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Vaccination in adult liver transplantation candidates and recipients

Florent Valour^{a-c}, Anne Conrad^{a-c}, Florence Ader^{a-c}, Odile Launay^{d-g,}*

^a Service des maladies infectieuses et tropicales, Hospices Civils de Lyon, Lyon, France;

^b Centre International de Recherche en Infectiologie, Inserm, U1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, Ecole Normale Supérieure de Lyon, Univ Lyon, F-69007, Lyon, France;

^c Université Claude Bernard Lyon 1, Lyon, France;

^d Inserm, CIC 1417, F-CRIN, Innovative clinical research network in vaccinology (I-REIVAC), Paris, France;

^f Université de Paris, Paris, France;

^g Assistance Publique-Hôpitaux de Paris, CIC Cochin Pasteur, Hôpital Cochin Paris, France.

*** Corresponding author:** Prof. Odile Launay, CIC Cochin Pasteur, Hôpital Cochin, 27 rue du Faubourg Saint-Jacques, 75679 Paris cedex 14, France. Tel: 00.33.1.58.41.28.60; Fax: 00.33.1.58.41.29.10; E-mail address: odile.launay@aphp.fr.

Abbreviations: BCG, Bacille Calmette-Guérin (tuberculosis vaccine); DTPP, Diphtheria, tetanus, poliomyelitis and pertussis; HPV, Human papilloma virus; HZ, Herpes zoster; IPD, Invasive pneumococcal diseases; LT, Liver transplantation; MMR, Measles mumps and rubella; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent polysaccharide vaccine; SOT, Solid organ transplantation; VHA, Viral hepatitis A; VHB, Viral hepatitis B; VHC, Viral hepatitis C; VZV, Varicella zoster virus.

Summary

In patients with chronic liver disease and liver transplant recipients, cirrhosis-associated immune dysfunction syndrome and immunosuppressant drug regimens required to prevent graft rejection lead to a high risk of severe infections, associated with acute liver decompensation, graft loss and increased mortality. In addition to maintain their global health status, vaccination represents a major preventive measure against specific infectious risks of particular concern in this population, such as invasive pneumococcal diseases, influenza or viral hepatitis A and B. However, immunization in this setting raises several issues: i) recommended vaccination schedules rely on sparse immunogenicity data without clinical efficacy and effectiveness trials designed for this specific population; ii) dynamics of immunosuppression makes timing of immunization challenging; iii) live attenuated vaccines are contraindicated after transplantation; and iv) vaccines tolerance is poorly known in cirrhotic patients. This review outlines the rational for vaccination in adult liver transplant candidates and recipients and available data regarding immunization in this specific population.

Keywords: Influenza; Invasive pneumococcal disease; Liver transplantation; Vaccination; Viral hepatitis A; Viral hepatitis B.

Introduction

Chronic liver disease is associated with an overall impairment of the immune system, referred as cirrhosis-associated immune dysfunction syndrome, leading to an increased risk of infections which represent a major cause acute liver decompensation and mortality [1,2]. Liver transplantation (LT) currently represents the main therapeutic option for end-stage liver disease and localized hepatocellular carcinoma. The risk of infection increases in the pre-transplantation period with the severity of liver disease, and is maximal during the 6 first months post-LT due to intensive immunosuppressive drugs regimens used to prevent graft rejection [3]. In addition, to maintain the global health status of cirrhotic patients and LT recipients as in general population, vaccination represents a pivotal preventive measure against infections of particular concern in this population, including invasive pneumococcal diseases (IPD), influenza or viral hepatitis A (VHA) and B (VHB). However, current guidelines rely on very little data regarding vaccine efficacy and effectiveness in this specific population [4–7]. Additionally, the establishment of immunization schedules is challenging, having to take into account the balance between a decreased efficacy of vaccines in immunosuppressed hosts, an accelerated loss of antibody titers, the dynamics of immunosuppression in the peri-transplantation period, and the contraindication of live attenuated vaccines after LT.

The present review summarizes the rationale for immunization in the peri-LT period, focusing on risk evaluation and available data regarding vaccine efficacy in this specific population.

Immune status of patients with chronic liver disease and after transplantation

Cirrhosis – and *a fortiori* liver failure – is associated with an overall dysfunction of the immune response [2], responsible for an increased infection risk, related to: i) a destruction and shunt of the intrahepatic reticuloendothelial system, impeding bacterial and toxin clearance; ii) a disturbed innate immunity, with impairment of mobilization, phagocytic functions and half-life of neutrophils and monomacrophagic cells, and of hepatic synthesis of the components of the complement system; and iii) a dysfunction of specific immunity, with impaired B-, T-, and NK-cells activities, and a decrease in

immunoglobulin synthesis. Hypersplenism might indirectly impact the immune response, causing neutropenia and impaired phagocytic functions. Finally, these immune dysfunctions are potentially amplified by malnutrition and chronic alcohol consumption frequently encountered in this population [8,9]. In addition, immune and circulatory changes observed during cirrhosis increase the severity of infections, with a higher risk of sepsis/septic shock, multi-organ failure and mortality [10,11]. Consequently, bacterial infections are responsible for 30 to 50% of deaths in cirrhotic patients, and are the leading cause of acute liver decompensation [12].

In the post-transplantation period, a maximal immunodeficiency is observed in the six first months, related to induction and subsequently maintenance immunosuppression protocols, classically based on basiliximab or anti-thymocyte globulins, and a combination of calcineurin inhibitors, mycophenolate and/or corticosteroids, respectively [13]. The risk is increased and prolonged if there is a need for acute antirejection therapy.

General principles of vaccination in the setting of solid organ transplantation

With respect to vaccine-preventable diseases, patients awaiting LT share issues of all immunosuppressed hosts: i) an increased incidence and severity of several vaccine-preventable infections requiring specific immunization recommendations; ii) a decreased immunogenicity of vaccines and an accelerated loss of protection, which may require specific vaccination schedules with additional booster doses; and iii) a contraindication of live attenuated vaccines after transplantation given the risk of active vaccine-induced infection.

Infection risk and vaccine efficacy may vary according to the dynamic of immunosuppression over time, increasing during the course of hepatic disease, and being maximal during the first six months after transplantation before long-term maintenance immunosuppression levels have been attained. Current guidelines recommend the implementation of required vaccination schedules as soon as possible before LT, because of the very low immunogenicity expected in end-stage hepatic disease and after transplantation [4–7]. Live attenuated vaccines are contraindicated after transplantation, and thus must also be proposed in the pretransplant period, with a minimal interval of four weeks between vaccination and transplantation [4–7]. In unvaccinated recipients, the timing of immunization after LT is

debated. In order to improve vaccine immunogenicity, an interval of 3- 6 months after transplantation is usually recommended, when immunosuppressive regimens have reached their maintenance dose, and in the absence of ongoing graft rejection, excepted for inactivated influenza vaccine which can be given as early as one month post-transplant.

Finally, despite a theoretical risk of vaccination-induced graft rejection, a causal link between vaccination and rejection has never been demonstrated. Seasonal influenza vaccination has been the most evaluated, showing no induction of anti-HLA antibodies [14]. In kidney transplant recipients, vaccination against influenza with the adjuvanted A(H1N1)2009 pandemic vaccine has been associated with an increase in anti-HLA antibodies without increasing acute rejection rate [15,16]. Some case series have suggested a link between adjuvanted influenza vaccination and acute rejection [17], but these observations have not been confirmed by larger studies [18]. To our knowledge, this point has not been specifically evaluated in LT recipients.

Another issue is the insufficient vaccine coverage in this at-risk population [19], which has also been documented in other solid organ transplantation (SOT) settings [20]. In this context, specific infectious diseases consultations for LT and SOT candidates in general, dedicated to the prevention of the infectious risk, might be of particular interest to improve vaccine uptake [21].

As vaccine protection can be impeded by the immunosuppressed status and low vaccine coverage of candidates and recipients of LT, vaccination of household contacts and healthcare workers represents an additional way to lessen the risk of vaccine-preventable diseases. Consequently, it is highly recommended that households and hospital workers be up-to-date regarding routine vaccinations, and additionally receive an annual injection of the inactivated influenza vaccine, a booster dose against pertussis, and that serogenative individuals be immunized against varicella-zoster virus (VZV) [4–7]. Of note, live-attenuated vaccines must be avoided in close contacts of immunosuppressed hosts when inactivated alternatives exist, because of the risk of transmission of the vaccine strain. However, this theoretical risk is negligible compared to the benefit of vaccination, especially against measles, mumps and rubella (MMR) and VZV [22].

Vaccine-preventable diseases and liver transplantation: risk assessment, vaccine evaluation and recommendations

Invasive pneumococcal diseases

IPD are more frequent and more severe in cirrhotic patients [23,24]. Lower respiratory tract infections are the third leading cause of infection in this population, the main etiologic agent being *Streptococcus pneumoniae*. Community-acquired pneumonia during cirrhosis is more frequently bacteremic, multi-lobar, associated with neurological, renal or multi-organ failure, and complicated by septic shock [25]. Globally, the mortality rate is 2 times higher than in the general population. Beyond the immunosuppression induced by cirrhosis, these specificities are related to a lack of pulmonary clearance of *S. pneumoniae* in these patients [26]. Additionally, *S. pneumoniae* is responsible for 50% of bacterial meningitis in patients with chronic liver disease which are associated with higher mortality than in the general population [27], and is a recognized cause of ascitic fluid infection [28].

LT recipients are among the highest risk recipients for post-transplant IPD, with an incidence of 354 / 100,000 person-years compared to 11.5 / 100,000 in the general population [29].

The two currently available pneumococcal vaccines are inactivated vaccines composed of the pneumococcal capsular polysaccharide: a 13-valent pneumococcal conjugate vaccine (PCV13) and a 23-valent non conjugated pneumococcal polysaccharide vaccine (PPSV23) [30]. There is no specific data regarding PCV13 in adults awaiting LT. However, its ability to elicit a long-term protection depending on a strong T-cell response with a B-cell memory advocates for its use in immunosuppressed patients to improve vaccine efficacy. Despite a lower immunogenicity without anamnestic reaction, the PPSV23 might allow to extend the protection to a wider range of serotypes, thus better fitting the current epidemiology of pneumococcal invasive circulating strains. However, in comparison to healthy subjects, the immunogenicity of PPSV23 was lower at 1 and 6 months post-vaccination in 45 cirrhotic patients awaiting transplantation, with a rapid post-transplantation drop in antibody titers [31]. There is no data regarding PCV13 in adults awaiting LT. The combined strategy (one dose of PCV13 followed at least two months later by a PPSV23 injection) demonstrated improved efficacy in other immunocompromised populations such as HIV-infected individuals or hematopoietic stem cell transplant recipients [32,33]. If this strategy did not show superiority over a single injection of PPSV23 in a randomized clinical trial including patients after hepatic or renal transplantation [34,35], it has never been evaluated in the pre-transplantation period. This strategy is now recommended in all LT candidates [4–7]. A booster injection of PPSV23 may be offered 5 years after the primary vaccination. The interest of subsequent revaccinations is not established. Individuals vaccinated with a

single injection of PPSV23 according to former immunization regimens should receive a dose of PCV13 at least one year interval after the last PPSV23 injection.

Influenza

There is limited data regarding the impact of influenza in patients with chronic liver disease. However, severe acute liver decompensations have been described in cirrhotic patients [36,37]. The risk of severe influenza is also increased after LT [38].

Immunogenicity of influenza vaccines has been poorly evaluated in patients with chronic liver disease. Compared with 113 unvaccinated patients, the rate of influenza-like illness, complications and proven influenza was lower in 198 cirrhotic patients vaccinated with the trivalent vaccine [39]. In transplant recipients, two studies found discordant results [40,41]. However, annual vaccination has been associated with a significant decrease in influenza severity in transplant recipients [42]. Therefore, an annual seasonal influenza vaccination of cirrhotic and LT patients is recommended, using the now available tetravalent vaccine [4–7].

These guidelines might be revised in the coming years in light of the evaluation of new strategies aiming to improve vaccine efficacy, including the use of adjuvanted or high-dose influenza vaccines. Seroconversion rate to the adjuvanted trivalent vaccine ranged from 75 to 85% among 20 cirrhotic patients compared to 100% in 8 age-matched healthy controls [43]. A randomized trial among 499 SOT recipients, including 159 LT recipients, evaluated the interest of a second booster dose of inactivated influenza vaccine dose 5 weeks after the first dose and found a higher seroconversion rates in SOT recipients vaccinated with two doses [44]. The interest of a double-dose regimen has also been suggested in this population [45]. A recent randomized clinical trial compared the efficacy of a double dose regimen (30 µg) to the standard dose (15 µg) of the trivalent vaccine in 63 kidney and 16 liver transplant recipients, showing a seroprotection rate against the three strains of 88% versus 69% [46]. A significant difference in antibody titers was observed for influenza B, only. Another recent randomized trial highlighted a significantly higher immunogenicity of the newly developed high-dose (60 µg from three circulating strains) compared to the standard-dose vaccine in adult SOT recipients [47]. Consequently, this new high-dose vaccine, currently under process of approval in Europe for individuals over than 65 years old, might replace the standard immunization in SOT recipients.

In all of these studies, influenza vaccination was well tolerated in patients with chronic liver disease, with no specific side effects.

Viral hepatitis A

The seroprevalence of VHA in developed countries is low, estimated at 10% in young adults in France [48]. Even if the risk of contracting VHA in these areas is low, there is a clear resurgence, specifically among men who have sex with men and travelers. The prevalence of VHA is not increased in cirrhotic patients, but VHA infections are associated with a risk of fulminant hepatitis and mortality [49,50]. In the first large prospective study describing the occurrence of VHA in 17 (3.9%) of 432 patients with chronic viral hepatitis C (VHC), 7 (41.1%) developed hepatocellular insufficiency and 6 of them died [49]. These severity data have been secondarily confirmed in other populations [51].

In a large immunogenicity study including 475 patients with chronic compensated liver disease and 188 healthy controls, the two-dose VHA vaccination regimen given 6 months apart was associated with a seroconversion rate of 95% and 98%, respectively [52]. Seroconversion was evaluated at 86% after two doses in 94 patients with chronic VHB-related liver disease [53], and 91.6% in 60 patients with chronic hepatitis or cirrhosis Child-Pugh A cirrhosis [54]. These encouraging results have to be weighted according to liver disease severity. Thus, it was shown that if the seroconversion rates after 1 and 2 doses were 71% and 98% in patients with chronic hepatitis and Child-Pugh A compensated cirrhosis, they decreased to 37% and 66% in Child-Pugh B and C cirrhotic patients [55]. In another study, the rate of seroconversion was only 50% in advanced cirrhosis [56]. The seroconversion rate after 2 doses was evaluated at 75-78% in 84 patients with chronic VHC and advanced fibrosis [57]. After transplantation, the immunogenicity of the VHA vaccine is also reduced [58], with a rapid decrease in antibody titers [59–61]. In all of these studies, anti-VHA vaccination was well tolerated in patients with chronic liver disease or after LT, with no specific side effects.

Consequently, current guidelines recommend vaccination of all seronegative patients with chronic liver disease against VHA by a 2-dose schedule administrated 6 months apart, as early as possible in the course of liver disease [4–7]. A serological control can be proposed one to two months after the last injection, some experts suggesting a booster dose in individuals with antibody titers < 20 UI/mL despite the two recommended injections.

Viral hepatitis B

Severe cases of superinfection with VHB in patients with chronic VHC hepatitis have been described [62,63]. In addition, VHB-infected immunosuppressed patients have an increased risk of progression to chronicity, cirrhosis and hepatocellular carcinoma.

The seroconversion rate measured 1 month after 3 doses of the VHB vaccine administered one month apart was 94% in 16 patients with hepatic steatosis versus 39% in 13 cirrhotic patients [64]. In another prospective study comparing 85 patients with chronic VHC to 46 healthy adults, the rate of nonresponse to the 3-injection regimen was 45% and 2%, respectively [65]. Older studies have reported response rates ranging from 69 to 100% in this population [66–68]. Lower immunogenicity has also been described in patients with chronic alcoholic liver disease, and LT candidates and recipients [69–74]. In a randomized clinical trial involving 110 alcoholic patients, a dual dose regimen (40 µg) at M0, M1, M2 and M6 was associated with a higher seroconversion rate (75%) than with the single dose regimen administered at M0, M1 and M6 [71]. Uncontrolled studies evaluating double-dose accelerated regimens have also suggested better efficacy in SOT candidates or recipients [73,74]. Finally, three doses of the adjuvanted HBV vaccine, currently labeled only in patients older than 15-year-old with renal insufficiency, has been evaluated in 93 LT candidates in a randomized control trial, showing a better response rate in comparison to the conventional four double doses, and could therefore represent a future improvement in vaccination strategies in this population [75].

Following LT, VHB vaccine immunogenicity is reduced, with a 40% response rate [76]. In addition, a rapid loss of antibodies was observed in this study, with only 17% of patient remaining protected at 1 year, justifying pre-transplant vaccination. In all of these studies, anti-HBV vaccination was well tolerated in patients with chronic liver disease, with no specific side effects.

As a consequence, vaccination against VHB of all seronegative patients with chronic liver disease is recommended with the 4 double dose (40 µg) injection schedule administered at M0, M1, M2 and M6, as early as possible in the course of liver disease [4–7]. A serological control must be proposed one to two months after the last injection, a booster double-dose injection being required in individuals with anti-HBs antibody titers <10 UI/mL despite the four recommended injections. In case of further exposition to VHB, a titration of anti-HBs antibodies is recommended to confirm a sufficient protection.

Other vaccinations recommended in general population

All vaccinations recommended in the general population must be implemented in the pre-transplantation period as soon as possible during the course of liver disease [4–7]. However, there is little data on the specific use of these vaccines in this population.

Diphtheria, tetanus, poliomyelitis and pertussis (DTPP). There is no data on the specific risk of these diseases in cirrhotic patients or LT recipients. There is little data on these vaccinations in this specific population [77–79]. Immunogenicity appears to be reduced after transplantation, especially for diphtheria, with a rapid decrease of antibody titers. Boost injections were well tolerated in renal transplant recipients. A recall injection is recommended every 10 years in patients with cirrhosis disease and LT recipients [4–7].

Meningococcal vaccine. The incidence of meningococcal invasive disease does not seem to be higher in SOT recipients. Therefore, there are no specific recommendations for vaccination of adult patients awaiting SOT. However, patients with specific risk factors must be vaccinated according to the general population guidelines. In the LT setting, a particular attention should be paid regarding patients with functional or anatomic asplenia who should receive two doses one month apart of the meningococcal B vaccine as well as two doses 6 months apart of the A, C, YnW meningococcal vaccine [4–7]. The need for subsequent revaccinations is not established.

Human papillomavirus (HPV) vaccine. An overall increased incidence of HPV-related genital warts and malignancies has been observed in SOT recipients [80,81]. There is no data regarding HPV vaccination in cirrhotic patients. In the post-transplantation setting, observational studies highlighted a reduced but acceptable immunogenicity [82,83]. Consequently, SOT candidates meeting the vaccine label criteria – i.e. male or female of 9 to 45-year-old – might be considered for a 3-dose vaccination schedule before LT [4–7].

Measles, mumps and rubella (MMR). Despite the absence of data regarding MMR vaccine in LT candidates or recipients, the current resurgence of measles as a worldwide epidemics and the existence of severe forms of measles in immunosuppressed patients [84,85] led to recommend the

administration of 1 to 2 doses (at least 1 month apart) of the combined MMR vaccine at least 4 weeks before transplantation in all patients seronegative for at least one of the 3 valences [4–7]. Individuals who already received one dose should only be prescribed a single booster injection. After transplantation, a decline in measles antibodies was observed in 22% of pediatric SOT recipients [85]. Two cases of vaccine-induced parotitis have been described after post-transplant vaccination [86]. As all live attenuated vaccines, MMR vaccination is contraindicated in immunocompromised patients, particularly in the post-transplantation period. Post exposure prophylaxis should be considered for all SOT recipients and intravenous immunoglobulin (IVIG) should be administered as soon as possible for seronegative patients.

Varicella and herpes zoster. VZV has been associated with rare cases of fulminant hepatitis mainly in immunosuppressed adults [87], which may suggest an increased risk in patients with severe liver disease and LT recipients. A higher risk of hospitalization and severe illness has been reported in transplanted children [88]. Severe cases have also been described in the 3 months following transplantation in adults, concerning 2.2% of LT recipients, with no identified risk factor [89]. There is little data regarding the use of the live-attenuated VZV vaccine in patients awaiting LT. Few studies in the pediatric population highlighted an acceptable efficacy and tolerance [90,91]. Consequently, two doses of the VZV live attenuated vaccine must be administered at least 1 month (ideally 3 months) apart to all seronegative patients, at least 4 weeks before transplantation [4–7,92]. After transplantation, 7.3% of the 172 vaccinated SOT recipients described in the literature presented a vaccine-induced infection, sometimes severe [86]. As for other live attenuated vaccines, anti-VZV vaccination is therefore discouraged in immunocompromised patients. However, a lower risk has been highlighted in post-transplant recipients receiving low-level immunosuppression. Thus, VZV live-attenuated vaccine could be proposed in selected seronegative LT recipients receiving very low-dose maintenance immunosuppression [4,92]. Post exposure prophylaxis

There is little data regarding the risk of herpes zoster (HZ) in cirrhotic patients. Even if the cirrhosis-related immune dysfunction theoretically leads to an increased risk of reactivation, a nationwide population based study performed in Taiwan highlighted a 1.8% incidence in the five years following the diagnosis of cirrhosis, with no increased risk compared to the general population after adjusting for potential confounders [93]. After LT, the incidence of HZ can reach 12%, and is mainly related to

immunosuppressive therapy [94]. Additionally, SOT recipients are more likely to develop disseminated zoster, visceral complications and post-herpetic neuralgia [92,95]. Consequently, older guidelines recommended the vaccination of seropositive SOT candidates older than 50 year-old with the live-attenuated HZ vaccine in the absence of severe immunosuppression [4]. Since then, an adjuvanted sub-unit HZ vaccine has been released. Even in the absence of data regarding its use in the specific population of LT recipients, more recent guidelines have recommended its use in the pre-transplantation period for seropositive SOT candidates older than 50 year-old, in particular in the most immunosuppressed patients [92]. In the post-transplantation period, the live-attenuated HZ vaccine must be avoided, as containing 12 to 14 times more infective dose than the VZV vaccine. The adjuvanted sub-unit HZ vaccine has been recently studied in a randomized trial including renal transplant at low risk of rejection [96]. In this selected population, the vaccine was safe and immunogenic, but no data is available regarding its clinical efficacy. Awaiting results of larger clinical trials, this vaccination is not recommended in the post-transplantation period [92]. Of note, the adjuvanted sub unit vaccine is not available excepted in Germany.

Post exposure prophylaxis should be considered for all SOT recipients and varicella zoster immune globulin should be administered as soon as possible for seronegative patients.

Yellow fever vaccine. Yellow fever has been associated with rare cases of fulminant hepatitis [97]. The specific risk in patients with cirrhosis or LT recipients has not been evaluated. A French study including 53 SOT recipients (18 LT) vaccinated against yellow fever in the pre-transplantation period showed satisfactory persistence of antibodies after transplantation [98]. Yellow fever vaccination is therefore recommended in patients awaiting for transplantation who intend to travel in an endemic area [4–7]. Although no serious adverse event has been reported after SOT [86], yellow fever vaccination is contraindicated in immunocompromised patients, and therefore after LT.

Conclusion

Chronic liver disease patients and LT recipients are at increased risk of infections, some of them being preventable by vaccination, especially IPD, influenza, viral hepatitis A and B, measles and chickenpox and HZ. National and international guidelines have been released regarding immunization of LT

candidates and recipients. However, knowledge on vaccine response in this specific population is scarce and there is a need for specific trials evaluating vaccine efficacy. While the tolerance of inactivated vaccines is well established, live-attenuated vaccines might induce vaccine-disease and are therefore contra-indicated after LT. Vaccine efficacy and coverage represent two issues of major importance in this population. Immunogenicity of many vaccine valences is lower than in healthy individuals and declines as liver disease and the associated cirrhosis-associated immune dysfunction syndrome progress. Therefore, it is crucial to anticipate vaccination early during the course of liver disease, for live-attenuated vaccines as well as for inactivated vaccines, in order to improve vaccine response. Specific vaccination schedules, with higher antigen doses (double doses, booster shots) are recommended for VHB and are debated for other valences like influenza. Finally, important efforts have to be done to improve vaccine coverage, which is usually very low in this population for patients and close contacts. The implementation of specific infectious diseases consultations for LT candidates is a promising strategy to increase vaccine compliance in this setting and could be the opportunity to assess prospectively vaccine response before and after LT.

Disclosure of interest

The authors declare that they have no competing interest.

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Table 1. Recommendations for vaccination in adults LT candidates and recipients, adapted from [4–7,92].

Vaccines	Pre-transplantation vaccination schedule ¹	Post-transplantation vaccination schedule
Inactivated vaccines		
IPD	Not previously vaccinated LT candidates: 1 dose of the PCV13 followed at least 2 months after by 1 dose of the PPV23 Patients already vaccinated by the PPV23: 1 dose of the PCV13 at least a year after the PPV23 injection, and one dose of the PPV23 at least 5 years after the first dose of PPV23 Patients already vaccinated by the PCV13-PPV23 combined strategy: 1 dose of the PPV23 at least 5 years after the initial vaccination. The need of further booster injections is not established.	For unvaccinated recipients, the same vaccination schedules can be applied after LT. A booster administration of the PPV23 can be proposed 5 years after the initial vaccination. The need of further booster injections is not established.
Seasonal influenza	1 dose of the tetravalent inactivated vaccine every year	1 dose of the tetravalent inactivated vaccine every year
VHA	2 doses 6 to 12 months apart (a booster injection can be proposed for patients with antibody titer < 20UI/mL 2 to 3 months after the last injection)	For unvaccinated recipients, the same vaccination schedules can be applied after LT.
VHB	3 high-dose (40 µg) administered at 0, 1 and 6 months	For unvaccinated recipients, the same vaccination schedules can be applied after LT.
DTPaP	1 dose every 20 years (10 years for immunocompromised patients and those > 65 years old)	1 dose every 10 years
HPV	3 doses at 0, 2 and 6 months for patients 9-45 years	For unvaccinated recipients, the same vaccination schedules can be applied after LT
Live attenuated vaccines²		
MMR	2 doses 4 weeks apart in seronegative LT candidates. Patients that have already received one injection must receive a second dose before LT	Contraindicated
VZV	2 doses 4 to 8 weeks apart in seronegative LT candidates	Contraindicated (vaccination of selected patients receiving low-dose immunosuppressive regimens can be discussed)
HZ	1 dose for seropositive patients > 50 years (the sub-unit adjuvanted vaccine can be used, in particular in immunosuppressed patients)	Contraindicated
Yellow fever	1 dose in LT candidates intending to travel in endemic areas	Contraindicated
BCG	Not recommended	Contraindicated

¹ Vaccinations must be implemented as soon as possible in the course of hepatic disease

² Live attenuated vaccines are contraindicated after transplantation. Required vaccinations must be administrated before transplantation, with a minimal interval of 4 weeks between the last vaccine injection and transplantation.

BCG, Bacille Calmette-Guérin (tuberculosis vaccine); DTPP, Diphtheria, tetanus, poliomyelitis and acellular pertussis; HZ, Herpes zoster; IPD, Invasive pneumococcal disease; LT, Liver transplantation; MMR, Measles, Mumps, Rubella; VHA, Viral hepatitis A; VHB, Viral hepatitis B; VZV, Varicella zoster virus.