Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Review article: Medical intelligence | Published 22 September 2014, doi:10.4414/smw.2014.14005
Cite this as: Swiss Med Wkly. 2014;144:w14005

Live viral vaccines in transplanted patients

Arnaud G. L'Huillier, Klara M. Posfay-Barbe

Paediatric Infectious Diseases Unit, Division of General Paediatrics, Department of Paediatrics, University Hospitals of Geneva & University of Geneva Medical School, Switzerland

Summary

Live attenuated viral vaccines (LAVV) have been used safely and with great success for decades to protect healthy patients against sometimes life-threatening diseases. The current recommendations usually contraindicate their use in immunocompromised hosts, despite an often increased risk for a severe presentation of disease. In this article, we review currently available LAVV, such as varicella-zoster, measles/mumps/rubella, influenza, polio, rotavirus, and yellow fever in patients with solid organ or haematopoietic stem cell transplantation. The current paediatric and adult experience with pre- and post-transplantation vaccination is discussed. To date, because of insufficient data, evidence-based recommendations to safely vaccinate transplant recipients are not available. Hopefully in the near future, specific recommendations will be implemented for certain LAVV in these patients.

Key words: *vaccine; viral vaccine; live-attenuated vaccine; adverse effects; immunosuppression; organ transplantation; haematopoietic stem cell transplant; antibody; cell-mediated immunity; immunocompromised host*

Introduction

Successfully used for more than 100 years, live vaccines contain live, but attenuated microorganisms, which are mostly viruses. There are essentially two ways to produce live attenuated viral vaccines (LAVV): by modifying the wild virus using repeated cultures and thus decreasing its virulence, or by using genetic re-assortment of a non-human virus (currently available LAVV in table 1). Viruses in LAVV, however, are still able to replicate inside the host [1]. Usually considered as safe, LAVV induce similar immune responses as wild-type microorganisms, including cell-mediated immunity (CMI), and in some cases induce a stronger immunogenicity and faster protection than inactivated vaccines, without the need of an adjuvant. Moreover, LAVV do not usually require booster doses and are cheaper to produce compared to inactivated vaccines. On the other hand, LAVV may interact with pre-existing specific antibodies (such as maternal antibodies) compromising their ability to induce an antibody response in certain patients (such as infants). They may also cause a vaccine virus-induced disease, which is a significant concern in transplant recipients [2].

The number of solid organ transplant (SOT) and haematopoietic stem cell transplant (HSCT) patients has dramatically increased in the last decades: the patients also live longer and their lifestyle is closer to that of healthy individuals [3]. They are therefore more often exposed to vaccine-preventable microorganisms in the community. However, their chronic, iatrogenic immunosuppression can affect their B or T-cell response (or both), and consequently induce poor or no antibody response to vaccination, as well as the loss of previously protective antibodies [4]. Some immune-modulators such as rituximab or mycophenolate mofetil are more strongly associated with reduced antibody responses [5–8]. Although rare (estimated, for example, as 1 out of 750'000 live poliovirus vaccines administration in the healthy population [1]), reversion to virulence is feared. This could lead to a possibly uncontrolled replication of the vaccine virus and, as a consequence, to a disease more severe than with community-acquired infection [9, 10]. This review examines the currently available literature on LAVV in SOT and HSCT recipients.

Varicella-Zoster virus vaccine

Varicella-zoster virus (VZV) is the aetiologic agent of chickenpox, a usually benign childhood disease. Serious complications are rare in healthy patients but may affect up to 10% of SOT recipients, with a mortality rate of 5–34% [11–13]. Immunocompromised patients usually require an intravenous antiviral treatment when VZV infection is recognised, as well as pre-emptive treatment with antivirals with or without specific intravenous immunoglobulins when exposed to disease [14]. The VZV vaccine was licensed in the US in 1995, but was developed by Takahashi et al. during the 1970s using the Oka strain [15]. Since then, its efficacy to decrease varicella-related hospitalisations in patients >1 year of age has been recognised [16]. Aiming to reduce the incidence of zoster and the post-herpetic neuralgia, in 2006 the FDA also authorised a live-attenuated vaccine against shingles (herpes zoster). This vaccine, which is only recommended in previously immune patients over 50 years of age, contains 14 times more plaque-forming units (PFU) than the varicella vaccine [17, 18]. Neut-

ralising antibodies are a good surrogate marker of protection against VZV, whereas they do not necessarily correlate with protection against shingles, where CMI plays a major role [19–21]. The zoster vaccine is licensed in Switzerland. As large studies are lacking concerning the VZV vaccine's efficacy and safety in SOT recipients, the VZV vaccine is currently contraindicated after SOT by most medical societies and experts, but encouraged before transplantation when possible (i.e. age >9 months-old) if the patient is seronegative [22–26]. Seroprotective titres after immunisation of transplant candidates are usually obtained in a large proportion of patients [27–29]. Table 2 reviews the American Society of Transplantation's (AST) recommendations for pre- and post-transplantation immunisation, as well as antibody titres monitoring.

A number of smaller studies have reported their experience in vaccinating patients after SOT [19, 27, 30–35]. Most of these patients were paediatric liver transplant recipients, at least 6 months after SOT, with stable organ function, and low dose immunosuppression. There was no efficacy or safety issue reported: seroconversion rates varied between 65% and 100% (table 3), and side effects were similar to the healthy population. When a follow-up of antibody titres was reported, they waned moderately, and breakthrough disease was rarely reported [36–38]. In our institution, VZV-specific CMI also increased significantly after immunisation, in a cohort of 36 paediatric liver transplant recipients [34]. Zoster vaccine is currently contraindicated after SOT (table 2), but studies are ongoing to evaluate its safety in adult kidney transplant recipients [25, 26].

In HSCT recipients, seronegative patients should be vaccinated before transplantation when possible [2], without a defined ideal time frame between vaccination and conditioning. Most recommendations suggest waiting at least 2 years between HSCT and immunisation: high seroconversion rates and low adverse events are then reported [39, 40]. However, one study also showed increasing CMI in all patients who where immunised 3–4 months after HSCT, but results were not significant [41]. Interestingly, Chou et al. could not demonstrate a difference in response between recipients of a matched-related or alternative donor graft, or between patients given a T cell-depleted or T-replete alternative donor graft [39].

Even if theoretically possible because of viral shedding, there is little or no risk of virus transmission from a recently immunised contact to a SOT or HSCT recipient [25]. Therefore, immunisation of VZV seronegative individuals close to SOT or HSCT patients is strongly encouraged [25, 42].

Table 1: Currently available live-attenuated viral vaccines and used definitions in vaccinology.

Live viral vaccines	Varicella Zoster Measles Mumps Rubella Influenza (live attenuated intranasal vaccine) Oral polio (OPV) Rotavirus Yellow fever Vaccinia
Definitions	
Seroprotection	Antibody level above a pre-defined cut-off value at which the probability of clinical protection is assumed to be 50% if exposed to an infectious agent
Seroconversion	Minimum 4-fold increase in specific antibody titres after exposition to an infectious agent, either natural or vaccinal
Adverse event	Any undesirable experience associated with the use of a medical product in a patient
Serious adverse event	Any adverse event associated with: Death Life-threatening disease Prolonged hospitalisation Disability/permanent sequelae Congenital Anomaly/Birth Defect Required Intervention to Prevent Permanent Impairment or Damage

Measles, mumps and rubella vaccine

Measles is a severe disease, with acute complications, such as severe pneumonia and measles-associated encephalopathy, or late-onset complications, such as sub-acute sclerosing panencephalitis. These complications can occur in immunocompetent as well as immunocompromised patients. Severe complications after measles infection have been reported in SOT patients [43–45].

The measles vaccine (Edmonston B strain) was developed in the 1950s, licensed in the 1960s and is nowadays recommended in most countries' vaccination plan, often combined with mumps and rubella vaccines (called MMR vaccine). A genetic component to explain differences in antibody production between individuals in response to MMR vaccination has been suggested [46, 47]. The MMR vaccine has been shown to be immunogenic in transplant candidates and no serious adverse events have been reported

Table 2: Recommendations concerning immunisation before and after solid organ transplantation and monitoring of vaccine titres.

Live vaccine	Recommended before SOT		Recommended after SOT		Monitor vaccine titres		Level of evidence	
	Children	Adults	Children	Adults	Children	Adults	Children	Adults
VZV	Yes		No		Yes		II-1	II-2
Zoster	NA	Yes	NA	No	NA	No	NA	III
MMR	Yes		No		Yes	No	II-1	II-2
Influenza (LAIV)	Yes		No		No		III	
Rotavirus	Yes	NA	No	NA	No	NA	III	NA
Yellow Fever	Yes		No		No		III	
Vaccinia	No		No		No		III	

SOT: Solid organ transplantation; VZV: Varicella-Zoster Virus; MMR: Measles-Mumps-Rubella; LAIV: Live Attenuated Influenza vaccine; NA: not applicable
Adapted from [25]

[4, 48, 49]. In SOT recipients, however, but only in small paediatric studies (N ≤35), the seroconversion rate was lower after SOT (range 41–100% for the measles component) but appeared to be safe in specific conditions, which included low immunosuppression (table 3) [27, 32, 33, 35, 36, 50]. However, recommendations still contraindicate its use in SOT patients (table 2) [25, 26].

Loss of immunity is frequent in previously seropositive HSCT patients, especially in children. In case of outbreaks, immunisation with the measles vaccine could be considered in patients without chronic graft versus host disease (GHVD) or ongoing immunosuppression [51]. Experts recommend immunising with MMR vaccine two years after HSCT [2, 52]. However, children have been immunised earlier in outbreak settings: all naïve children seroconverted and most patients with protective albeit low specific IgG titres <200 UI/ml showed a >4–fold increase in titres. Only mild adverse events were reported [53].

Almost no data is available for the mumps and rubella part of the MMR vaccine in immunosuppressed hosts, probably because of the low risk of severe mumps disease and the fact that the rubella vaccine is mainly administered to avoid congenital disease in pregnant women. Among a cohort of 15 paediatric liver transplant recipients immunised after transplantation, seroconversion rates for mumps and rubella were 100% [27].

Influenza vaccine

Up to 50 million cases of influenza occur yearly in the US [54]. Seasonal yearly immunisation is currently the only effective strategy to prevent and control influenza [55], and it is recommended for all patients older than 6 months in the US. In other countries, yearly vaccination is only recommended to certain patients especially at risk for severe disease, or people close to patients such as healthcare workers. Two types of vaccines are available at this time: an inactivated trivalent influenza vaccine (TIV) and a live-attenuated influenza vaccine (LAIV). TIV is used in the general population in most developed countries and is currently the only influenza vaccine recommended in transplanted and other immunocompromised patients [55]. Initially licensed in 2003 in the US for healthy patients 5–49 years old [56], LAIV is safe and immunogenic in this population [57–65]. The intranasal administration allows viral replication in the nasal mucosa [66], but not in the lungs because of the higher temperature in the lower respiratory tract [67, 68]. The administration route avoids painful injections, and induces a mucosal immunity that more closely resembles natural infection [69–72]. Unlike TIV, antibodies are not a reliable correlate for protection after LAIV [55]. IgA mucosal immunity [69–72] as well as CMI [73, 74] are better correlates for LAIV protection. Clinically, LAIV seems more effective than TIV in children [57, 58, 75], but not in adults [57, 64, 65, 75–77], with no difference regarding adverse events. LAIV may also provide longer protection than TIV [78], and possible cross-protection against non-vaccine serotypes [64, 75, 79].

SOT recipients with influenza illness are at high risk for severe influenza [80, 81]; they benefit from annual immunisation. Current recommendations contraindicate the use of LAIV in these patients, but recommend TIV (table 2) [25, 82–84]. Yearly TIV immunisation is recommended 4–6 months after HSCT, and LAIV is also contraindicated in HSCT patients and their household contacts [2, 51, 52, 85]. LAIV is currently not licensed in Switzerland.

Polio vaccine

Two forms of the polio vaccine are available: an injected inactivated polio vaccine (IPV or Salk vaccine), introduced in 1955, and an oral live-attenuated polio vaccine (OPV or Sabin vaccine), introduced in 1961 [86]. Most countries used OPV to eradicate polio because it was cheaper and easier to administer, induced longer immunity with a component of mucosal immunity, and provided indirect protection through viral shedding. When cases of vaccine-associated paralytic poliomyelitis (VAPP) outnumbered cases of wild polio after an effective mass OPV immunisation, recommendations changed: IPV is currently used in most countries for all patients, whether immunocompromised or not [87–89]. Due to outbreaks still occurring in some countries in Africa and Asia, OPV is still recommended in a few endemic countries or in countries in which there is an increased risk of import and subsequent spread [86, 90]. Due to the risk of VAPP, OPV is contraindicated in immunosuppressed patients or in their household contacts [91–93]. Therefore, OPV is also contraindicated in SOT recipients [84, 94]. IPV alone is recommended 6–12 months after HSCT and in household contacts [2, 51, 52, 85, 95]. OPV is not licensed anymore in Switzerland.

Table 3: Interventional studies on VZV and MMR immunisation in solid organ transplant recipients.

First author, year	Type of patient	Type of organ	Number of patients	Vaccine	Best seroconversion rate
Rand, 1993 [50]	Paediatric	Liver	18	Measles or MMR	41% measles
Zamora, 1994 [30]	Paediatric	Kidney	17	VZV	75% VZV
Kano, 2002 [27]	Paediatric	Liver	15	MMR / VZV (re-immunisation)	85% Measles 100% Mumps/ Rubella 71% VZV
Chaves, 2005 [19]	Paediatric	Kidney	6	VZV	67% VZV
Weinberg, 2006 [31]	Paediatric	Liver/Intestine	16	VZV	87% VZV
Khan, 2006 [32]	Paediatric	Liver	26 MMR / 31 VZV	MMR / VZV	73% Measles 65% VZV
Shinjoh, 2008 [33]	Paediatric	Liver	18	MMR / VZV	100% Measles, Rubella 87% VZV
Posfay-Barbe, 2012 [34]	Paediatric	Liver	36	VZV	100% VZV
Levitsky, 2002 (case report) [37]	Adult	Liver	1	VZV	Post-exposure vaccine: disease
Kraft, 2006 (case report) [38]	Adult	Heart	1	VZV	Post-vaccine disease

VZV: Varicella-Zoster virus; MMR: Measles-Mumps-Rubella; SOT: Solid organ transplantation

Rotavirus vaccine

Rotavirus is one of the leading causes of diarrhoea worldwide, with about 500'000 yearly deaths among young children, 90% of them in developing countries [96, 97]. Protection against rotavirus depends on humoral and CMI [98]. In immunosuppressed patients, rotavirus disease is usually not associated with severe or prolonged diarrhoea [96].

Two oral LAVV directed against rotavirus surface proteins are available and induce viral replication in the gut. All doses for both vaccines need to be administered before the age of 8 months. A recent Cochrane review reported that vaccine efficacy is lower in countries with high mortality rates, but because of the burden of disease, the absolute benefit remains high [99]. The World Health Organization (WHO) recommends including the rotavirus vaccine in the global immunisation schedules in countries with high mortality rates [96] for all children without prior HIV testing but some experts recommend avoiding this vaccine in known, symptomatic HIV+ children [100]. In several European countries and in the US, the vaccine has been included in national immunisation schedules [101]. In Switzerland however, because of a cost-benefit ratio which was unfavourable and a reluctance of primary care physicians to introduce a new vaccine in an already crowded schedule, the introduction of this vaccine in the national recommendations was declined by the Swiss Federal Committee for Immunisations.

For SOT (table 2) and HSCT recipients little data are available, probably because rotavirus disease affects mainly very young children. The vaccine is however contraindicated in these patients [25, 52]. The Centers for Disease Control and Prevention (CDC) recommends rotavirus vaccine use in immunodeficient patients with caution and the WHO contraindicates it in severely immunosuppressed patients [96, 101]. More studies are needed to determine safety and immunogenicity of rotavirus vaccine in this population.

Yellow fever vaccine

Yellow fever is a severe viral haemorrhagic fever caused by an arbovirus transmitted through Aedes mosquito bites in sub-Saharan Africa and South America. The LAVV is the only available vaccine and is recommended in all patients in the yellow fever endemic areas from 9 months of age, except for severely immunosuppressed patients [102]. In developed countries, the yellow fever vaccine (YFV) is contraindicated in immunosuppressed patients [93]. Major complications of the YFV are vaccine-associated viscerotropic disease, and neurologic disease that occur in 0.4 and 0.8 cases per 100'000 doses, respectively.

In countries endemic for yellow fever or patients living in countries endemic for yellow fever, or patients planning to travel in endemic countries in the future (work, leisure) should be immunised before SOT whenever possible, as YFV is permanently contraindicated after SOT, and antibody response may be decreased by immunosuppressive therapies (table 2) [25, 26, 103]. Experts recommend checking seroprotection after SOT in previously immunised patients if travelling is planned: medium to long term persistence of antibodies against yellow fever has been identified after SOT [104]. Among a cohort of 19 SOT patients inadvertently immunised against yellow fever, the only reported side-effect was a mild reaction at the injection site [105]. Time between transplantation and YFV ranged between 3 to 340 months (mean 65 months, median 36 months). However, more studies are needed to evaluate safety of YFV in SOT patients.

In HSCT recipients, YFV is contraindicated and patients should be discouraged from travelling to endemic area. Only case-reports describe safe and immunogenic immunisation in this population [106, 107]. However, the risk/benefit balance may favour immunisation for HSCT patients travelling or living in endemics areas; YFV can therefore be considered >2 years after HSCT in patients without immunosuppression, GVHD, or recurrent malignancy [2, 52, 95, 102].

Vaccinia (smallpox)

Smallpox was caused by variola virus and had a high mortality rate (1/3 of cases). Thanks to vaccination, it was officially eradicated in 1979. Since then, threats of biological warfare have regularly re-emerged, and vaccines against smallpox have been administered pre-emptively to selected populations. There are no studies in SOT recipients, and the smallpox vaccine is not recommended in immunosuppressed individuals because of a high risk for severe, life-threatening disease secondary to vaccinia viremia (table 2) [25, 108, 109]. However, SOT experts recommend immediate smallpox vaccination in case of "face-to-face" contact with a case of confirmed smallpox [25].

General considerations are pre-transplantation assessment and post-vaccine monitoring

During the pre-transplantation assessment, the patient should have a complete documented vaccine history and serological control to ensure VZV and MMR protective titres before transplantation. Catch-up immunisation must be performed in case of low or absent antibody titres, with a subsequent serological control 4 to 6 weeks later and re-vaccination if needed.

Proof of seroconversion and regular serological follow-up is usually recommended after transplantation for VZV and MMR (children), or VZV only (adults) (table 2) [25]. In our opinion, MMR serologies should also be checked in adults in countries in which measles, for example, is endemic or epidemic. While antibody concentration above a predetermined threshold can be insufficient to protect against disease, we currently have no better marker of protection. It is important to follow over time that protective antibody levels are maintained, because antibody waning has been recognised [4]. In our institution, we monitor antibody levels at least once a year after transplantation, which could be increased in case of exposure.

To increase herd immunity and improve passive protection, experts currently recommend VZV (in case of negative history) and MMR immunisation, as well as yearly influenza vaccination (use TIV and avoid LAIV whenever possible)

for household contacts and healthcare workers. They also suggest avoiding giving OPV and smallpox vaccines to household contacts [2, 25, 52].

Future vaccines and research fields

Dengue fever is widespread worldwide and has a broad range of manifestations, from non specific viral disease to severe haemorrhagic symptoms. As with yellow fever, the disease is due to a flavivirus transmitted through Aedes mosquito bites. A LAVV against dengue fever (CYD-TDV) has been evaluated in phase I and II studies with encouraging safety and immunogenicity profiles in healthy adults and children [110–117]. No study currently reports results of dengue vaccine in immunosuppressed patients. New vaccines, such as a CMV vaccine or vaccines against other herpes viruses, as well as a universal influenza vaccine would be useful, but it is unlikely at this point that they will be LAVV.

Further studies are also needed to determine different criteria for safe LAVV administration: it is, for example, important to identify the best timing for immunisation: is it 6–12 months or 12 months after transplantation? It is also important to clearly define "low immunosuppression" using measurable criteria, such as lymphocytes count or CD4 T-cell count, immunosuppressive or immunomodulating drugs dosing (steroids, tacrolimus, ciclosporine, mycophenolate mofetil, monoclonal antibodies), and time since receiving immunoglobulins. Host factors, potentially an important factor in immune response, have also been studied- for example- in genome-wide association studies [118, 119].

Conclusion

Despite encouraging results, there is not enough evidence to date to safely recommend routine use of LAVV in transplant recipients. For these reasons, it is paramount to immunise with LAVV before transplantation whenever possible, to confirm seroconversion, and to follow antibody titres thereafter. More studies are needed to evaluate seroresponse and specific CMI, kinetics of immune responses, and long-term protection, as well as best circumstances for immunisation (timing, immunosuppression). It is possible that LAVV will be recommended in the future after transplantation in well-defined patients.

Funding / potential competing interests: No financial support and no other potential conflict of interest relevant to this article were reported.

Correspondence: *Klara Posfay-Barbe, M.D., M.S., Children's Hospital of Geneva, 6, rue Willy-Donzé, CH-1211 Geneva 14, Switzerland, Klara.PosfayBarbe[at]hcuge.ch*

References

1 Siegrist CA. Mechanisms underlying adverse reactions to vaccines. J Comp Pathol. 2007;137(Suppl 1):S46–50.

2 Ljungman P, Engelhard D, de la Camara R, Einsele H, Locasciulli A, Martino R, et al. Vaccination of stem cell transplant recipients: recommendations of the Infectious Diseases Working Party of the EBMT. Bone Marrow Transplant. 2005;35:737–46.

3 Jain A, Reyes J, Kashyap R, Dodson SF, Demetris AJ, Ruppert K, et al. Long-term survival after liver transplantation in 4,000 consecutive patients at a single center. Ann Surg. 2000;232:490–500.

4 L'Huillier AG, Wildhaber BE, Belli DC, Diana A, Rodriguez M, Siegrist CA, et al. Successful serology-based intervention to increase protection against vaccine-preventable diseases in liver-transplanted children: a 19–yr review of the Swiss national reference center. Pediatr Transplant. 2012;16:50–7.

5 Smith KG, Isbel NM, Catton MG, Leydon JA, Becker GJ, Walker RG. Suppression of the humoral immune response by mycophenolate mofetil. Nephrol Dial Transplant. 1998;13:160–4.

6 Salles MJ, Sens YA, Boas LS, Machado CM. Influenza virus vaccination in kidney transplant recipients: serum antibody response to different immunosuppressive drugs. Clin Transplant. 2010;24:E17–23.

7 Puissant-Lubrano B, Rostaing L, Kamar N, Abbal M, Fort M, Blancher A. Impact of rituximab therapy on response to tetanus toxoid vaccination in kidney-transplant patients. Exp Clin Transplant. 2010;8:19–28.

8 Kapetanovic MC, Kristensen LE, Saxne T, Aktas T, Morner A, Geborek P. Impact of anti-rheumatic treatment on immunogenicity of pandemic H1N1 influenza vaccine in patients with arthritis. Arthritis Res Ther. 2014;16:R2.

9 Banovic T, Yanilla M, Simmons R, Robertson I, Schroder WA, Raffelt NC, et al. Disseminated varicella infection caused by varicella vaccine strain in a child with low invariant natural killer T cells and diminished CD1d expression. J Infect Dis. 2011;204:1893–901.

10 Jean-Philippe P, Freedman A, Chang MW, Steinberg SP, Gershon AA, LaRussa PS, et al. Severe varicella caused by varicella-vaccine strain in a child with significant T-cell dysfunction. Pediatrics. 2007;120:e1345–9.

11 Lynfield R, Herrin JT, Rubin RH. Varicella in pediatric renal transplant recipients. Pediatrics. 1992;90:216–20.

12 Feldhoff CM, Balfour HH, Jr., Simmons RL, Najarian JS, Mauer SM. Varicella in children with renal transplants. J Pediatr. 1981;98:25–31.

13 Fehr T, Bossart W, Wahl C, Binswanger U. Disseminated varicella infection in adult renal allograft recipients: four cases and a review of the literature. Transplantation. 2002;73:608–11.

14 Pergam SA, Limaye AP, Practice ASTIDCo. Varicella zoster virus (VZV) in solid organ transplant recipients. Am J Transplant. 2009;9(Suppl 4):S108–15.

15 Takahashi M, Okuno Y, Otsuka T, Osame J, Takamizawa A. Development of a live attenuated varicella vaccine. Biken J. 1975;18:25–33.

16 Gershon AA. Varicella zoster vaccines and their implications for development of HSV vaccines. Virology. 2013;435:29–36.

17 de Boer PT, Pouwels KB, Cox JM, Hak E, Wilschut JC, Postma MJ. Cost-effectiveness of vaccination of the elderly against herpes zoster in The Netherlands. Vaccine. 2013;31:1276–83.

18 Weaver BA. Update on the advisory committee on immunization practices' recommendations for use of herpes zoster vaccine. J Am Osteopath Assoc. 2011;111:S31–3.

19 Chaves Tdo S, Lopes MH, de Souza VA, Dos Santos Sde S, Pereira LM, Reis AD, et al. Seroprevalence of antibodies against varicella-zoster virus and response to the varicella vaccine in pediatric renal transplant patients. Pediatr Transplant. 2005;9:192–6.

20 Tang H, Moriishi E, Okamoto S, Okuno Y, Iso H, Asada H, et al. A community-based survey of varicella-zoster virus-specific immune responses in the elderly. J Clin Virol. 2012;55:46–50.

21 Prelog M, Schonlaub J, Jeller V, Almanzar G, Hofner K, Gruber S, et al. Reduced varicella-zoster-virus (VZV)-specific lymphocytes and IgG antibody avidity in solid organ transplant recipients. Vaccine. 2013;31:2420–6.

22 Geel A, Zuidema W, van Gelder T, van Doornum G, Weimar W. Successful vaccination against varicella zoster virus prior to kidney transplantation. Transplant Proc. 2005;37:952–3.

23 Prelog M, Zimmerhackl LB. Varicella vaccination in pediatric kidney and liver transplantation. Pediatr Transplant. 2010;14:41–7.

24 Pittet LF, Posfay-Barbe KM. Immunization in transplantation: review of the recent literature. Curr Opin Organ Transplant. 2013.

25 Danziger-Isakov L, Kumar D. Vaccination in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):311–7.

26 Vaccinations CFpl. Recommendations for immunization of solid organ transplant (SOT) candidates and recipients. 2014.

27 Kano H, Mizuta K, Sakakihara Y, Kato H, Miki Y, Shibuya N, et al. Efficacy and safety of immunization for pre- and post- liver transplant children. Transplantation. 2002;74:543–50.

28 Furth SL, Hogg RJ, Tarver J, Moulton LH, Chan C, Fivush BA, et al. Varicella vaccination in children with chronic renal failure. A report of the Southwest Pediatric Nephrology Study Group. Pediatr Nephrol. 2003;18:33–8.

29 Broyer M, Tete MJ, Guest G, Gagnadoux MF, Rouzioux C. Varicella and zoster in children after kidney transplantation: long-term results of vaccination. Pediatrics. 1997;99:35–9.

30 Zamora I, Simon JM, Da Silva ME, Piqueras AI. Attenuated varicella virus vaccine in children with renal transplants. Pediatr Nephrol. 1994;8:190–2.

31 Weinberg A, Horslen SP, Kaufman SS, Jesser R, Devoll-Zabrocki A, Fleckten BL, et al. Safety and immunogenicity of varicella-zoster virus vaccine in pediatric liver and intestine transplant recipients. Am J Transplant. 2006;6:565–8.

32 Khan S, Erlichman J, Rand EB. Live virus immunization after orthotopic liver transplantation. Pediatr Transplant. 2006;10:78–82.

33 Shinjoh M, Miyairi I, Hoshino K, Takahashi T, Nakayama T. Effective and safe immunizations with live-attenuated vaccines for children after living donor liver transplantation. Vaccine. 2008;26:6859–63.

34 Posfay-Barbe KM, Pittet LF, Sottas C, Grillet S, Wildhaber BE, Rodriguez M, et al. Varicella-zoster immunization in pediatric liver transplant recipients: safe and immunogenic. Am J Transplant. 2012;12:2974–85.

35 Kulcsar A TZ, Kolozsi T, Lukacs A. Vaccination of the liver transplant recipients in Hungary. How we do it… European Society of Pediatric Infectious Diseases (ESPID) Annual meeting 2013; 2013; Milano, Italy.

36 Danerseau AM, Robinson JL. Efficacy and safety of measles, mumps, rubella and varicella live viral vaccines in transplant recipients receiving immunosuppressive drugs. World J Pediatr. 2008;4:254–8.

37 Levitsky J, Te HS, Faust TW, Cohen SM. Varicella infection following varicella vaccination in a liver transplant recipient. Am J Transplant. 2002;2:880–2.

38 Kraft JN, Shaw JC. Varicella infection caused by Oka strain vaccine in a heart transplant recipient. Arch Dermatol. 2006;142:943–5.

39 Chou JF, Kernan NA, Prockop S, Heller G, Scaradavou A, Kobos R, et al. Safety and immunogenicity of the live attenuated varicella vaccine following T replete or T cell-depleted related and unrelated allogeneic hematopoietic cell transplantation (alloHCT). Biol Blood Marrow Transplant. 2011;17:1708–13.

40 Kussmaul SC, Horn BN, Dvorak CC, Abramovitz L, Cowan MJ, Weintrub PS. Safety of the live, attenuated varicella vaccine in pediatric recipients of hematopoietic SCTs. Bone Marrow Transplant. 2010;45:1602–6.

41 Ljungman P, Wang FZ, Nilsson C, Solheim V, Linde A. Vaccination of autologous stem cell transplant recipients with live varicella vaccine: a pilot study. Support Care Cancer. 2003;11:739–41.

42 Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. MMWR Recomm Rep. 2000;49:1–125, CE1–7.

43 Turner A, Jeyaratnam D, Haworth F, Sinha MD, Hughes E, Cohen B, et al. Measles-associated encephalopathy in children with renal transplants. Am J Transplant. 2006;6:1459–65.

44 Klapper PE, Cleator GM, Clarke MC, Postlethwaite RJ. Measles immunisation. Arch Dis Child. 1991;66:369.

45 Kalman S, Bakkaloglu SA, Ozkaya O, Buyan N, Soylemezoglu O. Measles: a rare communicable disease in a child with renal transplantation. Pediatr Transplant. 2002;6:432–4.

46 Ovsyannikova IG, Pankratz VS, Vierkant RA, Jacobson RM, Poland GA. Human leukocyte antigen haplotypes in the genetic control of immune response to measles-mumps-rubella vaccine. J Infect Dis. 2006;193:655–63.

47 Dhiman N, Ovsyannikova IG, Vierkant RA, Ryan JE, Pankratz VS, Jacobson RM, et al. Associations between SNPs in toll-like receptors and related intracellular signaling molecules and immune responses to measles vaccine: preliminary results. Vaccine. 2008;26:1731–6.

48 Flynn JT, Frisch K, Kershaw DB, Sedman AB, Bunchman TE. Response to early measles-mumps-rubella vaccination in infants with chronic renal failure and/or receiving peritoneal dialysis. Adv Perit Dial. 1999;15:269–72.

49 Mori K, Kawamura K, Honda M, Sasaki N. Responses in children to measles vaccination associated with perirenal transplantation. Pediatr Int. 2009;51:617–20.

50 Rand EB, McCarthy CA, Whitington PF. Measles vaccination after orthotopic liver transplantation. J Pediatr. 1993;123:87–9.

51 Machado CM. Reimmunization after hematopoietic stem cell transplantation. Expert Rev Vaccines. 2005;4:219–28.

52 Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009;15:1143–238.

53 Machado CM, de Souza VA, Sumita LM, da Rocha IF, Dulley FL, Pannuti CS. Early measles vaccination in bone marrow transplant recipients. Bone Marrow Transplant. 2005;35:787–91.

54 Lambert LC, Fauci AS. Influenza vaccines for the future. N Engl J Med. 2010;363:2036–44.

55 Fiore AE, Uyeki TM, Broder K, Finelli L, Euler GL, Singleton JA, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Recomm Rep. 2010;59:1–62.

56 Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2004;53:1–40.

57 Ashkenazi S, Vertruyen A, Aristegui J, Esposito S, McKeith DD, Klemola T, et al. Superior relative efficacy of live attenuated influenza vaccine compared with inactivated influenza vaccine in young children with recurrent respiratory tract infections. Pediatr Infect Dis J. 2006;25:870–9.

58 Fleming DM, Crovari P, Wahn U, Klemola T, Schlesinger Y, Langussis A, et al. Comparison of the efficacy and safety of live attenuated cold-adapted influenza vaccine, trivalent, with trivalent inactivated influenza virus vaccine in children and adolescents with asthma. Pediatr Infect Dis J. 2006;25:860–9.

59 Belshe RB, Mendelman PM, Treanor J, King J, Gruber WC, Piedra P, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children. N Engl J Med. 1998;338:1405–12.

60 Bergen R, Black S, Shinefield H, Lewis E, Ray P, Hansen J, et al. Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents. Pediatr Infect Dis J. 2004;23:138–44.

61 Mendelman PM, Cordova J, Cho I. Safety, efficacy and effectiveness of the influenza virus vaccine, trivalent, types A and B, live, cold-adapted (CAIV-T) in healthy children and healthy adults. Vaccine. 2001;19:2221–6.

62 Ambrose CS, Wu X. The safety and effectiveness of self-administration of intranasal live attenuated influenza vaccine in adults. Vaccine. 2013;31:857–60.

63 Nichol KL, Mendelman PM, Mallon KP, Jackson LA, Gorse GJ, Belshe RB, et al. Effectiveness of live, attenuated intranasal influenza virus vaccine in healthy, working adults: a randomized controlled trial. JAMA. 1999;282:137–44.

64 Ohmit SE, Victor JC, Rotthoff JR, Teich ER, Truscon RK, Baum LL, et al. Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. N Engl J Med. 2006;355:2513–22.

65 Treanor JJ, Kotloff K, Betts RF, Belshe R, Newman F, Iacuzio D, et al. Evaluation of trivalent, live, cold-adapted (CAIV-T) and inactivated (TIV) influenza vaccines in prevention of virus infection and illness following challenge of adults with wild-type influenza A (H1N1), A (H3N2), and B viruses. Vaccine. 1999;18:899–906.

66 Ambrose CS, Luke C, Coelingh K. Current status of live attenuated influenza vaccine in the United States for seasonal and pandemic influenza. Influenza Other Respi Viruses. 2008;2:193–202.

67 Gruber WC. The role of live influenza vaccines in children. Vaccine. 2002;20(Suppl 2):S66–73.

68 Murphy BR, Coelingh K. Principles underlying the development and use of live attenuated cold-adapted influenza A and B virus vaccines. Viral Immunol. 2002;15:295–323.

69 Gorse GJ, Otto EE, Powers DC, Chambers GW, Eickhoff CS, Newman FK. Induction of mucosal antibodies by live attenuated and inactivated influenza virus vaccines in the chronically ill elderly. J Infect Dis. 1996;173:285–90.

70 Boyce TG, Gruber WC, Coleman-Dockery SD, Sannella EC, Reed GW, Wolff M, et al. Mucosal immune response to trivalent live attenuated intranasal influenza vaccine in children. Vaccine. 1999;18:82–8.

71 Barria MI, Garrido JL, Stein C, Scher E, Ge Y, Engel SM, et al. Localized mucosal response to intranasal live attenuated influenza vaccine in adults. J Infect Dis. 2013;207:115–24.

72 Horvath KM, Brighton LE, Herbst M, Noah TL, Jaspers I. Live attenuated influenza virus (LAIV) induces different mucosal T cell function in nonsmokers and smokers. Clin Immunol. 2012;142:232–6.

73 Treanor J, Wright PF. Immune correlates of protection against influenza in the human challenge model. Dev Biol. (Basel) 2003;115:97–104.

74 Forrest BD, Pride MW, Dunning AJ, Capeding MR, Chotpitayasunondh T, Tam JS, et al. Correlation of cellular immune responses with protection against culture-confirmed influenza virus in young children. Clin Vaccine Immunol. 2008;15:1042–53.

75 Belshe RB, Edwards KM, Vesikari T, Black SV, Walker RE, Hultquist M, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. N Engl J Med. 2007;356:685–96.

76 Monto AS, Ohmit SE, Petrie JG, Johnson E, Truscon R, Teich E, et al. Comparative efficacy of inactivated and live attenuated influenza vaccines. N Engl J Med. 2009;361:1260–7.

77 Tennis P, Toback SL, Andrews E, McQuay LJ, Ambrose CS. A post-marketing evaluation of the frequency of use and safety of live attenuated influenza vaccine use in nonrecommended children younger than 5 years. Vaccine. 2011;29:4947–52.

78 Rhorer J, Ambrose CS, Dickinson S, Hamilton H, Oleka NA, Malinoski FJ, et al. Efficacy of live attenuated influenza vaccine in children: A meta-analysis of nine randomized clinical trials. Vaccine. 2009;27:1101–10.

79 Belshe RB, Gruber WC, Mendelman PM, Cho I, Reisinger K, Block SL, et al. Efficacy of vaccination with live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine against a variant (A/Sydney) not contained in the vaccine. J Pediatr. 2000;136:168–75.

80 Duchini A, Hendry RM, Redfield DC, Pockros PJ. Influenza infection in patients before and after liver transplantation. Liver Transpl. 2000;6:531–42.

81 Vilchez RA, Fung J, Kusne S. The pathogenesis and management of influenza virus infection in organ transplant recipients. Transpl Infect Dis. 2002;4:177–82.

82 Kumar D, Blumberg EA, Danziger-Isakov L, Kotton CN, Halasa NB, Ison MG, et al. Influenza vaccination in the organ transplant recipient: review and summary recommendations. Am J Transplant. 2011;11:2020–30.

83 Kumar D, Morris MI, Kotton CN, Fischer SA, Michaels MG, Allen U, et al. Guidance on Novel Influenza A/H1N1 in Solid Organ Transplant Recipients†. Am J Transplant. 2010;10:18–25.

84 Ballout A, Goffin E, Yombi JC, Vandercam B. Vaccinations for adult solid organ transplant recipient: current recommendations. Transplant Proc. 2005;37:2826–7.

85 Hilgendorf I, Freund M, Jilg W, Einsele H, Gea-Banacloche J, Greinix H, et al. Vaccination of allogeneic haematopoietic stem cell transplant recipients: report from the international consensus conference on clinical practice in chronic GVHD. Vaccine. 2011;29:2825–33.

86 Polio vaccines and polio immunization in the pre-eradication era: WHO position paper. Wkly Epidemiol Rec. 2010;85:213–28.

87 Prevots DR, Burr RK, Sutter RW, Murphy TV. Poliomyelitis prevention in the United States. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2000;49:1–22; quiz CE1–7.

88 Recommendations of the Advisory Committee on Immunization Practices: revised recommendations for routine poliomyelitis vaccination. MMWR Morb Mortal Wkly Rep. 1999;48:590.

89 Prevention of poliomyelitis: recommendations for use of only inactivated poliovirus vaccine for routine immunization. Committee on Infectious Diseases. American Academy of Pediatrics. Pediatrics. 1999;104:1404–6.

90 Polio vaccines and polio immunization in the pre-eradication era: WHO position paper – recommendations. Vaccine. 2010;28:6943–4.

91 Prolonged poliovirus excretion in an immunodeficient person with vaccine-associated paralytic poliomyelitis. MMWR Morb Mortal Wkly Rep. 1997;46:641–3.

92 Sutter RW, Prevots DR. Vaccine-associated paralytic poliomyelitis among immunodeficient persons. Infect Med. 1994;11:429–38.

93 Kotton CN. Vaccination and immunization against travel-related diseases in immunocompromised hosts. Expert Rev Vaccines. 2008;7:663–72.

94 Avery RK. Immunizations in adult immunocompromised patients: which to use and which to avoid. Cleve Clin J Med. 2001;68:337–48.

95 Singhal S, Mehta J. Reimmunization after blood or marrow stem cell transplantation. Bone Marrow Transplant. 1999;23:637–46.

96 Rotavirus vaccines. WHO position paper – January 2013. Wkly Epidemiol Rec. 2013;88:49–64.

97 Parashar UD, Gibson CJ, Bresee JS, Glass RI. Rotavirus and severe childhood diarrhea. Emerg Infect Dis. 2006;12:304–6.

98 Angel J, Franco MA, Greenberg HB. Rotavirus immune responses and correlates of protection. Curr Opin Virol. 2012;2:419–25.

99 Soares-Weiser K, Maclehose H, Bergman H, Ben-Aharon I, Nagpal S, Goldberg E, et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database Syst Rev 2012;11:CD008521.

100 Mphahlele MJ, Mda S. Immunising the HIV-infected child: a view from sub-Saharan Africa. Vaccine. 2012;30(Suppl 3):C61–5.

101 Cortese MM, Parashar UD. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2009;58:1–25.

102 Vaccines and vaccination against yellow fever. WHO position paper – June 2013. Wkly Epidemiol Rec 2013;88:269–83.

103 Staples JE, Gershman M, Fischer M. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2010;59:1–27.

104 Wyplosz B, Burdet C, Francois H, Durrbach A, Duclos-Vallee JC, Mamzer-Bruneel MF, et al. Persistence of Yellow Fever Vaccine-Induced Antibodies After Solid Organ Transplantation. Am J Transplant. 2013.

105 Azevedo LS, Lasmar EP, Contieri FL, Boin I, Percegona L, Saber LT, et al. Yellow fever vaccination in organ transplanted patients: is it safe? A multicenter study. Transpl Infect Dis. 2012;14:237–41.

106 Gowda R, Cartwright K, Bremner JA, Green ST. Yellow fever vaccine: a successful vaccination of an immunocompromised patient. Eur J Haematol. 2004;72:299–301.

107 Yax JA, Farnon EC, Cary Engleberg N. Successful immunization of an allogeneic bone marrow transplant recipient with live, attenuated yellow Fever vaccine. J Travel Med. 2009;16:365–7.

108 Dropulic LK, Rubin RH, Bartlett JG. Smallpox vaccination and the patient with an organ transplant. Clin Infect Dis. 2003;36:786–8.

109 Blanchard TJ, Alcami A, Andrea P, Smith GL. Modified vaccinia virus Ankara undergoes limited replication in human cells and lacks several immunomodulatory proteins: implications for use as a human vaccine. J Gen Virol. 1998;79(Pt 5):1159–67.

110 Capeding RZ, Luna IA, Bomasang E, Lupisan S, Lang J, Forrat R, et al. Live-attenuated, tetravalent dengue vaccine in children, adolescents and adults in a dengue endemic country: randomized controlled phase I trial in the Philippines. Vaccine. 2011;29:3863–72.

111 Thomas SJ, Eckels KH, Carletti I, De La Barrera R, Dessy F, Fernandez S, et al. A phase II, randomized, safety and immunogenicity study

of a re-derived, live-attenuated dengue virus vaccine in healthy adults. Am J Trop Med Hyg. 2013;88:73–88.

112 Morrison D, Legg TJ, Billings CW, Forrat R, Yoksan S, Lang J. A novel tetravalent dengue vaccine is well tolerated and immunogenic against all 4 serotypes in flavivirus-naive adults. J Infect Dis. 2010;201:370–7.

113 Sun W, Cunningham D, Wasserman SS, Perry J, Putnak JR, Eckels KH, et al. Phase 2 clinical trial of three formulations of tetravalent live-attenuated dengue vaccine in flavivirus-naive adults. Hum Vaccin. 2009;5:33–40.

114 Edelman R, Wasserman SS, Bodison SA, Putnak RJ, Eckels KH, Tang D, et al. Phase I trial of 16 formulations of a tetravalent live-attenuated dengue vaccine. Am J Trop Med Hyg. 2003;69:48–60.

115 Watanaveeradej V, Simasathien S, Nisalak A, Endy TP, Jarman RG, Innis BL, et al. Safety and immunogenicity of a tetravalent live-attenuated dengue vaccine in flavivirus-naive infants. Am J Trop Med Hyg. 2011;85:341–51.

116 Simasathien S, Thomas SJ, Watanaveeradej V, Nisalak A, Barberousse C, Innis BL, et al. Safety and immunogenicity of a tetravalent live-attenuated dengue vaccine in flavivirus naive children. Am J Trop Med Hyg. 2008;78:426–33.

117 Poo J, Galan F, Forrat R, Zambrano B, Lang J, Dayan GH. Live-attenuated Tetravalent Dengue Vaccine in Dengue-naive Children, Adolescents, and Adults in Mexico City: Randomized Controlled Phase 1 Trial of Safety and Immunogenicity. Pediatr Infect Dis J. 2011.

118 Kennedy RB, Ovsyannikova IG, Pankratz VS, Haralambieva IH, Vierkant RA, Poland GA. Genome-wide analysis of polymorphisms associated with cytokine responses in smallpox vaccine recipients. Hum Genet. 2012;131:1403–21.

119 Haralambieva IH, Oberg AL, Ovsyannikova IG, Kennedy RB, Grill DE, Middha S, et al. Genome-wide characterization of transcriptional patterns in high and low antibody responders to rubella vaccination. PLoS One. 2013;8:e62149.