issue surrounding suboptimal efficacy of vaccination in this specific population.

5. Conclusion

An adequate functioning of an individual's immune system is vital to resist and/or recover from COVID-19 and reduce risk of reinfection. Lung transplant patients are at a higher risk of developing severe symptoms and a fatal outcome due to their immunosuppressive medications and a compromised functioning of the transplanted lung. Indeed, in a recent overview it was shown that solid organ transplant recipients who contracted COVID-19 had a 30% higher risk of death or need for mechanical ventilation compared with matched controls [110].

COVID-19 vaccines therefore should be added to the recommended vaccination schedule for lung transplantation candidates and transplanted patients. For most vaccines where the immune response is studied, adequate humoral and cellular responses are found, at least in patients on the waiting list. It should be noted that for a number of recommended vaccines, no information on immunogenicity is available.

As for any other target group for (COVID-19) vaccination, for lung transplant patients the most important aspects of vaccination against COVID-19 are safety, efficacy, and durability. In the above sections it is shown that the vast majority of available vaccines can be safely administered to lung transplant patients. Live attenuated viral vaccines are contraindicated. None of the current COVID-19 vaccines are live-attenuated and therefore there is no safety concern to be expected. The first reports on efficacy of the vaccines and the durability of the immune response are now published. The antibody response to mRNA vaccines is severely impaired. Vaccine-associated allograft rejection has not been found after COVID-19 vaccination. In a series of 187 solid organ transplant patients which included 9 lung transplant patients, no cases of acute rejection were found after vaccination with COVID-19 mRNA vaccines [95].

In a Perspective in the Journal of Heart and Lung Transplantation March 2021 on COVID-19 vaccination in our transplant recipients, Aslam et al. correctly state: 'The time is now' [111]. It has to be added that responses should be carefully monitored, and additional doses may be needed.

6. Expert opinion

The obvious and ultimate aim of vaccination is to prevent infections, for lung transplant patients first and foremost preventing respiratory infections. Despite elaborate pre- and post-transplant vaccination, close clinical, bacteriological and virological monitoring and targeted treatment, infectious episodes remain a major cause for morbidity and mortality of lung transplant patients. Reasons for the high frequency of infectious episodes can be suboptimal efficacy of existing vaccines as well as infections for which no vaccines are available.

A major determinant of suboptimal efficacy of vaccination is the use of immunosuppressive drugs, which are necessary to prevent rejection. The primary series of vaccinations are administered during the screening phase for lung transplantation, when immunosuppressants are not given yet. The presented data show that memory responses are relative resistant to immunosuppressive drugs. Booster doses vaccine thus could still be effective after the transplantation, under an immunosuppressive regimen.

The COVID-19 pandemic has triggered an immediate, joint, and huge investment of medical, academic and pharmaceutical research teams aimed at the development of SARS-Cov-2 vaccines. These global efforts have resulted in a number of highly effective vaccines which became available within one year after the outbreak of the disease and are currently implemented. It has been anticipated that lung transplant patients, a special risk-group because of a transplanted organ being the major target for SARS-CoV-2, could benefit from these vaccines. The first available data do indicate that

mRNA vaccines induce only a limited antibody response. Important research questions now are: what is the optimal vaccine schedule and vaccine type for lung transplant recipients? What is the optimal vaccination strategy for lung transplant recipients; e.g. do they require higher-dose vaccine? Would additional booster doses be needed? What is the optimal timing for vaccination in lung transplant candidates and recipients? Are there (any) immune status markers that can predict serologic response to SARS-CoV-2 vaccines? Are serologic responses predictive of clinical protection against (severe) COVID-19? Some of these questions have been discussed by Scanlon and colleagues [112] in the context of systems vaccinology for solid organ transplant recipients.

Lung transplant patients also would benefit from protection against any other respiratory infection. The recommended vaccines for these patients therefore include pneumococcal and influenza vaccines, amongst others. There is a range of respiratory viruses causing mild infections in the general population, and for which no vaccines exist to data. These include circulating corona viruses (229E, HKU1, NL63, OC43), rhinoviruses, adenoviruses and others. For lung transplant patients any of these viruses can cause significant morbidity, with impact for the allograft [113]. The technology successfully used for the SARS-CoV-2 mRNA vaccines can also be applied for other respiratory viruses, and thus provide a wider protection for this patient category. It is therefore hope that the international collaborations which have been so successful in development of SARS-CoV-2 vaccines will use the momentum to take these next steps.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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