Review



# VACCINATON POLICIES IN SOLID ORGAN TRANSPLANT ADULT CANDIDATES AND RECIPIENTS

Mauro Viganò *, Marta Beretta, Marta Lepore, Raffaele Abete, Simone Vasilij Benatti, Maria Vittoria Grassini, Stefania Camagni, Greta Chiodini, Simone Vargiu, Claudia Vittori, Marco Iachini, Amedeo Terzi, Flavia Neri, Domenico Pinelli, Fabiano Di Marco, Piero Ruggenenti, Marco Rizzi, Michele Colledan, Stefano Fagiuoli

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*Review*

# Vaccinaton Policies in Solid Organ Transplant Adult Candidates and Recipients

**Mauro Viganò [1,*], Marta Beretta [2], Marta Lepore [3], Raffaele Abete [4], Simone Vasilij Benatti [5] Maria Vittoria Grassini [1,6], Stefania Camagni [7], Greta Chiodini [2], Simone Vargiu [2], Claudia Vittori [4], Marco Iachini [3], Amedeo Terzi [8], Flavia Neri [7], Domenico Pinelli [7], Fabiano Di Marco [2,9], Piero Ruggenenti [3,10], Marco Rizzi [5], Michele Colledan [7] and Stefano Fagiuoli [1,10]**

[1] Gastroenterology Hepatology and Transplantation Unit, ASST Papa Giovanni XXIII, Bergamo, Italy; mvittoriagrassini@gmail.com (M.V.G.); sfagiuoli@asst-pg23.it (S.F.)
[2] Pulmonary Medicine Unit, ASST Papa Giovanni XXIII, Bergamo, Italy; m.beretta@asst-pg23.it (M.B.); greta.chiodini@unimi.it (G.C.); simone.vargiu@unimi.it (S.V.); fdimarco@asst-pg23.it (F.D.M.)
[3] Unit of Nephrology and Dialysis, ASST Papa Giovanni XXIII, Bergamo, Italy; mlepore@asst-pg23.it (M.L.); m.iachini1@campus.unimib.it (M.I.); pruggenenti@asst-pg23.it (P.R.)
[4] Cardiology Division, ASST Papa Giovanni XXIII, Bergamo, Italy; rabete@asst-pg23.it (R.A.); cvittori@asst-pg23.it (C.V.)
[5] Infectious Diseases Unit, ASST Papa Giovanni XXII, Bergamo, Italy; sbenatti@asst-pg23.it (S.V.B.); mrizzi@asst-pg23.it (M.R.)
[6] Section of Gastroenterology & Hepatology, Department of Health Promotion Sciences Maternal and Infant Care, Internal Medicine and Medical Specialties, PROMISE, University of Palermo, Palermo, Italy
[7] Department of Organ Failure and Transplantation, ASST Papa Giovanni XXIII, Bergamo, Italy; scamagni@asst-pg23.it (S.C.); fneri@asst-pg23.it (F.N.); dpinelli@asst-pg23.it (D.P.); mcolledan@asst-pg23.it (M.C.)
[8] Cardiothoracic Department, ASST Papa Giovanni XXII, Bergamo, Italy; aterzi@asst-pg23.it
[9] Department of Health Sciences, University of Milan, Milan, Italy
[10] Department of Renal Medicine, Clinical Research Centre for Rare Diseases "Aldo e Cele Daccò": Institute of Pharmacologic Research "Mario Negri IRCCS", Ranica, Bergamo, Italy
[11] Department of Medicine, University of Milan Bicocca, Milan, Italy
* Correspondence: mvigano@asst-pg23.it; Tel: +39 0352674259 Fax: +39-035-2674964

**Abstract:** Prevention of infections is crucial in solid organ transplant (SOT) candidates and recipients. These patients are exposed to an increased infectious risk due to previous organ insufficiency and to pharmacologic immunosuppression. Besides infectious-related morbidity and mortality, this vulnerable group of patients is also exposed to the risk of acute decompensation and organ rejection or failure in the pre- and post-transplant period respectively, since antimicrobial treatments are less effective than in the immunocompetent patients. Vaccination represents a major preventive measure against specific infectious risks in this population but as responses to vaccines are reduced, especially in the early post-transplant period or after treatment for rejection, an optimal vaccination status should be obtained prior to transplantation whenever possible. This review reports the currently available data on the indications and modalities of vaccination in SOT adult candidates and recipients.

**Keywords:** solid organ transplantation; vaccination; chronic diseases; liver; lungs; heart; kidney; infections; prevention

## 1. Introduction

Immunosuppression is the major predisposing factor for the development of infections, influencing both their incidence and severity. Immunodepressed population includes not only patients treated with immunosuppressive (IS) drugs for solid organ transplant (SOT), but also individuals with end-stage diseases. These patients bear a remarkable risk of infections due to

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immune system dysfunction and dysregulation of innate and adaptive immunity [1–7]. In particular, in patients with kidney and liver failure, expression of toll-like receptors (TLR), and B and T lymphocytes proliferation may be decreased, response to antigenic stimuli is impaired, capacity of phagocytosis is limited and apoptosis is increased. Moreover, there is an impairment of leukocyte and endothelial function and a low-grade inflammation with overproduction of inflammatory cytokines inducing oxidative stress. Additional contributors to the risk of infection in all these SOT candidates could be the presence of IS related co-morbidities and diabetes mellitus.

Among the different approaches for preventing infections, vaccines are paramount, especially in the perspective of a future SOT, when IS will boost the infectious risk and further limit the immune system responsiveness. On the other hand, due to the compromised immune response, serological response to vaccines in the end-stage of most chronic diseases may not be as optimal as in healthy controls [8,9]. As vaccines demonstrate superior immunogenicity when given earlier in the course of any inflammatory or chronic disease, even if the definition of most of the schedules is still uncertain, the best strategy is to verify as soon as possible the vaccination status and the response to previous vaccines in all patients with advanced organ disease to resolve any possible immunity gaps.

However, immunization in the setting of SOT candidates and recipients raises several issues as recommended vaccination schedules rely on few immunogenicity data without clinical efficacy and effectiveness trials designed for this specific population

- dynamics of immunosuppression makes timing of immunization challenging
- live attenuated vaccines (LAV) are contraindicated after SOT whereas inactivated vaccines have been proven safe and not significantly associated with rejection
- vaccines tolerance is poorly known in end-stage chronic diseases.

The aim of this review is to assess all the main indications to active immunization in adult patients with advanced heart, kidney, liver and lungs disease and in SOT recipients, evaluating the most relevant vaccination policies in this setting of population.

## 2. Heart Transplant Candidates

All heart transplant (HT) candidates should undergo serological testing for the most common viruses: Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Varicella Zoster Virus (VZV), Herpes Simplex Virus (HSV 1-2), Hepatitis B Virus (HBV), Hepatitis A Virus (HAV), Human Immunodeficiency Virus (HIV), Measles Mumps and Rubella (MMR) and SARS-CoV-2, and vaccination, whenever available, is recommended in non-immunized patients according to guidelines [10,11]. Before HT, candidates should be vaccinated with recombinant vaccine against HBV and mRNA vaccines against SARS-CoV-2, influenza, tetanus, HAV, meningococcus, pneumococcus. Effective protection against HBV may allow a broader use of hepatitis core antibody (anti-HBc) positive grafts.

All vaccinations should be completed preferably one month before HT, since during this period the immune response to the vaccine may vary depending on the patient's clinical conditions (Table 1).

**Table 1.** Vaccines recommended in heart transplant (HT) candidates and recipients.

| | **Pre transplant** | | **Post transplant** | |
|---|---|---|---|---|
| | **Timing** | **Schedule** | **Timing** | **Schedule** |
| Influenza | Each winter | Single dose | 3-6 months after HT | Single dose |
| *Streptococcus pneumoniae* | PCV e PPV prior HT | 1-8 week | 3-6 months after HT | 1-8week |
| HBV | 2 doses, 1month prior HT | 0-1-6 months | 3-6 months after HT | Last doses also after HT |

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| | | | | |
|---|---|---|---|---|
| HAV | 1 dose prior HT | 0-6 months | 3-6 months after HT | Second dose also after HT |
| SARS-CoV-2 | 2 doses, 1month prior HT | 0-1 month | 3-6 months after HT | 3 doses also after HT |
| HZV | completed 1month prior HT | Two doses 0-2 months | 3-6 months after HT | Two doses 0-2 months |
| HPV§ | - | 0-2-6 months | 3-6 months after HT | Last dose also after HT |
| Tdap/Td, *Haemophilus influenzae* type B | at least 2 weeks prior HT | as general population | 3-6 months after HT | as general population |
| Rabies | at least 2 weeks prior HT | as general population | 3-6 months after HT | 0, 7, 21 days |
| Tetanus | 1 month prior HT | if never vaccinated 0-2-6/12 months, otherwise 1 booster dose | 3-6 months after HT | - |

HAV, hepatitis A virus; HBV, hepatitis B; HPV, human papilloma virus; HZV, herpes zoster virus; MMR, measles mumps and rubella; TDap, tetanus toxoid, reduced diphtheria toxoid, acellular pertussis; Td, tetanus diphtheria; BCG, bacille Calmette-Guerin; §<50 years, MMR in non-immune pre-HT patients but not recommended in post-HT patients. Yellow fever, Polio, type B Rotavirus, BCG, Cholera are not recommended in HT candidates and recipients.

## 3. Heart Transplant Recipients

After HT, vaccinations should be avoided for the first 3-6 months, during which patients should lead a reduced social and work life [12]. Between the 9th and 12th months post-HT, patients can return to work and wider social engagements. Depending on medical conditions, patients can now be vaccinated. The immune response is not predictable, but it is certainly reduced, especially in patients undergoing aggressive IS regimens. After HT, LAV are not recommended. The use of mRNA technology vaccines is possible, but efficacy may be reduced [13] (Table 1).

### *3.1. Influenza*

Vaccinations against influenza is recommended on a yearly basis. Influenza vaccination with inactivated virus is safe and effective without increasing the risk of either rejection episodes or infections, because it does not induce allo-sensitization. However, response in transplant recipients is reported to be lower compared with healthy subjects [14–16]. The less expensive influenza vaccines without adjuvants can provide similar efficacy in protecting HT recipients compared to those with adjuvants [17].

### *3.2. Streptococcus pneumoniae*

Pneumococcal vaccination is safe and effective in HT recipients under IS as in healthy individuals.

### *3.3. HBV*

Vaccination against HBV is necessary in HT because they may experience more severe and rapid progression of HBV infection, as well as reactivation of latent infection under IS treatment [18].

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*3.4. SARS-CoV-2*

A case-control study in 436 HT recipients, 106 of which had SARS-CoV-2 infection, showed that patients with coronavirus disease 2019 (COVID-19) are at greater risk of severe infection and death compared with immunocompetent individuals, and that SARS-CoV-2 vaccination was associated with fewer complications, hospitalizations and deaths [19]. Even if the ideal timing of vaccination is still undefined, the International Society for Heart and Lung Transplantation (ISHLT) COVID-19 Task Force in the post-HT, advises in delaying vaccination at least 1 month from HT and at least 3 months from the use of T-cell depleting agents (i.e., anti-thymocyte globulin) or specific B-cell depletion agents (i.e., Rituximab); vaccination should be delayed 3 months in patients that received monoclonal antibodies for COVID-19. All the currently available vaccines against SARS-CoV-2 are acceptable in HT recipients [20]. Based on current evidence, a third dose of mRNA vaccine is recommended for patients who have previously completed a series of 2 doses of mRNA vaccines. The repeated use of booster vaccines should be supported by additional evidence. Reported cases of allograft rejection post SARS-CoV-2 vaccination or infection should not discourage vaccinating this population. A meta-analysis conducted by Alhumaid et al. reported only one cellular rejection episode among HT recipients, and that the protective benefits of SARS-CoV-2 vaccination far outweighs the risks [21].

*3.5. Other vaccinations*

Traveling to high-risk destinations is not recommended, but travelling in these areas after the first 2 years post-HT in patients without complications is not contraindicated. Specific travel vaccinations are often based on LAV which are contraindicated in HT recipients and therefore such patients should receive information on the most appropriate health-related behaviours to be adopted during travel. HT recipients aged ≥ 19 years should be vaccinated with 2 doses of recombinant zoster vaccine (RZV) for the prevention of herpes zoster and related complications [22].

## 4. Kidney Transplant Candidates

All-stage chronic kidney disease (CKD) patients should receive all routinely recommended vaccines according to their age group and associated risk factors [8]. There is no consensus on the ideal CKD stage to administer vaccines, since too early administration might lead to "unnecessary" immunizations, while administration in advanced stages may be less immunogenic [9]. As a general recommendation, appropriate complete vaccination should be performed in the pre-kidney transplant (KT) period, at least 4 weeks prior to transplant for LAV and at least 2 weeks prior to transplant for inactivated vaccines [2,12]. Since LAV are contraindicated after KT, it is mandatory to assess baseline serologic status for measles, mumps and rubella (MMR) in KT candidates, and to vaccine non-immune patients. If seroconversion does not occur, the dose can be repeated once [2,23]. Table 2 reported the vaccines recommendations in CKD patients and KT recipients.

**Table 2.** Vaccines recommendations in chronic kidney disease (CKD) patients and kidney transplant (KT) recipients.

| | **Pre transplant** | | **Post transplant** | |
|---|---|---|---|---|
| | **Timing** | **Schedule** | **Timing** | **Schedule** |
| Influenza | Each winter, at least 2 weeks prior KT | Single dose | 3-6 months after KT (as early as 1 month after KT in case of outbreak but avoiding LAV) | Single dose |
| *Streptococcus pneumoniae* | at least 2 weeks prior KT | PCV13 followed by PPSV23 8 weeks later | 3-6 months after KT | PCV13 followed by PPSV23 8 weeks later |
| HBV | at least 2 weeks prior KT | 0,1, and 2 and/or 6 months depending on type of vaccine | 3-6 months after KT | 0,1 and 6 months |

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| | | | | |
|---|---|---|---|---|
| HAV | at least 2 weeks prior KT | as general population | 3-6 months after KT | as general population |
| SARS-CoV-2 | at least 2 weeks prior KT | as general population | 3-6 months after KT | as general population |
| HZV | 2 weeks for RZV | as general population | HZV not recommended, RZV, 3- 6 months after KT | 2 doses at least 8 weeks apart |
| Meningococcal | at least 2 weeks prior KT | as general population | 3-6 months after KT | as general population |
| HPV | at least 2 weeks prior KT | as general population | 3-6 months after KT | 0,2,6 months, nonavalent vaccine up to 45 years |
| MMR | at least 4weeks pre-KT | as general population | not recommended | - |
| Tetanus, Tdap/Td, Haemophilus influenza type B | at least 2 weeks prior KT | as general population | 3-6 months after KT | as general population |
| Yellow fever | at least 4weeks pre-KT | as general population, in case of travel to at-risk areas | not recommended | - |
| Polio | at least 4weeks pre-KT | as general population | Inactivated, 3-6 months after KT | as general population |
| Rabies | at least 2 weeks prior KT | as general population | 3-6 months after KT | 0, 7, 21 days |
| Rotavirus, BCG, Smallpox, Cholera | at least 4weeks pre-KT | as general population | not recommended | - |

KT, kidney transplant; CKD, chronic kidney disease; LAV, live attenuated vaccines; LZV, live-attenuated zoster vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; RZV, recombinant zoster vaccine; HAV, hepatitis A virus; HBV, hepatitis B; HPV, human papilloma virus; HZV, herpes zoster virus; MMR, measles mumps and rubella; Tdap, tetanus toxoid, reduced diphtheria toxoid, acellular pertussis; Td, tetanus diphtheria; BCG, Bacille Calmette-Guerin.

### *4.1. Influenza*

Inactivated influenza vaccine should be administered annually since infection exposes CKD patients to considerable morbidity and mortality [2–4,8]. Reported rates of seroconversion in dialysis patients are lower than in healthy controls and ranges from 33 to 80%, but vaccine administration is associated with decreased mortality and hospitalization [8]. Potential ways to increase efficacy include increased dose (especially in >65 years), booster doses and adjuvants [3].

### *4.2. Streptococcus pneumoniae*

Pneumonia is a common infection in CKD patients, associated with increased morbidity and mortality, and is frequently caused by *Streptococcus pneumoniae*. Therefore, pneumococcal immunization is recommended for CKD patients [8,24]. Dosing schedule in naive patients contemplates the 13-valent pneumococcal conjugate vaccine that induce a T-cell-dependent response, stimulating the production of antibodies with higher affinity and also leading to the formation of

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memory B cells (PCV13), followed by the 23-valent pneumococcal polysaccharide vaccine that induces a T-cell-independent response (PPSV23) at least 8 weeks later. Patients who previously received PPSV23, should be given PCV13 at least one year later. A PPSV23 booster should be administered 5 years after initial PPSV23 in subjects <65 years [25]. Evidence on pneumococcal vaccines efficacy in CKD patients is limited, however both vaccines are immunogenic in patients on dialysis (PCV13 more than PPSV23), with antibody titre waning over time [3,8,24]. Co-administration with inactivated influenza vaccine may have synergistic positive effects [2].

### *4.3. HBV*

HBV infection still represent a risk for haemodialysis patients, who are exposed to blood-born pathogens, especially in endemic regions. HBV vaccine therefore represent an important protective measure for patients and for the staff who cares for them [8]. One of the major challenges is due to a poor serologic response to HBV vaccine in this population, particularly when already on dialysis at the time of vaccination: a seroconversion rate of 44% in case of end-stage renal disease (ESRD) vs 90% in CKD stage 3/4 vs 96% in healthy controls is reported [26].

Classical vaccination schedule is based on 3 doses of recombinant vaccine at time 0, 1 and 6 months. Repeating the full vaccination schedule can be attempted in non-responders, while a booster dose is recommended when anti hepatitis B surface antigen (anti-HBs) titre declines below <10 mIU/mL at annual periodic monitoring [2,3,8,24]. Several methods have been evaluated to enhance vaccine response in CKD patients, like high dose (40 ug vs 20 ug), intra-dermal administration, novel epitopes and adjuvant [2,3,26].

### *4.4. SARS-CoV-2*

CKD patients, especially those on dialysis, are at increased risk of SARS-CoV-2 infection, hospitalization and mortality [27–29]. Available data suggest a suboptimal humoral response to vaccines in comparison with general population, particularly in dialysis patients and with adenoviral vectors respect to mRNA vaccines [27]. More recent observations suggest a significant increase in antibody levels after a third vaccine dose [27,30,31].

Since a gradual waning of antibody levels has been described over time, the administration of a booster dose of vaccine against SARS-CoV-2 4-6 months after primary series has to be encouraged in all patients on dialysis. Further data on long-term outcomes and vaccine efficacy are needed to adopt the best vaccination strategy, since also cellular response, required for an optimal clinical protection, seems to be inferior in dialysis population compared to controls [32].

### *4.5. Herpes Zoster Virus*

CKD patients have higher incidence of Herpes Zoster Virus (HZV) than general population, and it has been suggested that HZV infection can promote renal function deterioration [3,8]. The two currently available anti HZV vaccines, the live-attenuated and the inactivated recombinant, can be both administered in CKD patients, although the recombinant one is preferred due to greater efficacy and long-lasting immunity [3,8]. Vaccination within 2 years of starting dialysis was associated with greater protection [3].

### *4.6. Other vaccinations*

Patients submitted to splenectomy or for whom therapy with eculizumab is expected (before or after transplant), should receive meningococcal vaccine with 2 doses of quadrivalent vaccine (against serogroups A, C, Y and W) and 2 doses of serogroup B vaccine [24]. CKD patients should receive usual routine immunizations, such as *Tetanus-Diphtheria* (Td) booster every 10 years (or earlier in the setting of wound care) or *Tetanus-Diphtheria-Acellular Pertussis* (TDaP) if they did not receive a previous vaccine as a child [2]. Existing data suggest a lower tetanus vaccine immunogenicity in case of renal diseases when compared to healthy individuals [33].

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Since it has been described that KT boys and girls have a decreased response to Human Papillomavirus (HPV) vaccination compared to CKD and dialysis patients, it is important to advocate for HPV immunization prior to KT [34].

In case of travel to at-risk regions, specific vaccinations, i.e., HAV, yellow fever, cholera, typhoid, should be administered according to usual recommendations. Safety and efficacy data are generally not available. If a travel to yellow fever zones is expected after KT, vaccine should be considered at least one month before transplantation [24].

## 5. Kidney Transplant Recipients

An optimal timing for vaccines administration after KT has not been established, but most recommendations agree to wait 3 to 6 months after transplant or treatment for rejection to vaccinate patients [8,9,24]. LAV, such as MMR, HZV and yellow fever are contraindicated in the post-KT period because of the risk of viral replication, while inactivated vaccines revealed to be safe and effective and can be administered without significant risk of rejection [8].

### *5.1. Influenza*

Annual administration of one of the inactivated vaccine formulations (quadrivalent or trivalent) is strongly recommended [3]. If a community outbreak of infection occurs before the third month after KT, anticipation of influenza vaccine, as early as one month after transplant should be considered [3,8,9,24,35]. KT recipients treated with a daily dose ≥2 g of mycophenolate mofetil (MMF) and >65 years have shown a reduced humoral response to vaccination [8]. Different approaches to improve response rates have been tested, such as repeating vaccination after 4 to 8 weeks or administering a higher dose of antigen [2,3,8]. The latter strategy has been associated with increased immunogenicyty and is generally recommended in patients >65 years [2,3,8,24].

### *5.2. Streptococcus pneumoniae*

Immunization with PCV13 followed PPSV23 at least 8 weeks later should be given to all KT recipients. Repeating PCV13 administration may be considered in patients >65 years [3,8,9]. Data on the response to PCV13 followed by PPSV23 in KT recipients are not available in the literature [9]. Available heterogeneous data, using various regimen and 7-valent conjugate vaccine, showed a serological response not significantly different from that of general population, but with lower antibody titres and a faster decline [36].

### *5.3. HBV*

Thanks to the policy of universally vaccinate haemodialysis patients, the majority of KT recipients should have been immunized before KT [9]. The immunological status by dosing anti-HBs titres should be periodically assessed after KT, especially in case of ongoing risk for HBV exposure or traveling to high-risk area [35]. Revaccination can be considered in non-immune patients or in those with declining immunity (anti-HBs <10 mIU/mL) [35]. Response rates after vaccine administration for HBV in post-transplantation period varies greatly, titres decline more rapidly, and booster doses produce suboptimal responses [37].

### *5.4. SARS-CoV-2*

Available data suggest a significant lower vaccine response in KT recipients despite additional booster doses, warranting an augmented adherence of patients to protective measures and the need for alternative strategies to prevent severe infection, like the use of monoclonal antibodies or antiviral therapies [38].

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*5.5. HZV*

KT recipients are exposed to a high risk of HZV infection and related complications. The recombinant adjuvanted inactivated varicella zoster vaccine should be given to all KT recipients, ideally 6 to 12 months after transplantation [8,9]. Available data show the vaccine to be safe and immunogenic after two doses compared to placebo [39].

*5.6. Other vaccinations*

Vaccination against meningococcal disease in KT patients deserves a special consideration in those scheduled to receive eculizumab, whether for prevention of graft rejection or for treatment of atypical haemolytic-uremic syndrome. Immunization program should include vaccines against serotype B and against serotypes A, C, Y, and W, and optimal timing should be at least two weeks before initiation of eculizumab therapy. Unfortunately, responses to vaccines are generally poor, even after a repeated dose and nearly 50% developed protective antibodies, [8] and antibiotic prophylaxis against Neisseria meningitides is usually provided [8,9,24]. Other safe and recommended vaccination in post-KT (according to previous immunological status) may include HAV, HPV, *Tetanus, Diphtheria, Pertussis*.

KT recipients should be advised about the potential risks of visiting regions which require special vaccination. LAV, as for yellow fever, oral *Salmonella typhi*, and *Cholera*, are not recommended, while inactivated vaccines, i.e., intramuscular *Salmonella typhi, Japanese encephalitis*, Tick Borne Encephalitis and *Rabies* are safe and strongly recommended according to regional indications [8,9,24].

In order to ensure an adequate protection from infections, vaccination strategies are crucial also in close contacts: family members, health care workers, and eventual pets. This category of people should receive all recommended immunization, especially annual influenza vaccine and SARS-CoV-2 immunization. Live oral polio is contraindicated in close contacts due to the risk of transmission [9,37]. For most LAV no special precautions are required, but some cases do. In particular, KT patients should be isolated from vaccines recipients presenting rash, while other precaution involve risk of virus shedding in the stool for one week after live attenuated cholera vaccine, and for two to four weeks after rotavirus vaccines [8,9,37].

## 6. Liver Transplant Candidates

Current guidelines recommend that in chronic liver disease vaccines should be administered as soon as possible due to a higher immunogenicity in a prior phase of the natural course of the disease. For the same reason, it's better to vaccinate patients before liver transplant (LT), prior to administering high levels-IS regimes [40,41]. Particularly, inactivated vaccines should be used at least two weeks prior to IS while live vaccines should be given ≥ 4 weeks prior to IS and should be avoided within two weeks of the start of these drugs regimens [10]. Table 3 reported the vaccines recommendations in chronic liver disease (CLD) patients and in LT recipients.

**Table 3.** Vaccines recommendations in chronic liver disease and in liver transplant (LT) recipients.

| | **Pre transplant** | | **Post transplant** | |
|---|---|---|---|---|
| | **Timing** | **Schedule** | **Timing** | **Schedule** |
| Influenza | inactivated, at least 2 weeks prior LT | Single dose | inactivated, 1 month after LT | Single dose |
| *Streptococcus pneumoniae* | at least 2 weeks prior LT | Not previously vaccinated: one dose of PCV 13 followed at least 8 weeks by one dose of PPV23. Vaccinated with PPV23: one dose of PCV 13 at least 1 year after PPV23 and one dose of PPV23 at least 5 years after the first dose | 3-6 months after LT | PCV13 followed by PPSV23 8 weeks later |

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| | | | | |
|---|---|---|---|---|
| HBV | at least 2 weeks prior LT | 0,1, and 6 months | 3-6 months after LT | 0,1, and 6 months |
| HAV | at least 2 weeks prior LT | Two doses six months apart or if combined with HBV vaccine 3 doses over a six months period | 3-6 months after LT | Two doses six months apart or if combined with HBV vaccine 3 doses over a six months period |
| SARS-CoV-2 | at least 2 weeks prior LT | as general population | 3-6 months after KT | as general population |
| HZV | at least 4 weeks pre-LT | Two LAV doses 4 weeks apart for varicella vaccine; one dose for zoster in HZV IgG positive candidates | not recommended | - |
| Meningococcal, HPV | at least 2 weeks prior LT | as general population | 3-6 months after LT | as general population |
| MMR | at least 4weeks pre-LT | as general population | 3-6 months after LT | as general population |
| Tetanus, Tdap/Td, *Haemophilus influenza* type B, Rabies | at least 2 weeks prior LT | as general population | 3-6 months after LT | as general population |
| Yellow fever | at least 4weeks pre-LT | as general population | not recommended | - |
| Polio | at least 4weeks pre-LT | as general population | inactivated, 3-6 months after LT | as general population |
| Rotavirus, BCG, Smallpox, Cholera | at least 4weeks pre-LT | as general population | not recommended | - |

LAV, live attenuated vaccines; LZV, live-attenuated zoster vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; RZV, recombinant zoster vaccine; HAV, hepatitis A virus; HBV, hepatitis B; HPV, human papilloma virus; HZV, herpes zoster virus; MMR, measles mumps and rubella; Tdap, tetanus toxoid, reduced diphtheria toxoid, acellular pertussis; Td, tetanus diphtheria; BCG, Bacille Calmette-Guerin.

### *6.1. Influenza*

Many studies demonstrate the safety and tolerability of influenza virus vaccination in cirrhotic patients with the reduction of episodes of decompensation. The dose recommended is one dose of the tetravalent inactivated vaccine every year while the LAV can be administered before LT, with a temporary contraindication to transplant for two weeks after vaccination [42,43].

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*6.2. Streptococcus pneumoniae*

The pneumococcal invasive disease is one of the most important causes of hospitalization and mortality in patients with advanced chronic liver disease. Adults with chronic liver disease and LT candidates should receive a dose of PPSV23 if they have never received a prior dose. When both PPSV23 and PCV13 are indicated, PCV13 should be administered 8 weeks prior to PPSV23. If the patient was already vaccinated for PPV23 it is recommended the injection of a dose of PCV13 at least a year after the PPV23 injection and another dose of PPV23 at least 5 years after the first dose. If the patient is already vaccinated by PCV13 and PPV23, one more dose of PPV23 may be administered at least 5 years after the previous one. A small study evaluating serological response of 45 candidates for LT receiving PPSV23 suggested that this vaccine was not very effective after LT [44].

*6.3. HBV*

Patients with chronic liver disease have a global lower immune response and this is established for HBV vaccine too. After HBV vaccine the seroconversion rate was 94% vs 39% in patients with steatosis and cirrhosis, respectively [45]. A prospective study in chronic HCV infected patients undergoing 3 doses at 0, 30 and 180 days has shown 38% vs 85% seroprotection rates in CLD or cirrhotic patients compared to healthy subjects [46]. HBV vaccination is recommended in all anti-HBs negative CLD patients. If a post-vaccination anti-HBs concentration of ≥ 10 mIU/mL is not attained, a second 3-dose series of HBV vaccine should be administered using standard or high doses [10].

*6.4. SARS-CoV2*

Patients with advanced liver disease have high risk of acute decompensation and liver failure with increased mortality because of SARS-CoV-2 infection and its sequelae [47]. For these reasons, despite long-term safety data are not available, EASL guidelines suggest mRNA vaccines (Pfizer-BioNTech® and Moderna® with a schedule of two doses 21 and 28 days apart, respectively) to all patients with advanced cirrhosis, liver decompensation and hepatobiliary cancers [48].

*6.5. HZV*

Two doses of RZV for the prevention of herpes zoster and related complications are recommended for adults aged ≥ 19 years who are or will be immunodeficient or immunosuppressed because of disease or therapy [10].

*6.6. Other vaccinations*

In the setting of an advanced chronic liver failure, HAV infection can brings to acute decompensation and increased mortality. For this reason, vaccination is recommended in all cirrhotic patients and, due to a significantly major immune response in the earlier phases of the disease, it should be administered as soon as possible [49].

Data on HPV infections in cirrhotic patient are lacking. HPV vaccine is a non-infectious recombinant vaccine prepared from purified virus-like particles of the L1 proteins of HPV and it is recommended in general population before viral exposure. The immunization protocols in LT candidates should follow the current guidelines:

- HPV vaccination is recommended at age 11 or 12 years through age 26 years for "naïve" patients
- For adults aged 27-45 years, HPV vaccination can be administered on the basis of patient's benefit, since most of people in this age range could have been already exposed to the virus [50]
- In patients who have already received 2 doses of HPV at 12 years of age it is not necessary to do other doses, instead if the SOT candidate has never been vaccinated 3 doses are recommended (0-2-6 months).

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## 7. Liver Transplant Recipients

### *7.1. Influenza*

Influenza vaccine in post LT recipients usually reduce disease severity [51]. The recommended schedule is one dose of the tetravalent inactivated vaccine once a year, while the LAV should not be used after transplantation [52]. A study comparing the high- and standard-dose of the influenza vaccines in 172 SOT recipients has shown seroconversion in 79% and 56% respectively in SOT recipients [53].

### *7.2. Streptococcus pneumoniae*

If the transplant recipient is naïve for PCV13/PPSV23 vaccines before LT, vaccination should be considered 3 to 6 months after LT. PPSV23 should be administered ≥ 8 weeks after PCV13 [10].

### *7.3. HBV*

HBV vaccine is recommended in all patients who didn't receive previously HBV immunization and the schedule is a 3-high dose at 0, 3 and 6 months, 2 to 6 months after LT [10]. A study conducted in 140 LT recipients reported a 40% response rate to HBV vaccine with however a rapid decline of antibodies titres probably due to immunosuppression [54].

### *7.4. SARS-CoV-2*

The current recommendation is to vaccinate as soon as possible before starting IS because the immunogenicity and efficacy could be lower in transplanted patients. A prospective study evaluating 658 SOT recipients receiving 2 doses of SARS-CoV-2 mRNA vaccine showed that 15% of them had measurable serum antibody levels after 2 doses, 46% had no response after dose 1 or dose 2; 39% had no response after dose 1 but subsequent developed measurable serum antibody levels after dose 2 [13]. Another study in 80 LT recipients receiving 2 doses of SARS-CoV-2 mRNA vaccine showed that only 47% of LT recipients developed antibodies vs 100% of healthy controls, and that in LT recipients with a measurable serology, mean SARS-CoV-2 IgG titres were lower compared to the healthy controls: 95 vs 200 AU/mL, respectively [55]. A study conducted in Germany compared 24 LT recipients to 19 healthy controls who received up to four doses of an mRNA vaccine for SARS-CoV-2 infection. Even if LT recipients had significantly lower levels of spike-specific IgG after three mRNA vaccine doses compared to the control group, most of them showed an overall robust humoral and cellular memory response [56]. About additional booster doses, they have to be administered on individual immune response for a possible personal benefit.

### *7.5. HZV*

Two doses of RZV, for the prevention of herpes zoster and related complications, are recommended in adults aged ≥19 years who are or will be immunodeficient or immunosuppressed because of disease or therapy [22].

### *7.6. Other vaccinations*

The antibody response after HAV vaccination in post LT period have shown a seroconversion in 41% of the patients after the primary dose and a response rate of 97% of the patients receiving the secondary dose, in line with healthy controls [57].

In LT recipients there is an increased risk of HPV-associated cancers of the anogenital area and oropharynx [58]. Due to a consistent increase of cervical neoplasia and invasive cervical cancer it's mandatory a long-term surveillance and treatment for a continued risk long after LT, accentuating the need for screening throughout a woman's lifetime. The dose recommended for immunocompromised persons is a three-dose series at 0, 2 and 6 months.

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## 8. Lung Transplant Candidates

Lung transplant (Lu-T) candidates are at increased risk of infectious complications that lead to substantial morbidity and mortality. In order to improve survival and quality of life, infections in such patients should be prevented by vaccination (Table 4). The vaccination status must be assessed beforehand and Lu-T candidates should be immunized as early as possible to optimize protection against vaccine-preventable illness, because vaccine responses are reduced after transplantation, due to the IS therapy. Patients waitlisted for Lu-T should follow the indication for vaccination of the guidelines for SOT candidates and recipients, published in 2013 by the Infectious Diseases Society of America (IDSA) [10]. In healthy adults, vaccines induce a humoral and T-cell-mediated immune response and offer clinical protection against the pathogen, while in Lu-T candidates and recipients the ability to mount adequate immune responses may be compromised. Therefore, it is still uncertain whether they offer a proper clinical protection.

**Table 4.** Vaccines recommendations in lung transplant (Lu-T) candidates and recipients.

| | **Pre transplant** | | **Post transplant** | |
|---|---|---|---|---|
| | **Timing** | **Schedule** | **Timing** | **Schedule** |
| Influenza | inactivated, at least 2 weeks prior Lu-T | Single dose | inactivated, 1 month after Lu-T | Single dose |
| *Streptococcus pneumoniae* | at least 2 weeks prior Lu-T | A single dose of conjugate vaccine and a dose of polysaccaride vaccine at least 8 weeks after. A second dose can be administred after 5 years | 3-6 months after Lu-T | same as pre-Lu-T schedule |
| HBV | at least 2 weeks prior Lu-T | 3-dose series with the first 2 doses separated by ≥ 4 weeks, and a third dose after 4-6 months | 3-6 months after Lu-T | same as pre-Lu-T schedule |
| HAV | At least 2 weeks prior Lu-T | 2-dose series separated by 6-12 months | 3-6 months after Lu-T | same as pre-Lu-T schedule |
| SARS-CoV-2 | at least 2 weeks prior Lu-T | 3-dose series + 2 boosters' dose | 1st vaccination/second dose for at least 1 month after Lu-T and for at least 3 months | same as pre-Lu-T schedule |
| HZV | at least 2 weeks pre-Lu-T | RZV 2 doses, spaced 2 to 6 months apart | not recommended | same as pre-Lu-T schedule |
| Meningococcal | at least 2 weeks prior Lu-T | single dose | 3-6 months after LT | same as pre-Lu-T schedule |
| HPV | At least 2 weeks pre-Lu-T | 3-dose series at 0-2-6 months | 3-6 months after Lu-T | same as pre-Lu-T schedule |
| MMR | At least 4 weeks pre-Lu-T | 2-dose series, at least 4 weeks apart. Should be completed at least 2 weeks before Lu-T | not recommended | - |
| Tetanus | At least 2 weeks pre-Lu-T | Repeat vaccination every 10 years | 3-6 months after Lu-T | same as pre-Lu-T schedule |
| Tdap/Td | At least 2 weeks pre-Lu-T | a single dose, repeat vaccination every 10 years | 3-6 months after Lu-T | same as pre-Lu-T schedule |

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| | | | | |
|---|---|---|---|---|
| *Haemophilus influenza* type B | At least 2 weeks pre-Lu-T | single dose | 3-6 months after Lu-T | same as pre-Lu-T schedule |
| Rabies | At least 2 weeks pre-Lu-T | 3-dose series at 0-1-12 months | 3-6 months after Lu-T | same as pre-Lu-T schedule |
| BCG | not recommended | - | not recommended | - |
| Yellow fever | At least 4 weeks pre-Lu-T | a single dose, at least 10 days before entering an endemic area | not recommended | - |
| Polio | At least 2 weeks pre-Lu-T | 3-dose series with the first 2 doses separated by 4-8 weeks, and a third dose after 6-12 months | 3-6 months after Lu-T | same as pre-Lu-T schedule |
| Smallpox | At least 4 weeks pre-LT | single dose | not recommended | - |
| Cholera | At least 2 weeks pre-LT | Two doses 1-6 weeks apart. The course should be completed at least 1 week before any exposure to cholera. For continued protection, a single booster dose within 2 years is recommended | not recommended | - |

LAV, live attenuated vaccines; LZV, live-attenuated zoster vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; RZV, recombinant zoster vaccine; HAV, hepatitis A virus; HBV, hepatitis B; HPV, human papilloma virus; HZV, herpes zoster virus; MMR, measles mumps and rubella; Tdap, tetanus toxoid, reduced diphtheria toxoid, acellular pertussis; Td, tetanus diphtheria; BCG, Bacille Calmette-Guerin.

### *8.1. Influenza*

Influenza is a common infection in SOT recipients and correlates with high morbidity, mortality and risk of rejection. Thus, annual administration of the seasonal inactivated influenza vaccine is recommended for all Lu-T candidates.

### *8.2. Streptococcus pneumoniae*

Pre-vaccination immune status assessment of Lu-T candidates revealed that more than half had serum concentrations below the normal range for IgM, IgA, IgG, IgG1 and/or IgG2 immunoglobulin isotype and/or subclass levels. Post-vaccination assessment resulted in a higher fraction of candidates with protective antibody levels, but a majority had titres that did not reach protective levels (>1.3 μg/L). The 2013 IDSA guidelines recommend administering PCV13 and PPSV23 pneumococcal vaccines to Lu-T candidates. In vaccine-naïve patients, PCV13 should be administered first, followed by PPSV23 at least 8 weeks later. A booster of PPSV23 can also be administered after 5 years.

### *8.3. HAV and HBV*

HAV (2-dose series separated by 6-12 months) and HBV (3-dose series with the first 2 doses separated by ≥ 4 weeks, and a third dose after 4-6 months) inactivated vaccines can be administered before Lu-T. Unvaccinated HBV adults who are immunocompromised should receive 2 doses of Engerix-B 20 mcg/mL administered concomitantly in a 4-dose schedule at 0, 1, 2, and 6 months. If people are not vaccinated or not fully covered, the missing doses should be given to complete the 3-dose series of the HBV vaccine. The 2$^{nd}$ is administered 1 month after the 1$^{st}$ dose; the 3$^{rd}$ ≥ 2 months after the 2$^{nd}$ dose (and ≥ 4 months after the 1$^{st}$ dose). Adults can be given the HAV vaccine in combination with the HBV vaccine in a schedule of 3 doses: at 0, 1, and 6 months. The first and second

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doses should be separated by ≥ 4 weeks, and the second and third by ≥ 5 months. Alternatively, the vaccine can be administered with an accelerated schedule of 4 doses: on days 0, 7 and between days 21 and 30, followed by a booster at 12 months after the first dose. Hepatitis A vaccines are prepared from inactivated virus. Depending on the type of vaccine, adults are given the vaccine in a series of 2 doses at 0 and 6 to 12 months (Havrix) or 0 and 6 to 18 months (Vaqta).

*8.4. SARS-CoV-2*

Lu-T patients are a particularly vulnerable group for COVID-19 as lungs are the primary target for SARS-CoV-2. All transplant candidates are eligible for vaccination, unless contraindicated, i.e., hypersensitivity to the vaccine or its components.

*8.5. HZV*

The recombinant vaccine for herpes zoster is recommended in Lu-T candidates aged ≥50 years. It is administered in two doses, spaced 2 to 6 months apart. It should be completed at least two weeks prior to Lu-T, to help ensure maximal immune response. Transplant candidates <50 years could still be considered for HZV vaccine, if risk factors are present as a previous episodes of herpes zoster or a state of immunodeficiency or immunodepression due to disease or therapy.

*8.6. HPV*

The quadrivalent HPV vaccine is recommended before Lu-T for all individuals between the ages of 9 and 26 to prevent cervical cancer, anal cancer and anogenital wart. It is administered to transplant candidates in the aforementioned age group who have never received the HPV vaccine or have not completed the 3-dose series.

*8.7. Haemophilus influenzae type B*

*Haemophilus influenzae* type B vaccines help in preventing infections by this strain of Haemophilus, but not those caused by other strains. It is recommended before Lu-T.

*8.8. Other vaccinations*

Quadrivalent conjugate meningococcal vaccine (ACYW) and vaccine for serogroup B should be administered in Lu-T candidates only in presence of risk factors: travellers to high-risk areas, properdin-deficient patients, terminal complement component deficient patients (including acquired complement deficiency such as prior to starting eculizumab) and those with functional or anatomic asplenia. Current recommendations for tetanus, tetanus and diphtheria (Td), or tetanus, diphtheria, and pertussis (Tdap) booster vaccines are the same for healthy individuals and Lu-T patients, implying repeated vaccinations every 10 years.

**9. Lung Transplant Recipients**

Several factors might predispose Lu-T recipients to infections, such as previous colonization by multi drug resistant microorganisms, contact of the graft with the external environment, suppression of the cough reflex, disruption of the lymphatic drainage system, impaired mucociliary clearance, need of high levels of IS - the highest among SOT recipients - and the fact that in this cohort of patients the antimicrobial therapy is often less effective than in the immunocompetent ones. The planning of the vaccination strategy in transplant recipients must consider that the LAV, i.e., MMR, varicella and the intranasal influenza vaccine are contraindicated post-transplantation, because of elevated risk of reactivation. IDSA recommends waiting a minimum of 4 weeks between LAV administration and subsequent Lu-T, whenever possible. Inactivated vaccines are considered safe in SOT and, ideally, they should be completed at least 2 weeks before Lu-T. To prevent organ rejection, patients are treated with heavy doses of IS during the first six months post-transplantation. For this reason, administration of vaccines in the post-transplant period should be resumed not earlier than 3-6

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months after the transplant. A considerable exception is the flu vaccine, that can be administered as early as one month after transplantation [59].

*9.1. Influenza*

Annual administration of the seasonal inactivated influenza vaccine is recommended for all transplant recipients, starting from the first month following transplantation. Conversely, live attenuated influenza vaccine in the post-transplant period is not recommended because of the high risk of active viral reactivation. Lu-T recipients who have inadvertently received a live formulation of influenza vaccine or have been exposed to influenza are valid candidates for antiviral prophylaxis. In the post-Lu-T period, randomized studies [60,61] show that protective serum antibody levels are achieved in only about 30% of Lu-T recipients, 4 weeks after influenza vaccination. Also, in terms of cell-mediated immune response, Lu-T recipients did not demonstrate any response within 4 weeks after vaccination, measured by levels of IL-2, IL-10, IFN- gamma, and granzyme B. Supporting this evidence, a 5-year longitudinal study showed that antibody responses in Lu-T patients who received influenza vaccine before the transplant were higher compared to those of patients who received vaccine between 13 and 60 months post-transplant (p=0.002), suggesting that patients have a stronger pre-transplant response and that annual seasonal vaccination should therefore begin before transplantation. [62]. Furthermore, randomized studies have shown that the administration of high doses or boosters in the same season should be preferred over a single standard dose, since they both warrant greater immunogenicity [63]. In addition to this, trivalent seasonal influenza vaccines have shown variable results among different strains and they may be more immunogenic than others, although the clinical protection is variable. Antibody levels to the three viral antigens included in trivalent vaccines are different between non-transplant patient (group-control) and transplant patients. The humoral immune response to influenza vaccination was significantly lower in the transplant group for all three viral antigens. To A/Sydney (H3N2), 95% of the control group and 40% of the transplant group developed protective levels (p=0.0009); to A/Beijing (H1N1), 71% of the control group and 30% of the transplant group developed protective levels (p=0.004); and to Yamanashi (B), 48% of the control group and 19% of the transplant group developed protective levels (p=0.02) [63,64].

When considering the effect of the various IS drugs on immune response, it is known that the effect of prednisone on antibody response to influenza vaccination is variable, with evidence of normal responses for the monovalent H1N1 vaccine and normal or lower responses for the trivalent vaccine. On the other hand, mTOR inhibitors are known to impair H1N1 antibody titres. Instead, very few data are available regarding Basiliximab and azathioprine in the context of influenza vaccination response. Long-lasting data from the literature have shown that azathioprine is not hampering the response to live vaccines when administered at a dose ≤3 mg/kg, while there is conflicting information regarding the recombinant influenza vaccine (Flublok Quadrivalent). A single study has suggested that Basiliximab might enhance antibody response to influenza vaccine [64].

*9.2. Streptococcus pneumoniae*

The 2013 IDSA guidelines recommend administering PCV13 and PPSV23 pneumococcal vaccines to Lu-T recipients. Today, the new conjugate PCV-20 vaccine has been approved and recommended vaccine for SOT candidates and recipients.

Considering the effects of IS, the available literature confirms that prednisone or dexamethasone, especially when combined with other IS, severely impair the humoral response and consequently the efficacy of 23-valent pneumococcal vaccines [65–67]. Besides, MMF has been documented to interact with the immune response in reducing the efficacy of vaccination: it completely disrupts primary and secondary humoral responses to pneumococcal polysaccharide vaccines [68,69].

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*9.3. HAV and HBV*

HAV and HBV vaccines can be administered after Lu-T because they are inactivated vaccines. Only Scattered data on HAV vaccination on Lu-T patients are present in the literature [70]. Regarding HBV vaccine, the existing data show how anti-HBs serum levels >10 mIU/L provide adequate protection against the infection [71]. However, the level of anti-HBs in Lu-T recipients declines rapidly after transplantation, likely due to extremely high doses of IS in the setting of Lu-T. Nevertheless, data show that recipients who respond to the vaccine before transplantation tend to maintain a T-cell mediated "memory" response to HBsAg comparable to that of healthy subjects, despite the rapid decrease in serum antibody titres [72,73]. Corticosteroids, among IS drugs, bear the highest impact on the impaired response to these vaccines, interfering with HBV replication.

*9.4. SARS-CoV-2*

The AST recommends vaccinating at least two weeks before Lu-T and indicates that the vaccines are unlikely to trigger rejection episodes and to induce more severe side effects than in other at-risk groups. For patients that are not vaccinated prior to Lu-T and those who have been transplanted between vaccine doses, it is suggested to delay the vaccination/second dose for at least 1 month after transplantation and for at least 3 months whenever a T or B cell-depleting agent has been used for induction. Emerging data indicate a poor antibody response to mRNA vaccines in Lu-T patients. In a small cohort of 73 LT patients given a two-dose mRNA vaccine, only 25% had IgG (specific to spike protein) above the defined cut-off [74]. Long term efficacy is still unknown; therefore, it is recommended that patients should be monitored on the long-term, and in the future additional vaccine doses and/or types might be needed. For Lu-T patients monoclonal antibodies against SARS-CoV-2 are always indicated in case of a pre-exposure prophylaxis.

*9.5. HZV*

The recombinant vaccine for herpes zoster is recommended in Lu-T recipients. It is administered in two doses, spaced 2 to 6 months apart. It should be completed at least two weeks prior to transplantation, to help ensure maximal immune response. All transplant candidates aged ≥50 years should receive Herpes Zoster vaccination. Transplant candidates and recipients <50 years could still be considered for herpes zoster vaccine, if risk factors are present as a previous episodes of herpes zoster or a state of immunodeficiency or immunodepression due to disease or therapy.

*9.6. HPV*

The quadrivalent HPV vaccine is recommended after Lu-T for all individuals between the ages of 9-26 to prevent cervical cancer, anal cancer and anogenital wart. It is administered to transplant candidates in the aforementioned age group who have never received the HPV vaccine or have not completed the 3-dose series. Immunogenicity studies [75] concluded that the HPV vaccine is safe and well tolerated in Lu-T recipients, but lung transplantation was associated with lower antibody response compared to other transplanted organs. Current available data show that high daily IS schedules severely hamper the response to HPV vaccine [76]. Similarly, MMF significantly impairs HPV vaccines efficacy since it lowers HPV 6 and 8 seroconversion rates after 12 months, and is associated with a decline of anti-HPV-16 antibody titres 7 months after Lu-T.

*9.7. Haemophilus influenzae type B*

Nowadays, in most countries this vaccine is a routine childhood vaccination, but it is also strongly recommended for immunocompromised adults such as SOT recipients who bear a peculiar risk of acquiring an invasive form of the infection. Haemophilus influenzae type B vaccines help in preventing infections by this strain of Haemophilus, but not those caused by other strains of Haemophilus influenzae bacteria. Being a conjugated vaccine, it can be administered in the post-transplant period.

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*9.8. Other vaccinations*

Quadrivalent conjugate meningococcal vaccine (ACYW) and vaccine for serogroup B should be administered in Lu-T recipients only in presence of risk factors: travellers to high-risk areas, properdin-deficient patients, terminal complement component deficient patients (including acquired complement deficiency such as prior to starting eculizumab) and those with functional or anatomic asplenia. The efficacy of meningococcal vaccine is not well studied in Lu-T. Current recommendations for tetanus, tetanus and diphtheria (Td), or tetanus, diphtheria, and pertussis (Tdap) booster vaccines are the same for healthy individuals and Lu-T patients, implying repeated vaccinations every 10 years. 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 postvaccination [77]. Considering that antibody seroprotection almost guarantees clinical protection, it is recommended to monitor antibody levels in Lu-T patients at regular intervals to ensure patient safety. Immunosuppressant drugs, such as high-dose prednisone, MMF and m-TOR inhibitor, reduce the efficacy of vaccination. LAV for measles and mumps are contraindicated after Lu-T. For naïve patients, the last dose of live vaccine should be administered at least 4 weeks before transplantation.

## 10. Conclusions

Despite the advances in immunosuppression and medical management, infectious diseases are a well-known cause of morbidity and mortality in SOT recipients compared to immunocompetent individuals. Vaccination is the most efficient and cost-effective intervention to prevent infectious diseases; the response to vaccines, however, is highly dependent on a fully functioning immune system.

Patients with organ failure waiting for transplantation are at increased risk of infections and acute decompensation with subsequent high morbidity and mortality. On the other hand, in post-transplant recipients, immunosuppression is the major predisposing factor for the development of infectious diseases, bearing a strong impact on rate and severity of infection's manifestations as well as patients' survival, since antimicrobial treatments are usually less effective than in the immunocompetent patients.

In order to ensure an adequate protection from infections, vaccination strategies are crucial also in close contacts: family members, health care workers, and eventual pets. This category of people should receive all recommended immunization, especially annual influenza vaccine preferably with inactivated influenza vaccine as well as against MMR and varicella, in order to minimize the possibility of exposure to wild-type viruses, and SARS-CoV-2 immunization.

Vaccination represents a major preventive measure against specific infectious risks in this populations especially in the perspective of a future SOT, when IS will boost the infectious risk and further limit the immune system responsiveness. Although the patients with end stage organ disease may have a reduced serological response to vaccines due to the compromised immune response compared to healthy controls, vaccines clearly demonstrate superior immunogenicity when administered earlier in the course of the chronic disease. Accordingly, the "ideal" strategy is to timely verify the vaccination status of all the patients with advanced diseases aiming to promptly identifying and resolving any possible immunity gaps before SOT.

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