

# World Journal of *Transplantation*

*World J Transplant* 2018 June 28; 8(3): 52-83





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*World Journal of Transplantation* (*World J Transplant*, *WJT*, online ISSN 2220-3230, DOI: 10.5500) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

*WJT* covers topics concerning organ and tissue donation and preservation; tissue injury, repair, inflammation, and aging; immune recognition, regulation, effector mechanisms, and opportunities for induction of tolerance, thoracic transplantation (heart, lung), abdominal transplantation (kidney, liver, pancreas, islets), transplantation of tissues, cell therapy and islet transplantation, clinical transplantation, experimental transplantation, immunobiology and genomics, and xenotransplantation. The current columns of *WJT* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography.

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*World Journal of Transplantation* is now indexed in PubMed, PubMed Central.

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**NAME OF JOURNAL**  
*World Journal of Transplantation*

**ISSN**  
ISSN 2220-3230 (online)

**LAUNCH DATE**  
December 24, 2011

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**PUBLISHER**  
Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
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Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>

**PUBLICATION DATE**  
June 28, 2018

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## Vaccination practices in End Stage Renal Failure and Renal Transplantation; Review of current guidelines and recommendations

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**Conflict-of-interest statement:** No potential conflicts of interest relevant to this article were reported.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited manuscript

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Telephone: +44-94-773737644

Received: November 24, 2017

Peer-review started: November 24, 2017

First decision: January 6, 2018

Revised: February 2, 2018

Accepted: March 13, 2018

Article in press: March 13, 2018

Published online: June 28, 2018

### Abstract

Due to the increased burden of infectious complications following solid organ transplantation, vaccination against common pathogens is a hugely important area of discussion and application in clinical practice. Reduction in infectious complications will help to reduce morbidity and mortality post-transplantation. Immunisation history is invaluable in the work-up of potential recipients. Knowledge of the available vaccines and their use in transplant recipients, donors and healthcare providers is vital in the delivery of quality care to transplant recipients. This article will serve as an aide-memoire to transplant physicians and health care professionals involved in managing transplant recipients as it provides an overview of different types of vaccines, timing of vaccination, vaccines contraindicated post solid organ transplantation and travel vaccines.

**Key words:** Immunization; Travel vaccines; Infection; Immunosuppression; Inactivated vaccines; Vaccination post-transplant

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**Core tip:** Patients in end-stage renal failure and those after renal transplantation have a higher risk of opportunistic infections with catastrophic complications and poor response to standard vaccines. Special individualized consideration is needed to immunize these

patients within the existing vaccination protocols.

Gunawansa N, Rathore R, Sharma A, Halawa A. Vaccination practices in End Stage Renal Failure and Renal Transplantation; Review of current guidelines and recommendations. *World J Transplant* 2018; 8(3): 68-74 Available from: URL: <http://www.wjgnet.com/2220-3230/full/v8/i3/68.htm> DOI: <http://dx.doi.org/10.5500/wjt.v8.i3.68>

## INTRODUCTION

End stage renal disease (ESRD) and long-term haemodialysis results in a state of immune compromise with increased risk of systemic infections. Similarly, Renal transplant (RT) recipients on maintenance immunosuppression, also have an increased life-time risk of opportunistic infections. Post-transplant infectious complications are one of the leading causes of morbidity and mortality in these patients. Although immunization against common pathogens can avoid potentially catastrophic complications, questions remain regarding safety, optimal timing and efficacy in these patients.

Transplant recipients are usually excluded from vaccine trials, leading to a scarcity of data regarding their safety and efficacy in these patients<sup>[1,2]</sup>. However, several guidelines have emerged based on individual case series and experience with other immunocompromised patients<sup>[3]</sup>. Nevertheless, there exists a clinical hiatus between published guidelines and routine clinical practice, due to safety concerns and fears of increased graft rejection after immunization<sup>[4]</sup>.

## IMMUNE STATUS AND IMMUNIZATION

Post-transplant immunosuppression has a cumulative effect on the immune system, including suppression of antigen presentation, T and B-cell proliferation and antibody production. Therefore, the host serological response to vaccination is suppressed and variable compared to the non-transplant individual<sup>[5]</sup>. Furthermore, transplant recipients have a state of hypogammaglobulinaemia, contributing to the low sero-conversion rates<sup>[6]</sup>. Therefore, patients with ESRD require a detailed and careful immunization history before enlisting for RT.

## TYPE OF VACCINATION: LIVE, KILLED OR INACTIVATED

The place of live attenuated vaccines in transplant recipients remains an area of significant concern. Active viral replication following live vaccines has been demonstrated in immunocompromised hosts, leading to systemic infection. Viral replication can persist for several weeks after vaccination and such vaccines

are recommended at least 6 wk prior to the planned transplant<sup>[7]</sup>.

Killed and inactivated vaccines are safe in the transplant recipient. These can be administered in line with the immunization schedule for general population. Nevertheless, vaccination in general, is best avoided in the initial 6 mo after RT, where the immunosuppression is maximal. An exception is the influenza vaccine, which is safe as early as 4 wk after RT, to coincide with seasonal outbreaks<sup>[8,9]</sup>.

## TIMING OF VACCINATION

The optimum time for primary vaccination is the pre-transplant phase (Tables 1 and 2). Primary immunization should be carried out early after enlisting for RT due to the variable serological response rates<sup>[10]</sup>. This allows use of all types of vaccines including live vaccines, achieving adequate antibody titres and managing possible vaccine related reactions without compromising graft outcome. Live vaccination may interfere with the reading of Tuberculin skin test (TST) which is commonly done in most transplant centres for all potential recipients. Therefore, the TST should be performed simultaneously with live vaccination or delayed by at least 28 d<sup>[11]</sup>. Similar difficulties with interpretation have also been reported with the newer interferon gamma release assay (IGRA)<sup>[12]</sup>.

## DOSING

Crespo *et al*<sup>[13]</sup> observed that following influenza vaccination, seroconversion rates were 33%, 42% and 82% in ESRD, post-RT and healthy controls respectively. A similar trend of poor sero-conversion is noted with other standard vaccinations among patients with ESRD and after RT. Furthermore, antibody titres tend to decline faster in these patients compared to healthy adults, requiring frequent monitoring of titres and booster vaccination in those who remain sero-negative or have suboptimal antibody levels.

## VACCINATION OF HEALTH CARE PERSONNEL AND CARE GIVERS

Certain vaccines such as hepatitis-B are mandatory for all health care workers prior to assuming duties. Other vaccines (*e.g.*, Varicella, influenza) are recommended in most centers and have shown to minimize hospital-acquired infection. All killed or inactivated vaccines are safe in health care workers and close contacts of RT patients. However, live vaccines should be avoided as it can lead to viral shedding and active infection in the transplant recipient<sup>[14]</sup>.

## VACCINATION IN LIVING DONORS

In live donor RT, all donors need to be comprehensively



**Table 1** Vaccination in end stage renal disease and pre-transplant

Vaccine	Live/inactivated	Comments
Hepatitis B	Inactivated	Higher concentration in 3-4 divided doses Check seroconversion after 6-12 wk Repeat dosing if HBsAb titre < 10 IU/L
Pneumococcal	Inactivated	(1) Adults ( $\geq 19$ yr), previously unvaccinated; PCV-13 followed 8 wk later by PPSV-23 (2) Previously vaccinated; Single dose of PCV-13, one year after the last PPSV-23
HPV	Inactivated	All patients aged 9-26 yr
Influenza	Live (LAV) Inactivated (TIV)	Contra-indicated Recommended annually
MMR	Live	Mandatory for all paediatric patients; 2 doses given 4 wk apart Single dose booster for all sero-negative adult patients
Rubella		For all seronegative female patients of child-bearing age
Varicella	Live attenuated	For all paediatric and adolescent patients, completed 6 wk before transplant
HZV	Live	Recommended for all elderly (> 60 yr) patients Optional for those 50-60 yr with a history of varicella or zoster No evidence of benefit in those < 50 yr
DTP	Inactivated	For all paediatric patients
Td/ Tdap	Inactivated	Td; Formerly (before 2005) recommended to all adult patients as a booster Tdap to all as a one-time dose followed by Td booster every 10 yr
BCG	Live	Routine neonatal vaccination done in Asia, Eastern Europe, Middle East, Africa and South America Elsewhere, recommended children < 5 yr deemed to be at high risk (see text)

HPV: Human papilloma virus; MMR: Mumps and rubella; DTP: Diphtheria, tetanus and pertussis; BCG: Bacille Calmette-Guérin; LAV: Live attenuated vaccine; TIV: Trivalent inactivated vaccine.

checked for their immunization history. Potential donors should be up-to-date in their age appropriate immunization schedule. Live vaccinations should be avoided within 4 wk of a planned organ donation<sup>[7]</sup>.

## COMMON VACCINES IN THE TRANSPLANT PATIENT

### Hepatitis B vaccine

Patients on long-term haemodialysis and after RT have a higher risk of hepatitis-B infection. It may manifest as an aggressive primary infection or reactivation of latent infection, requiring mandatory vaccination of all patients with ESRD, ideally before initiating dialysis. In case it had been missed, it is safe to be given while on dialysis or after RT. However, these patients have poor seroconversion rates (67%-86%), and require higher dosing, given as 20 or 40 (instead of the usual 10) micrograms of recombinant hepatitis-B in 3-4 doses at 0, 1, 2 and 6 mo<sup>[9,10,15]</sup>.

Hepatitis-B surface antibody (HBsAb) titre should be checked 6-12 wk after completing the vaccination schedule and annually thereafter continuing beyond the transplantation. Those who fail to achieve desired titres (10 IU/L) are recommended a second course of vaccination. Those who fail to achieve the desired titres after two courses should be tested for active infection<sup>[3]</sup>. Booster dosing is also recommended for those with sub-optimal HBsAg titres at annual monitoring after RT.

### Pneumococcal vaccine

*Streptococcus pneumoniae* infection can lead to severe and life-threatening pneumonia in ESRD and following

RT. Furthermore, the incidence of invasive pneumococcal infection is also significantly higher in patients after RT compared to the general population. Therefore, routine vaccination is recommended in all patients with chronic kidney disease<sup>[15]</sup>. There are two common vaccine variants; the polysaccharide 23-valent (PPSV-23) and conjugated 13-valent (PCV-13), effective against different serotypes of the pathogen<sup>[16]</sup>. Both are inactivated vaccines and safe in the immunosuppressed host. Adult ( $\geq 19$  years) patients with chronic kidney disease who have not been previously vaccinated should receive a single dose each of PCV-13 followed 8 wk later by PPSV-23<sup>[15]</sup>. If previously vaccinated with PPSV-23, they should receive a single dose of PCV-13 after 1 year from the last dose of PPSV-23<sup>[17]</sup>. In immunocompromised hosts including those after RT, a second dose of PPSV-23 is recommended 5 years after the initial dose.

### Human papilloma virus vaccine

Human papilloma virus (HPV) infection is one of the commonest prevalent infections among female transplant recipients. In the immunosuppressed host, specific strains of human papilloma virus may result in an increased risk of cervical, vulval or anal carcinoma<sup>[18]</sup>. The available trivalent and quadrivalent vaccines are both inactivated and safe in the immunocompromised host. It is recommended for all prospective male and female recipients aged 9-26 years, given prior to RT<sup>[4,15]</sup>.

### Influenza vaccine

Influenza infection can have devastating consequences in the immunosuppressed host. Early studies described prolonged viral shedding and risk of allograft rejection

**Table 2 Common vaccinations contra-indicated post-transplant**

Vaccine	Remarks
Influenza-Live attenuated	Inactivated is recommended annually
MMR	Recommended pre-transplant to all paediatric patients and sero-negative adult patients
Varicella	Recommended pre-transplant to all paediatric and adolescent recipients
HZV	Recommended pre-transplant to all those > 60 yr and those with a history of varicella or zoster infection (50-60 yr)
BCG	Trials under way for inactivated vaccine-currently not in routine clinical use post-RT
Oral polio vaccine	Inactivated injectable vaccine recommended when indicated
Typhoid	Travel vaccine, not routinely recommended
	Inactivated variant available for emergency travel

MMR: Mumps and rubella; BCG: Bacille Calmette-Guérin.

with influenza infection, leading to reservations regarding vaccination<sup>[19]</sup>. However, a direct causal effect of the vaccine on graft rejection has not been substantiated<sup>[20,21]</sup>.

Two common vaccine variants exist; the live attenuated vaccine (LAV) and the trivalent inactivated vaccine (TIV). LAV and its intra-nasal variant are contraindicated after RT. The newer adjuvant vaccine is also contra-indicated as it has been shown to induce *de novo* anti-HLA donor specific antibodies, although with no proven clinical implications on the allograft<sup>[3]</sup>.

Safety and efficacy of TIV is well documented and is recommended annually to all patients with ESRD and post-RT. It has been shown to be safe as early as one month after RT in line with seasonal influenza outbreaks. This current trend has led to a significant shift in practice pertaining to influenza vaccination after RT. A survey by Chon *et al*<sup>[22]</sup> covering 239 transplant centers across United States found that 95% of centers recommended influenza vaccine to their recipients compared to 84% in 1999.

### **Measles, mumps and rubella vaccine**

Mumps and rubella (MMR) vaccine is a live attenuated vaccine and is contraindicated after RT. It is mandatory in all prospective paediatric recipients, recommended as a two-dose regimen approximately 4 wk apart after enlisting for RT<sup>[23]</sup>. In adults, serological testing is recommended and a single dose vaccination is undertaken for those who are seronegative.

Testing of rubella antibodies is recommended for all prospective female recipients of child-bearing age and vaccination performed if seronegative. Although adult rubella infection is self-limiting, immunization provides protection against congenital rubella syndrome in the event of post-RT pregnancy.

### **Varicella vaccine**

Varicella can cause overwhelming disseminated disease in the immunosuppressed host. The varicella vaccine is live-attenuated and is contra-indicated after RT. It is recommended in all prospective paediatric and adolescent transplant recipients, completed at least 6 wk prior to transplantation<sup>[7,23]</sup>. If a deceased donor offer is received before completing 6 wk, RT can still

proceed with a prophylactic regimen of acyclovir. In a study by Broyer *et al*<sup>[24]</sup>, pre-transplant vaccination showed a dramatic reduction in post-RT varicella from 45% to 12%. Furthermore, the rate of late reactivation as zoster following vaccination (7%) was significantly lower than following primary infection (38%). In the event of a post-RT exposure in seronegative patients, prophylaxis is recommended with acyclovir, valacyclovir or intravenous immunoglobulins<sup>[25]</sup>.

### **Herpes zoster virus vaccine**

Herpes zoster reactivation (shingles) after transplant can lead to disseminated infection or troublesome herpetic neuralgia. Therefore, vaccination is recommended for all prospective elderly recipients ( $\geq 60$  years) at least 1 mo before RT. In those aged 50-60 years, vaccination is optional and can be considered in those who have a history of varicella or zoster infection<sup>[11]</sup>. There is no clear evidence for its benefit in recipients younger than 50 years.

### **Polio vaccine**

The live oral polio vaccine is contra-indicated in transplant recipients and their contacts. Hence, paediatric transplant recipients and their household contacts are excluded from routine polio vaccination programs<sup>[3]</sup>. Instead, they are given the inactivated injectable vaccine in-line with the normal immunization schedule.

### **Diphtheria, tetanus and pertussis vaccine**

Diphtheria, tetanus and pertussis (DTP) is an inactivated vaccine and is recommended to all prospective paediatric RT recipients. Until 2005, all prospective adult recipients were recommended a booster dose of tetanus-diphtheria (Td) only. However, a resurgence of pertussis related respiratory illness prompted the inclusion of pertussis vaccine to this schedule. The currently available tetanus toxoid-diphtheria-acellular pertussis (Tdap) vaccine is inactivated and safe in ESRD and after RT. Hence the current recommendation for both groups is a one-time dose of Tdap followed by Td boosters every 10 years<sup>[3,23]</sup>.

### **Tuberculosis vaccine**

The frequency of post-transplant active tuberculosis is

estimated to be 20-74 times higher than the general population, with a mortality rate reaching 30%<sup>[26]</sup>. Immunosuppressive medication may interfere with TST and IGRA used in diagnosis. Despite active disease, sputum smears may remain negative while the clinical manifestations are often atypical, leading to significant diagnostic delays. Furthermore, the disease may actively contribute to allograft dysfunction, resulting in the high morbidity and mortality<sup>[27]</sup>.

The Bacille Calmette-Guérin (BCG) vaccine is a live vaccine and is contra-indicated after RT. Attempts at producing an effective inactivated vaccine have been largely unsuccessful. The only human trials to show efficacy of an inactivated vaccine was the Dar-Dar and DAR-901 trials conducted in Tanzania for patients with human immunodeficiency virus who were previously vaccinated with BCG at birth. The DAR-901 phase III study showed the inactivated vaccine was well tolerated and did not cause post-vaccination tuberculosis<sup>[28]</sup>.

Countries in Asia, Eastern Europe, Middle East, Africa and South America have universal neonatal BCG vaccination. In contrast, North America, United Kingdom, Australasia and Western Europe do not practice routine BCG vaccination due to low prevalence of TB, recommending it only to those neonates and children considered to be at a higher risk than the general population. This includes children < 5 years who live in an area of high prevalence, who have parents or grandparents born in a country of high prevalence, who live 3 or more months per year in a country with high prevalence or who have a close contact with diagnosed pulmonary TB<sup>[29]</sup>.

### **Meningococcal vaccine**

Meningococcal vaccine is usually recommended for patients undergoing splenectomy, those with complement deficiency or with HIV infection. In the transplant patients, it is widely recommended for those intending to travel to endemic regions. More recently, the meningococcal vaccine has been recommended for selected transplant candidates who are likely to receive eculizumab as immunosuppression<sup>[15]</sup>. Eculizumab is a complement inhibitor and has been linked to an increased incidence of meningococcal infection<sup>[30]</sup>. Accordingly, highly sensitized recipients who are likely to be given eculizumab post-transplant are recommended a two-dose regimen given 8 wk apart in the lead up to RT.

## **TRAVEL VACCINATION**

Vaccinations of transplant recipients who intend to travel overseas to areas where certain infections are endemic, need special consideration. Preplanning allows serological testing before the intended travel to ensure protective serological status. In emergency travel circumstances, passive immunization with immunoglobulins can be

considered<sup>[31]</sup>.

### **Hepatitis-A vaccine**

Transplant recipients have a poor seroconversion rate to hepatitis-A vaccination and show rapid decline in antibody titres<sup>[32]</sup>. For those travelling to endemic regions, the vaccine is recommended in two divided doses given six to twelve months apart. In addition to being a travel vaccine, hepatitis A vaccination is also recommended to RT recipients who are male homosexuals, recreational drug users, receive platelet regular concentrates and those who also have concomitant chronic liver disease<sup>[23]</sup>.

### **Typhoid vaccine**

The oral live attenuated vaccine is contraindicated after RT. If it is to be given, it must be done prior to transplant for those who reside in or travel to endemic areas. If emergency travel is needed, the inactivated injectable vaccine is recommended<sup>[33]</sup>.

### **Polio vaccine**

The live oral vaccine is contraindicated after transplant. Any transplant recipient travelling to endemic regions should receive a booster dose of the inactivated injectable vaccine<sup>[7]</sup>.

### **Meningitis vaccine**

The meningococcal vaccine is inactivated and is recommended to all travelers to endemic areas. This becomes especially important for transplant recipients who travel to regions such as Sub-Saharan Africa and Saudi Arabia, where it is a pre-requisite for travel<sup>[34]</sup>.

### **Yellow fever vaccine**

Yellow fever becomes endemic in peak seasons in Sub-Saharan Africa and certain regions of South America. The vaccine is a live attenuated and is contraindicated after RT. Hence, those who live or intend to travel to these regions need to be vaccinated before the transplant<sup>[35]</sup>.

### **Rabies vaccine**

Transplant recipients who are at constant risk of animal exposure such as veterinarians, should be considered for pre-transplant pre-exposure prophylaxis<sup>[15]</sup>. In all other transplant recipients, rabies vaccination becomes relevant only after possible rabid exposure. Such patients require comprehensive post-exposure prophylaxis. This comprises of injectable intramuscular vaccines in divided doses coupled with human rabies immunoglobulin<sup>[36]</sup>.

### **Japanese encephalitis vaccine**

Transplant recipients travelling to endemic East Asia and South-East Asia are recommended Japanese encephalitis vaccination. The newer killed inactivated vaccine is safe and recommended in two doses given 4



wk apart prior to intended travel<sup>[37]</sup>.

## CONCLUSION

Patients with ESRD and after RT are a distinct cohort that carry an increased risk of common infections, potentially catastrophic complications of such infections as well as reduced immunogenicity following immunization. In general, all immunization related details should be obtained prior to enlisting for RT. Any planned vaccines should be administered early in the pre-transplant phase at least 4 wk before the RT. While inactivated vaccines are considered safe beyond the first 6 mo after RT, live vaccines are contra-indicated throughout the post-transplant period. The reduced seroconversion rates and faster antibody clearance in these patients mandates regular screening for antibody titres and administration of booster doses when necessary.

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