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# Live vaccines after pediatric solid organ transplant: Proceedings of a consensus meeting, 2018

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**Abbreviations:** ALC, absolute lymphocyte count; ATG, anti-thymocyte globulin; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; IDSA, Infectious Diseases Society of America; IV, intravenous; IVIG, intravenous immunoglobulin; MMR, measles/mumps/rubella vaccine; MMRV, combined measles/mumps/rubella/varicella vaccine; mTOR, mammalian target of rapamycin; PCR, polymerase chain reaction; pDGS, partial DiGeorge syndrome; PHA, phytohemagglutinin; PTLD, post-transplant lymphoproliferative disorder; SOT, solid organ transplant; TR, transplant recipients; VV, varicella vaccine; VZIG, varicella-zoster immunoglobulin; VZV, varicella-zoster virus; WHO, World Health Organization.

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## Abstract

Growing evidence suggests receipt of live-attenuated viral vaccines after solid organ transplant (SOT) has occurred and is safe and needed due to lapses in herd immunity. A 2-day consortium of experts in infectious diseases, transplantation, vaccinology, and immunology was held with the objective to review evidence and create expert recommendations for clinicians when considering live viral vaccines post-SOT. For consideration of VV and MMR post-transplant, evidence exists only for kidney and liver transplant recipients. For MMR vaccine post-SOT, consider vaccination during outbreak or travel to endemic risk areas. Patients who have received antiproliferative agents (eg. mycophenolate mofetil), T cell–depleting agents, or rituximab; or have persistently elevated EBV viral loads, or are in a state of functional tolerance, should be vaccinated with caution and have a more in-depth evaluation to define benefit of vaccination and net state of immune suppression prior to considering vaccination. MMR and/or VV (not combined MMRV) is considered to be safe in patients who are clinically well, are greater than 1 year after liver or kidney transplant and 2 months after acute rejection episode, can be closely monitored, and meet specific criteria of "low-level" immune suppression as defined in the document.

**KEYWORDS**
immunization, live vaccinations, measles-mumps-rubella vaccine, solid organ transplant, varicella-zoster vaccine

## 1 | INTRODUCTION

Vaccination of solid organ transplant (SOT) recipients prior to transplant has been standard of practice to maximize protection of the recipient prior to the onset of immune suppression.[1] However, factors such as age, disease severity, vaccine hesitancy, and urgency of transplant may preclude the completion of a vaccination schedule prior to transplantation.

Despite a concerted worldwide attention and effort toward routine childhood immunization, outbreaks of vaccine-preventable disease, such as measles and varicella, continue to occur, leaving non-immune individuals, especially immunocompromised hosts such as SOT recipients, at risk.[2-4] Recent lapses in herd immunity have resulted in unprecedented rates of measles in areas of previous elimination, with those unimmunized at highest risk for infection.[5,6] Vaccine-preventable diseases have been shown to cause significant morbidity and mortality in SOT recipients.[7-10] Specifically, primary varicella and measles infection can result in severe sequelae including dissemination, respiratory failure, end-organ involvement, allograft rejection, and mortality.[11-17] This has led to strategies to protect SOT recipients from these vaccine-preventable diseases. While the safety of non-live vaccines has been established for patients after organ transplantation, safety concerns have generally precluded the use of live-attenuated viral vaccines. In the absence of protection via vaccination, susceptible individuals may require post-exposure prophylaxis such as hyper-immune globulin products, intramuscular immunoglobulin, or antivirals with variable efficacy in prevention of disease.[18]

In most jurisdictions, live-attenuated MMR and VV are routinely given to healthy children starting at ≥12 months of age, and in outbreak settings or endemic areas, MMR or monovalent measles vaccine can be given as early as 6 months of age.[19-21] In the transplant setting, transplant candidates are generally put on hold for 3-4 weeks (depending on the center) after receiving a live-attenuated vaccine. In addition, live vaccines are usually contraindicated post-transplant.[1] However, emerging data suggest that use of live vaccines after transplant may be both safe and effective in carefully selected patients (Table 1).

Given the lack of consensus guidelines, a collaborative initiative with experts in pediatric transplantation, vaccinology, immunology, and infectious diseases was assembled. The aim of this initiative was to develop an international consensus to include minimum standards that should be in place in situations where clinicians deem it appropriate to administer live vaccinations after pediatric SOT. Factors to be addressed included, but were not limited to, the optimization of live-attenuated immunization prior to transplant, timing of vaccines after transplant, role of formal immunologic evaluation prevaccination, and implementation of consent, monitoring, and safety mechanisms. In addition, the need to assess the ever-changing risk of exposure to wild-type viruses based on geography, age, and epidemiology vs the risk of the vaccine was highlighted.

## 2 | METHODS

A 2-day, international, multispecialty consortium of physicians and allied health members from pediatric infectious diseases, immunology, pharmacy, and transplantation was held in February 2018. An English literature search of MEDLINE and EMBASE from January

**TABLE 1** Literature review—measles, mumps, rubella, and varicella vaccine administration post–solid organ transplant

| First author/ Publication year | Study type, age | Population organ/ Number | Vaccine | Time frame of follow-up | Timing of vaccine | Immune evaluation prevaccine | Efficacy | Adverse outcomes (number) |
|---|---|---|---|---|---|---|---|---|
| Zamora 1994 | Prospective cohort | Kidney (17) | VV—Oka (17) | 1-4 y | Not specified, average age | Varicella titers, lymphocyte count >1500/ $mm^3$ | Seroconversion:<br>94% titer >1/40 (16/17)<br>Clinical failure:<br>Attenuated varicella 2-4 y post-vaccination (3/17) | Mild varicella (1) |
| Weinberg 2006 | Prospective cohort, pediatric | Liver (14)<br>SB (1)<br>Liver + SB (1) | VV (Varivax®) | 3-66 mo | Median 393 d post-tx (range 257-2045), >1 mo post-rejection | Varicella titers, VZV-specific CMI response | Seroconversion:<br>VV—87% (13/15)<br>PBMC VZV-specific proliferation:<br>VV—86% (12/14)<br>Clinical failure:<br>Transaminitis post–varicella exposure (1/11) | Local reaction (5)<br>Disseminated rash (4)<br>Fever (4) |
| Posfay-Barbe 2012 | Prospective cohort, pediatric | Liver (36) seronegative immunized | VV (VariIrix®) | 4.1 y median f/u | 1 y post-tx<br>2 mo post–acute rejection | Varicella titers | Seroconversion: (n = 32, median 89.9 wks after): 97%<br>VZV CD4+ IFNγ Release: n = 20<br>0.085% → 0.16%<br>Clinical failure:<br>None at 4.14 yrs median f/u | Local adverse reaction (17/31)<br>Systemic reaction (20/31)<br>Vesicles[b] (5)<br>Rejection[c] (1) |
| Kawano 2015 | Prospective cohort | Liver (39) | M (26)<br>Mp (25)<br>R (28)<br>VV (19) | 2005-2013, 34 mo median f/u (range 5-48) | >1 y post-tx, >6 mo post-rejection requiring steroids | Other workup[e] | Seroconversion (after 1 dose):<br>M—44% (11/25)<br>Mp—48% (12/25)<br>R—70% (19/27)<br>VV—32% (6/19) | None reported |
| Shinjoh 2015 | Prospective cohort, pediatric | Liver (48) | M—AIKC (37)<br>Mp—Hoshino (34)<br>Mp—Tori (3)<br>R—TO-336 (35)<br>VV—Oka (35) | 5 y | Median 44 mo (range 34-396 mo) | Prevaccine titers and other workup[d] | Seroconversion (5 yrs):<br>M—63%<br>Mp—Hoshino—73%<br>R—100%<br>VV—40%<br>Clinical failure:<br>VV—8.6% (3/35) | Fever post-M (2)<br>Parotitis post-Mp (2)<br>PSC post-VV (1) |

(Continues)

**TABLE 1** (Continued)

| First author/ Publication year | Study type, age | Population organ/ Number | Vaccine | Time frame of follow-up | Timing of vaccine | Immune evaluation prevaccine | Efficacy | Adverse outcomes (number) |
|---|---|---|---|---|---|---|---|---|
| Pittet 2018 | Prospective cohort, pediatric | Liver (44) | MMR | 3 y | Median 76 mo (range 48-131 mo) | Prevaccine titers and other workup[f] | Seroconversion[g]: M—98% at 4 wk after 2 doses, 62% at 1 y, 86% at 2 y, 89% at 3 y | Fever (4)<br>Tiredness (3) Headache (2)<br>Headache/myalgia/GI complaints (1)<br>Coryza/conjunctivitis (1)<br>Rash (4)<br>Serious AE: [h]<br>Rejection (3)<br>PTLD (2)<br>Intestinal obstruction (1)<br>Hepatitis (1) |
| Dansereau 2008 | Systematic review, adult and pediatric | SOT (114) | MMR (59)<br>VV (82) | 1993-2006 | 1.5-201 mos | Prevaccine titers | Seroconversion:<br>M—62%-100%<br>Mp—100%<br>R—100%<br>VV 62-86 | Rash post-VV (10)<br>Rejection (1) |
| Croce 2017 | Systematic review, adult and pediatric | SOT (339)<br>Liver (271)<br>Kidney (62)<br>Heart (4) | VV (192)<br>MMR (172) | 1977-2016 | ~1 y | Prevaccine titers | Seroconversion:<br>M—44%-100%<br>Mp—48%-100%<br>R—70%-100%<br>VV—25%-87%<br>Clinical failure:<br>VV—3.6% | Moderate varicella (14)<br>Parotitis (2)<br>Rejection (3)[a] |
| Rand 1993 | Retrospective review, pediatric | Liver (18) | MMR (6)<br>Measles (12) | Unclear | 1.5-65 mo (mean 23 mo) | Unclear | Seroconversion:<br>41% immune (7/17)<br>18% indeterminate (3/17) | Rejection (1) |
| Kano 2002 | Retrospective review, age not specified | Liver (13) | MMR and VV (13) | 1994-2000 | >1 y post-tx | Unclear | Seroconversion:<br>M—85% (11/13)<br>Mp—100% (6/6)<br>R—100% (2/2)<br>V—71% (5/7) | None reported |
| Khan 2006 | Retrospective review, pediatric | Liver (42) | MMR (31)<br>VV (35) | 1989-2004 | MMR—median 26 mo (range 4-201)<br>VV—median 49 mo (range 4-173 mo) | Not reported | Seroconversion:<br>M—73% (19/26)<br>VV—64.5% (20/31) | Vesicular rash and fever (3) |

(Continues)

**TABLE 1** (Continued)

| First author/ Publication year | Study type, age | Population organ/ Number | Vaccine | Time frame of follow-up | Timing of vaccine | Immune evaluation prevaccine | Efficacy | Adverse outcomes (number) |
|---|---|---|---|---|---|---|---|---|
| Chaves 2005 | Cross-sectional cohort, pediatric | Renal (6) | VV (VariIrix®), | 2001-2002, no f/u specified | Median 36 mo (range 12-91 mo) | Varicella titers | Seroconversion: VV—66.6% (4/6) | None reported |
| Levitsky 2002 | Case report, adult | Liver (1) | VV (Varivax®) | 5 mo post-episode | 10 mo post-tx | Not measured | Seroconversion: IgG/IgM neg 3 wk post-transplant | Disseminated varicella, fever (1) |
| Kraft 2006 | Case report, adult | Heart (1) | VV (Varivax III®) | 2 mo post-episode | 2 y post-tx | Varicella titers | Not measured | Disseminated vaccine strain varicella (1) |
| Ortiz-Brizuela 2019 | Case report, adult | Kidney (1) | HZ (Zostavax®) | 10 d post-episode | 4 y post-tx | Not measured | Not measured | Disseminated zoster, cytopenia |

Abbreviations: HZ, herpes zoster vaccine; M, measles vaccine; Mp, mumps vaccine; PSC, primary sclerosing cholangitis; R, rubella vaccine; SB, small bowel; tx, transplant.

[a]Six episodes of rejection are documented in the literature. One patient developed an episode of acute rejection 3 wk after measles vaccination. The other patient showed chronic rejection at the time of vaccination and remained unchanged for 1 y. Another single rejection episode of the liver was reported, which occurred more than 1 y after a VV and was considered as unassociated to immunization. Pittet et al (2018) documented three episodes of rejection occurring at 6 mo, 9 mo, and 3 y post-vaccination that were considered non-attributable to vaccination.

[b]As diagnosed by primary care physician, 1-8 wk post-immunization.

[c]>1 y post-vaccine.

[d]Lymphocyte counts: >1500/L for children younger than 6 y/o and >1000/L for children 6 y/o and older. CD4 counts: >700/L for children younger than 6 y/o and >500/L for children 6 y/o and older, CD4/8: >approximately 1.0. Normal lymphocyte function: lymphocyte proliferation in response to phytohemagglutinin, PHA (lymphocyte-blast transformation test using PHA): normal. Immunoglobulin G: >500 mg/dL.

[e]CD4, CD8, and B-cell numbers, quantitative IgG, IgA, and IgM, and lymphocyte proliferation to PHA, ConA, and PWM.

[f]Low immunosuppression (steroids <2 mg/kg/d, tacrolimus <0.3 mg/kg/d and tacrolimus level <8 ng/mL for >1 mo) and a sufficient lymphocyte count (≥0.75 G/L).

[g]A maximum of two booster doses were offered to patients that did not maintain seroprotection at follow-up, all booster recipients had appropriate response.

[h]None of the documented serious adverse effects were attributed to vaccination.

1990 through January 2018 was conducted. Search terms are listed in Table A1. References from relevant literature were also hand-searched. All studies and case reports that described outcomes and adverse events with live vaccines after SOT were distributed to consortium participants to review prior to meeting. Additional literature on the subject up to May 2019 as well as current major international guidelines on vaccination of transplant patients was reviewed during creation of the manuscript.

Participants reviewed the relevant literature on live vaccination in the SOT recipient along with publications relating to the immunologic assessment of the immunocompromised host and tracking of vaccine safety. Additionally, unpublished evidence and special area expertise were formally presented to participants in a didactic format during the consortium. Following this, two concurrent, parallel panel discussions on the use of MMR and VV in pediatric SOT recipients were conducted. Summary recommendations of each panel were then discussed with all consortium participants, with consensus achieved via majority vote and ultimately collated into these guideline recommendations.

Strength of recommendations was ascertained by a previously used approach that reflected the degree of agreement among participants.[22] The majority of recommendations achieved consensus with >90% of consortium participants "strongly agreeing" with each recommendation. If the percentage of consortium participants that "strongly agree" with the recommendation was < 90%, the exact percentage of those that "strongly agree" with the recommendation is reported. Input from all authors and conference participants was obtained prior to publication.

## 3 | OUTCOME

### 3.1 | General evidence summary

Recommendations are based on evidence for MMR vaccine and monovalent VV. No studies using combined MMRV post-transplant have been done, and as such, use of the combined vaccine should not be undertaken at this point. Of note, the recommendations are based mostly on data from kidney and liver TR, as there is minimal literature on other organ types (Table 1[23-37]). Six prospective cohort studies encompassing about 200 pediatric liver and kidney TR were reviewed, in addition to systematic reviews, retrospective reviews, and case reports. The results are summarized below.

The prospective studies were all performed in well-defined pediatric and adult post-transplant populations. The largest of these studies, performed within the last decade,[23-28] showed vaccine seroconversion rates of 44%-63% for measles, 73%-100% for mumps, 100% for rubella, and 32%-97% for varicella. Seroconversion was higher in studies where two doses of varicella vaccine were given. Vaccine efficacy in these studies was not reported. Adverse events varied, ranging from fever or mild local reaction to disseminated rash. Disseminated varicella infection was noted in two case reports of adult liver and heart TR who were inadvertently given VV at 10 months and 2 years post-transplant, respectively.[33,34] Vaccine strain virus was identified in one report; neither case had severe outcome or morbidity, but both received intravenous acyclovir.[33,34] Only one case of rejection that was temporally correlated with vaccination was noted in a liver TR who developed acute, biopsy-proven rejection 3 weeks after measles vaccination.[36]

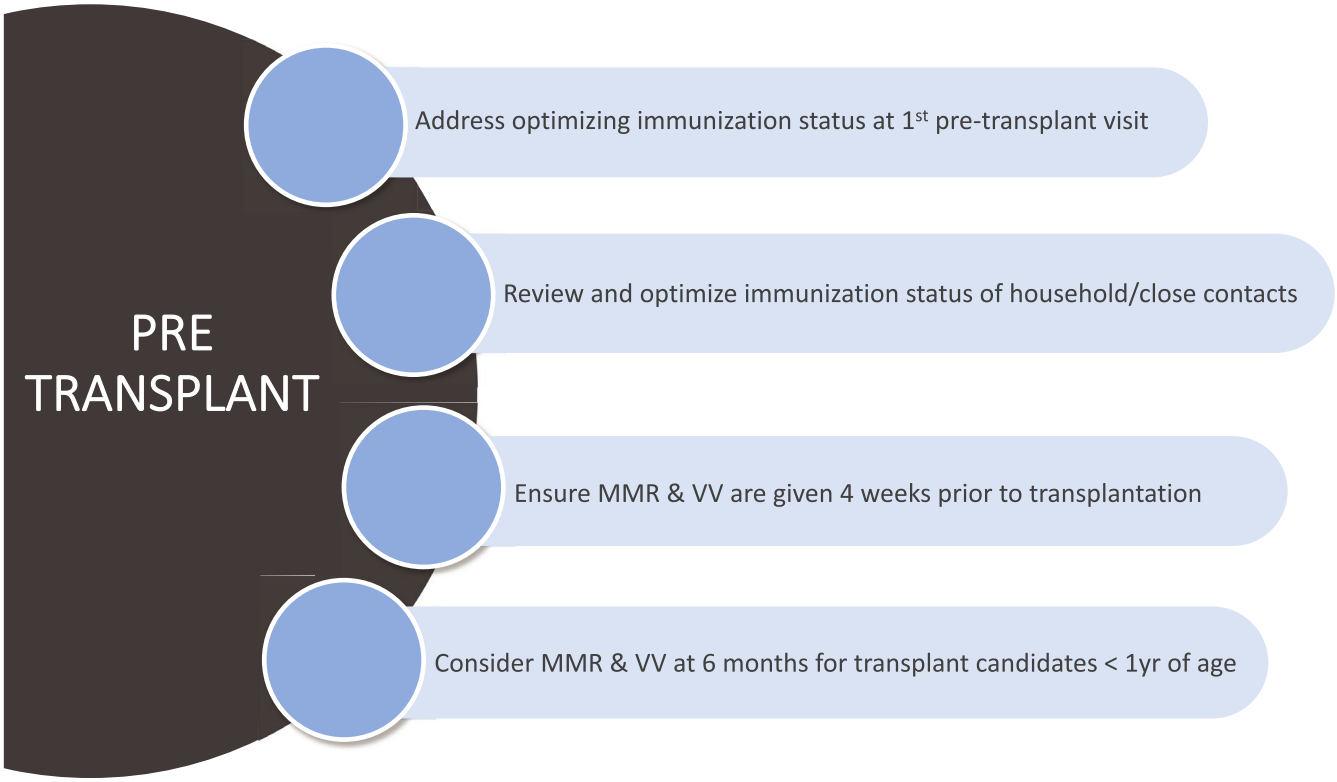


**FIGURE 1** Summary of recommended pretransplant considerations for MMR and VV administration. VV, varicella vaccine; y, year

### 3.1.1 | Outline of recommendations

Recommendations are structured according to the following sections:

1. Pretransplant optimization of vaccination with MMR and VV uptake.
2. Post-transplant patient evaluation and risk stratification prior to considering live vaccination.
3. Considerations specific to the vaccinating agent—MMR and VV.
4. Immunologic evaluation of the SOT recipient prior to live vaccination.
5. Informed consent prior to live vaccination.
6. Monitoring for adverse events following live vaccination.
7. Current knowledge gaps and future research endeavors.

*1. Pretransplant optimization of MMR and varicella vaccination*

*General pretransplant reccomendations.*

*Recommendations*:

(i) A review of immunization history should be part of the pretransplant evaluation (Figure 1). Pretransplant immunization optimization, including live viral vaccines, is critical and should be started at the first pretransplant visit (ie, prior to listing for transplant) and reviewed at every visit.

(ii) Household members and close contacts should have their immunization status reviewed and optimized. Vaccination of susceptible household contacts with MMR and varicella vaccines (or MMRV) is strongly recommended. Education for the family and the primary care physicians should specifically include the need to keep household members up to date for all vaccines even after transplantation of the candidate.

(iii) For VV and especially MMR, the benefits of administering live-attenuated vaccines should be weighed against potential risk of delay in active listing for transplantation as well as the risk of vaccine-derived disease, should transplantation occur in less than 4 weeks from the time of VV or MMR administration.

*Supporting information or evidence*:

Accelerated vaccine schedules are important for optimizing protection in a timely manner, especially prior to listing for transplant. National vaccine advisory committee recommendations are available to determine earliest age of administration of MMR and VV.[19-21] The risk of adverse events with vaccination prior to transplant is low, so even in geographic areas where the risk of exposure is low, immunizing prior to immunosuppression, if possible, affords the greatest benefit for patients.

When live vaccinations are given prior to 12 months of age, passive maternal antibody may impede effectiveness,[38] so repeat vaccination starting at 12 months of age, if practical, is typically recommended. Some centers accept a 4-fold rise in vaccine titer to MMR or VV, measured 4-6 weeks post-vaccination, as a marker of vaccine response when vaccine is given prior to 12 months of age. A further confounder is that patients on the transplant list frequently receive blood products, which can interfere with immune responses to vaccination. Published guidelines regarding minimum intervals for live vaccination after blood product administration are summarized in Table A2. For example, live vaccine administration is recommended 7 months after receipt of platelet transfusion. It should be recognized that while effectiveness will be impacted, there are no safety issues with administering MMR or VV in the presence of passive antibody either from blood products or maternally derived.

It is considered safe and prudent to vaccinate susceptible household contacts as transmission of vaccine-derived measles, mumps, and rubella viruses has not been described. While there is a theoretical risk of transmission of VV virus if a vaccinated person develops disseminated skin lesions, the risk of a SOT recipient developing severe disease is significantly less than if exposed to wild-type varicella virus infection. Since the risk of disseminated skin lesions from vaccine in an immune competent household member is low, we do not recommend separating family members unless lesions occur.

*Measles, mumps, and rubella vaccine pretransplantation*

*Recommendations*:

(i) MMR vaccine can be used as early as 6 months of age.[19-21] If transplant has not occurred by the age of 12 months, the schedule for the MMR vaccine should be restarted with two doses at a minimal interval of 4 weeks between doses.[21]

(ii) Ideally, MMR vaccine should be given at least 4 weeks prior to SOT. If an organ becomes available within 4 weeks of receiving MMR vaccine, a clinical decision must be made by weighing the risks of proceeding with transplant and starting immunosuppression in the face of recent live viral vaccine administration, and the efficacy of post-exposure prophylaxis such as IVIG, vs the risk of remaining on the wait list.

*Supporting information or evidence*:

There is a wide variation in practice across centers with respect to the MMR vaccination schedule in situations where the first dose of vaccine is given at 6 months. For example, some experts would recommend a second dose at 7 months of age. The long-term efficacy of MMR given at less than 9 months may be impacted by neutralizing maternal antibody, though systematic reviews of monovalent measles vaccine given at less than 9 months compared with 9-11 months show similar efficacy.[38-40] Regardless, WHO recommendations suggest that measles vaccine given at 6-9 months of age be considered a supplementary dose, with resumption of 2 doses according to the recommended national schedule.[21]

With respect to the interval between MMR vaccine and transplantation, a few centers would be willing to proceed within 3 weeks after receipt of MMR based on the known incubation periods of the viruses: measles 21 days, mumps 28 days, and rubella 14 days[18] (as mumps infection following SOT is unlikely to be fatal or lead to long-term sequelae). This is not uniform across all centers, as many clinicians are more concerned about period of viremia with MMR, and would prefer to delay organ acceptance until 4 weeks after MMR receipt. In

emergency situations, where an organ becomes available soon after a measles-containing vaccine has been given, provision of immunoglobulin as post-exposure prophylaxis should be considered.[18]

*Varicella vaccine pretransplantation*

*Recommendations*:

(i) The current practice of administering VV in some centers as early as 6 months of age is acknowledged. As with MMR vaccine, if transplant has not occurred by 12 months of age, we recommend restarting the VV schedule with two doses given at least 4 weeks apart, to optimize protection in the SOT recipient and prevent breakthrough disease.

(ii) Ideally, VV should also be given at least 3-4 weeks prior to transplant, due to the incubation period of up to 21 days. However, given the availability of effective antiviral therapy for varicella infection, some experts would consider using antiviral treatment (usually IV acyclovir) and proceeding with transplant even if the patient received VV within 3 weeks.

*Supporting information or evidence*:

Despite the potential for interference from transplacental maternal antibodies, and unclear efficacy, vaccination with VV prior to 12 months of age has been practiced.[19]

The incubation period of varicella would support transplantation 3 weeks after vaccination.[41] In situations where VV was administered within 3 weeks and transplant is deemed urgent, administering antiviral therapy (usually IV acyclovir) will decrease the risk of vaccine strain varicella-zoster virus disease.[42]

*2. Post-transplant patient evaluation and risk stratification prior to considering live vaccination*

*General post-transplant recommendations*

If optimal MMR and varicella immunization (defined by either seroconversion or receipt of two doses) is not achieved in the pretransplant period, administration of vaccines after SOT may be considered under certain circumstances post-transplant (Figure 2). The remainder of these guidelines will address these clinical circumstances.

The patient's clinical status, net state of immune suppression (including immunosuppressive medication, presence of opportunistic infections, rejection episodes, and rejection treatments), and a current immunologic evaluation are all important considerations when deciding about live virus vaccination. These factors should be carefully reviewed before live vaccines are administered after transplantation. Additionally, geographic and temporal differences in the epidemiology of these viruses might impact the decision to administer MMR or VV after transplantation, such as only administering MMR vaccine in times of outbreak or prior to travel to areas of endemic risk. Details regarding this are outlined in Section 3.

As mentioned above, current evidence supporting the use of live vaccines post-SOT is derived from kidney and liver transplant

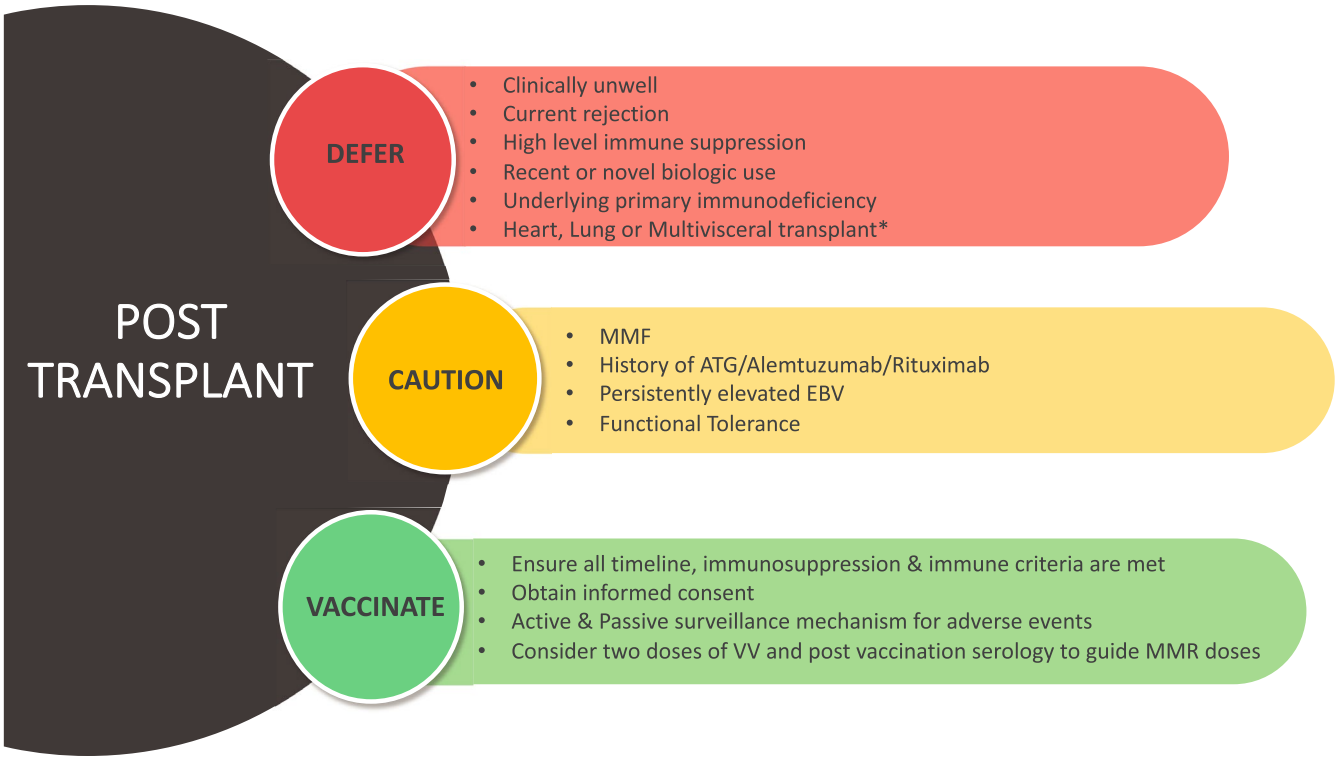


**FIGURE 2** Summary of recommended post-transplant considerations for MMR and VV administration. *Evidence to provide recommendations for live vaccination after heart, lung, intestine, or multivisceral transplant is insufficient, and therefore, these transplant groups may be excluded based on their net state of immune suppression or until further evidence is available. ATG, anti-thymocyte globulin; EBV, Epstein-Barr virus; MMF, mycophenolate mofetil/mycophenolate sodium; MMR, measles/mumps/rubella vaccine; VV, varicella vaccine

**TABLE 2** Patient considerations and evaluation prior to consideration of live vaccine administration in the pediatric SOT (liver and kidney) recipients

| | | |
|---|---|---|
| Group 1: Defer Vaccine | Patients in whom live vaccination post–solid organ transplant should be deferred | • Clinically unwell<br>• Cardiac, lung, and multivisceral TR[a]<br>• High-level immune suppression<br>• Patients with current rejection<br>• Use of novel biologic agents (other han those outlined in the table)<br>• Use of the following agents:<br>ATG <1 y prior<br>Alemtuzumab <2 y prior<br>Rituximab <1 y prior |
| Group 2: Proceed with Vaccine | Patients in whom live vaccination post-SOT is likely to be safe | Clinically well<br>Do not meet criteria in yellow or red boxes and meet all 3 of the following criteria:<br>1. Timeline criteria:<br>• 1 y post-transplant AND<br>• 2 mo post–rejection episode<br>*AND*<br>2. Intensity of Immunosuppression Criteria:<br>• Steroids (prednisone equivalent) <2 mg/kg/d or total cumulative <20 mg/d<br>• Tacrolimus <8 ng/mL for two consecutive readings<br>• Cyclosporine <100 ng/mL for two consecutive readings<br>*AND*<br>3. Minimum Immune Criteria:<br>• ALC<br>>1500 for children ≤6 y and >1000 cells/μL for children >6 y<br>• CD4<br>>700 cells/μL for children ≤6 y and >500 cells/μL for children >6 y<br>• Normal total serum IgG for age |
| Group 3: Vaccinate with Caution | Patient where evidence for safety and efficacy of live vaccination post-SOT is unclear. *Patients who meet these criteria may be eligible for live vaccination after more in-depth evaluation, and provided they meet the minimum timeline, immunosuppression and immunology criteria in Group 1* | • Patients who have received mycophenolate mofetil (MMF)/mycophenolate sodium<br>• Patients who have received the following T cell–depleting agents:<br>ATG—wait 1 y[b]<br>Alemtuzumab—wait 2 y[b]<br>• Use of rituximab—wait 1 y[b]<br>• Patients with persistently elevated EBV viral loads.<br>• Liver transplant recipients who are undergoing immune suppression withdrawal with the goal of cessation or those who are deemed to have "functional tolerance" |

Abbreviation: y, year(s).
[a]Evidence to provide recommendations for live vaccination after heart, lung, intestine, or multivisceral transplant is insufficient, and therefore, these transplant groups may be excluded based on their net state of immune suppression or until further evidence is available.
[b]Wait stated time interval prior to further evaluation and consideration for live vaccination.

recipients. As such, evidence to provide recommendations for live vaccination after heart, lung, intestine, or multivisceral transplant is currently insufficient, and therefore, these transplant groups may be excluded based on their net state of immune suppression.

Based on current evidence, susceptible patients were divided into three groups (Table 2):

*Group 1: Defer Vaccine: Patients in whom live vaccination post–solid organ transplant should be deferred*

*Recommendations*:

Based on their levels of immunosuppression and potentially more profound net state of immunosuppression, certain categories of patients should have live vaccines deferred. These patients:

- Are clinically unwell (eg, during evaluation of acute major intercurrent illness), or have suspected or confirmed systemic infection.
- Have current rejection or are on treatment for current rejection (antibody-mediated or cellular rejection)
- Have high levels of immune suppression, as determined by clinical care team, or not meeting criteria outlined in Sections 1 and 2:
  - Steroids (prednisone equivalent) >2 mg/kg/d
  - Tacrolimus trough level >8 ng/mL for two consecutive readings
  - Cyclosporine trough level >100 ng/mL for two consecutive readings
  - ATG administration within prior 12 months
  - Alemtuzumab administration within prior 24 months
  - Rituximab administration within prior 12 months
- Are receiving novel biologic agents (biologics other than ATG, alemtuzumab, rituximab)
- Are those with a suspicion of underlying primary immunodeficiency (specialist consultation is recommended prior to consideration of live vaccines in primary immunodeficiency)

- Are heart, lung, and multivisceral transplant recipients, until further evidence is available

*Supporting information or evidence*:

Patients who are clinically unwell, have suspected or confirmed systemic infection (such as CMV DNAemia requiring antivirals), are currently receiving augmented immunosuppression to treat current rejection, or are on high levels of immune suppression as defined above are recommended to have live vaccination deferred as was done in previous prospective studies.[23-27] CMV infection that requires antivirals can be a sign of underlying T-cell dysfunction, and as such, live vaccine should be held until episode resolved. T cell–depleting agents have persistent immunologic effects lasting 1-2 years such that live vaccinations are recommended to be deferred until the stated time period has elapsed—1 year after receipt of ATG and 2 years after receipt of alemtuzumab.[43-46] Novel biologic agents, for example, obinutuzumab, are increasingly being used for various indications in pediatric transplantation, and until long-term data regarding immune reconstitution after use of such agents are available, we recommend deferring live vaccination in these recipients.[47]

*Group 2: Proceed with vaccine: Patients for whom live vaccination is likely to be safe.*

*Recommendations*:

(i) Renal and liver transplant recipients in whom MMR and VV are likely to be safe are in recipients greater than 1 year post-transplant and greater than 2 months after an acute rejection episode, meet minimum immune suppression criteria (Table 2), and do not meet any of the criteria listed for Group 1.
(ii) An immune evaluation of patients who meet criteria outlined in (i) should be undertaken prior to consideration of live vaccination. This includes absolute lymphocyte count, absolute CD4 count, and immunoglobulin G level greater than or equal to age-related normal values. A more in-depth immune evaluation is suggested for patients that meet criteria for Group 3 (see below).
(iii) If the decision is made to offer both VV and MMR, consider administering VV first given the availability of effective antiviral treatment should the need arise.

*Supporting information or evidence*:

Criteria for timing, immune suppression, and immune evaluation were adapted from previously published prospective studies.[23-27] Posfay-Barbe et al, Kawano et al, and Pittet et al all considered initiating immunization 1 year post-transplant, whereas Shinjoh et al waited until 2 years post-transplant. Group consensus was based on current evidence, as well as recognition that 12 months post-transplant in stable SOT recipients is a time of maintenance immune suppression and low risk of opportunistic infections[48]; 1 year post-transplant would be reasonable to consider live vaccination.

Up to one-third of pediatric liver transplants have a rejection episode.[49] In the setting of allograft rejection, Posfay-Barbe et al administered MMR and/or VV at least 2 months after completion of treatment for rejection, while others administered MMR and/or VV 6 months post-rejection.

There are concerns that live viral vaccines could precipitate rejection.[49] Literature review found only one reported case of acute rejection temporally associated with live vaccination, which occurred 21 days after measles-containing vaccine in a liver transplant recipient (Table 1[37]). Based on evaluation of previous study protocols,[23-27] the consensus forum recommended live vaccine administration at a minimum of 2 months post–rejection episode. This requires that the transplant recipient is receiving low-level immune suppression, meets immunologic criteria, and has stable clinical status after the rejection episode. This recommendation took into account the common occurrence of rejection and the variability of severity and treatment of each episode.

Immune suppression thresholds believed to be safe for administration of live viral vaccines in previous studies ranged from (i) tacrolimus levels of <5 to <8 ng/mL, (ii) cyclosporine levels <100 ng/mL, and (iii) prednisone equivalent doses ranging from discontinuation for at least 6 months to <2 mg/kg/d.[23-27] Patients receiving sirolimus were not included in these studies. These are consistent with previously published definitions of "maintenance" immune suppression for pediatric liver transplantation where the goal is often low dose (3-10 mg prednisone) or cessation of steroid with calcineurin inhibitor monotherapy.[49] The consortium agreed on the following thresholds:

- tacrolimus trough levels of <8 ng/mL for two consecutive readings or cyclosporine levels of <100 ng/mL for two consecutive readings.
- prednisone dose equivalent to <2 mg/kg/d or total cumulative dose of <20 mg/d for those >10 kg.

Patients who meet these criteria are deemed to have "low-level immune suppression" and are thus eligible for consideration for live vaccination.

In previous studies, immune evaluations in patients prior to live vaccine administration varied in depth and complexity and were often institution-specific based on available immune function tests. Section 4 further details the evidence and recommendations for immune evaluation. In general, patients who have no clinical suspicion for an underlying immune deficiency and are not on novel (obinutuzumab) or high levels of immune suppression are recommended to have a CD4 count and absolute lymphocyte count to ensure current immune suppression is not causing significant lymphopenia/CD4+ lymphopenia (see Table 2 and Section 4), as defined in the literature.[23-27]

*Group 3: Vaccinate with Caution: Patients where evidence for safety and efficacy of live vaccination post-SOT in unclear. Patients who meet these criteria may be eligible for live vaccination after more in-depth evaluation (Section 4)*

*Recommendations*:

(i) Based on their variable net state of immunosuppression, certain categories of patients require in-depth immunologic evaluation prior to consideration of live vaccination (see Section 3,

immunologic evaluation). These patients are:

- Patients who have received mycophenolate mofetil (MMF), mycophenolate sodium (84*% of consortium participants strongly agree with this recommendation)*
- Patients who have received the T cell–depleting agents:

ATG—wait at least 12 months after administration prior to considering live vaccination (89*% of consortium participants strongly agree with this recommendation)*

Alemtuzumab—wait at least 24 months after administration prior to considering live vaccination (89*% of consortium participants strongly agree with this recommendation)*

- Patients who have received rituximab—wait at least 12 months after administration prior to considering live vaccination (89*% of consortium participants strongly agree with this recommendation)*
- Patients with persistently elevated Epstein-Barr virus (EBV) viral loads.
- Patients with complete thymectomy in the neonatal period (*63% of consortium participants strongly agree with this recommendation)*
- Liver transplant recipients who are in "clinical operational tolerance" (defined below)

*Supporting information or evidence*:

Mycophenolate mofetil (MMF) (or related antiproliferative such as mycophenolate sodium/mycophenolic acid) and azathioprine can be used in the immune suppression armamentarium post-transplant and have activity against T-cell proliferation and antibody production by B cells via DNA synthesis impairment.[50,51] It also has effects on antigen presentation as well as lymphocyte and monocyte recruitment.[50] Specifically, with regard to MMF, the duration of immunosuppressive effects is as yet unclear, and patients who have received MMF have higher rates of infectious complications when compared to other immune suppression regimens post-transplant.[50,51] In addition, patients who received antiproliferative agents encompassed only 27 of the ~250 patients in the 6 published cohort studies of live vaccines post-SOT.[23-27] Thus, the safety of live vaccination in patients who have received antiproliferative agents has not been well established, and though they may be eligible for live vaccination, further immunologic assessment or immunology consult should be considered prior to proceeding.

T cell–depleting agents, such as ATG and alemtuzumab, are used in transplant recipients most commonly for induction or treatment of rejection. ATG is a polyclonal antibody that depletes T cells in peripheral blood and to some extent lymphoid tissue. Long-term immunologic studies of patients who receive ATG indicate immune abnormalities persist up to 1-2 years after administration specifically with regard to T-cell function (proliferative capacity and cytokine production).[43-45] Thus, if ATG has been given in the past 24 months, further immunologic investigation is warranted prior to live vaccination, and live vaccination should be deferred if given less than 12 months ago.

Alemtuzumab exerts its T-cell depletion through inhibition of CD52, and in long-term studies after treatment of patients with multiple sclerosis, persistent immunologic effects are seen at 2 years post-therapy.[46] As these studies are small in number and done in other disease states, safety of live vaccine administration even 2 years after T cell–depleting agents for organ transplantation is as yet unclear and should prompt further immunologic investigation prior to consideration of live vaccines as well as deferral of live vaccination until 2 years after receipt. The significance of very remote use of T cell–depleting agents (eg, >5 years ago) is variable. Practitioners may or may not choose to evaluate these patients with greater depth prior to vaccination.

Rituximab is an anti-CD20 monoclonal antibody that efficiently depletes the peripheral B-cell pool and, in the transplant setting, is most often used to treat antibody-mediated rejection or sensitization, EBV disease including PTLD, or other underlying diseases.[52] Rituximab therapy significantly reduces vaccine immunogenicity and may increase the risk of adverse events after live vaccination. Vaccination with live virus vaccines is not recommended while on rituximab or during peripheral B-cell depletion.[53] Studies of live vaccines post-rituximab have not been done, and responses to killed vaccines given 6-18 months post-rituximab are variable.[54-56] Live vaccine safety and efficacy in patients who have received rituximab >1 year prior are unclear, and further immunologic workup is recommended, including B-cell studies, prior to vaccination.

Certain post-transplant conditions should also prompt further immunologic evaluation prior to consideration of live vaccination. Persistently elevated EBV viral loads are suggestive of potential T-cell dysfunction, and safety of live vaccination in this state is unclear.[57,58] T-cell dysfunction also likely contributes to elevations in CMV viral load; however, as it is the lytic replication of CMV that contributes to viral elevation, and this is responsive to antivirals (as indicated), live vaccinations can be held until episode resolution[59] and discontinuation of the antivirals, as antivirals will also inhibit VV efficacy. For elevated EBV viral loads, episode resolution may not occur as readily as it is often the latent virus that contributes to this persistence and antivirals are not efficacious in symptom resolution.[60] The immunomodulatory effects of this state are as yet unclear.[57,60] As such, these patients do not necessarily need to be completely excluded for live vaccination, but rather should be vaccinated with caution.

Total thymectomy in early infancy has effects on circulating T-cell pools for up to 5 years post-procedure. However, the functional and clinical significance of this state is unclear, and live vaccination efficacy and safety are unknown.[61] Thymectomy is thought to be rare in kidney and liver transplant recipients.

For some liver transplant recipients, a state of clinical operational tolerance can be achieved, where all immune suppressive medications can be withdrawn.[62] As mechanisms of immune homeostasis for this state are as yet unclear, the safety of live vaccination in this state in regard to the risk of triggering a rejection episode is unknown.

*3. Considerations specific to the immunizing agent—MMR and VV*

*Measles, mumps, and rubella vaccine post-transplantation*

*Recommendations:*

(i) In geographically low-incidence areas, we recommend restriction of MMR vaccination after transplantation to local outbreaks or upcoming travel to high-incidence areas.
(ii) No firm recommendations regarding number of doses of MMR to be administered post-transplant are made and are left to the discretion of the transplant and infectious disease teams. Post-vaccination serology may guide further doses. If more than one dose is planned, there should be a minimum interval of 4-8 weeks between doses, dependent on age and urgency.

*Supporting information or evidence*:

It is recognized that measles, mumps, and rubella viruses circulate with varied prevalence throughout the world. Given this, in geographically low-incidence areas (as defined by the WHO) MMR would not be given routinely after SOT based on currently available literature. In geographically low-incidence areas, it is presumed that risk of wild-type infection is lower than risks of complications of MMR post-SOT. However, in high-incidence areas or in outbreak situations, some centers would proceed to offer MMR vaccination post-SOT based on current evidence to prevent primary infection from these pathogens. This includes SOT recipients who are planning travel or travel regularly to high-incidence areas of measles or mumps. In these situations, ongoing risk/benefit analysis of providing MMR or monovalent measles vaccine (where available) post-SOT should be undertaken. Transplant teams should review local epidemiologic monitoring of measles, mumps, and rubella regularly, and if vaccination is considered, patient characteristics as outlined in Table 2 could be taken into consideration.

At this point, no firm recommendations can be made regarding the number of doses of MMR to be given post-transplant. In Khan et al's retrospective review of live vaccination post–liver transplantation, up to three doses of MMR were given without adverse events and with a measles seroconversion rate of 73%.[37] Kawano et al[24] also gave a maximum of three doses, using seroconversion 6-8 weeks post-transplantation to guide further doses. Shinjoh et al[25,26] gave separate vaccines for measles, mumps, and rubella and offered re-immunization to those who had either primary or secondary clinical vaccine failure, or if titers were low positive/borderline. Pittet et al[27] followed post-vaccine titers to MMR at yearly intervals to guide booster dosing to maximum of three doses, with good booster responses in those that required them. In general, seroconversion rates after one dose of vaccine were highest for rubella, followed by measles and then mumps (Table 1). Post-vaccination serology, where available, can guide number of doses or can be used as a marker of adequate protection against MMR.

At this time, there are no data on combined MMRV vaccine post-transplant, and therefore, we do not recommend its use after transplantation.

*Varicella vaccine post-transplantation.* ***Recommendations***:

(i) Reviews of evidence and worldwide prevalence of varicella suggest that VV should be considered in susceptible SOT recipients post-transplant in keeping with the categories defined above.
(ii) It may be reasonable to give VV as the first live vaccine post-transplant because effective antiviral therapy is available if rescue therapy is required and varicella is relatively common.
(iii) Evidence suggests that two doses of VV improve seroconversion rates and long-term persistence of antibodies.
(iv) A minimum interval of 4 weeks between doses of VV is recommended.

*Supporting information or evidence*:

Varicella incidence after implementation of a universal two-dose vaccination strategy is estimated to be 3.5-3.9 per 100 000 population,[63,64] with decreases observed in both varicella-related hospitalizations and outbreaks.[65] However, countries that do not have mandatory varicella vaccination (which includes most European countries) describe a much higher incidence of 15-16 per 1000 person/y.[66] Given these recent incidence rates of varicella, we recommend that VV be considered post-transplantation. Previous studies of VV post-transplant ranged from 1 to 3 doses, with efficacy rates ranging from 25% to 97% (Table 1). The majority of studies used post-vaccine seroconversion to guide further doses, and the majority of patients required at least two doses of vaccine for sustained antibody titers.[23-28,32] It is thus recommended that two doses of VV are likely required, with potential use of post-vaccine seroconversion guiding further doses. Currently, the safety of giving >3 doses of VV is unknown. Minimum interval dosing should also be in line with country-specific national advisory committee recommendations, and usually ranges from 4 to 12 weeks.[19-21] A practical suggestion brought forward during the consortium was the consideration of using VV as the first live vaccine post-transplant as acyclovir is likely to be effective if the child develops vaccine-associated varicella.

*4. Immunologic Evaluation of the SOT recipient prior to consideration of MMR and VV vaccination*

*Recommendations*:

(i) The minimum immunologic evaluation for patients who are being considered for live vaccines is described in Table 2 and includes an ALC, CD4+ T-cell count, and total IgG level.
(ii) For those in whom safety/efficacy of live vaccination post–solid organ transplant is unclear (Table 2, yellow section), a more in-depth immunologic evaluation may aid clinical decision-making.

*Supporting Information or Evidence*:

A patient who meets all the criteria described above to receive MMR or VV would still need to meet minimal immunologic criteria outlined in Table 2 prior to immunization. Thresholds for ALC and

CD4+ T-cell count were determined based on expert opinion, previously published prospective studies,[23-27] and live vaccination literature guidelines for other immunocompromised states such as HIV or pDGS.[67-71]

For patients who do not meet the immunologic criteria in the green section in Table 2 or fall into criteria outlined in the yellow section in Table 2, a more detailed immune evaluation is suggested. However, a prescriptive approach to what should be included in this more extensive immunologic evaluation is not feasible, since there is a wide range of possible clinical scenarios and access to immunologic tests across various centers. Accordingly, evidence is extrapolated from other immunosuppressive conditions to guide potential further workup.

In persons living with HIV infection, administration of live vaccines is recommended to patients ≤5 years of age with CD4+ T-cell percentages ≥15% for ≥6 months, and in those aged >5 years with CD4+ T-cell percentages ≥15% and CD4+ T-cell counts ≥200 lymphocytes/μL for ≥6 months.[67]

In pDGS, MMR vaccine was safely administered to patients with a CD4+ T-cell count >500 cells/μL, adequate proliferation to PHA, and anti-tetanus antibody levels at least above 0.15 IU/mL (dependent on last booster vaccine).[68] Mild reactions (fever and skin rash that did not require medical intervention) occurred in 6 (7.3%) of 82 patients, but moderate or severe reactions were not observed.[68] Similar observations were seen in 37 other pDGS patients vaccinated with MMR.[69,70]

The VV experience in pDGS has also shown similar results. In one cohort of 13 VV recipients with pDGS and CD4+ >500 cells/μL, no patient received VZIG or developed clinical vaccine-associated varicella infection.[69] Another 32 varicella-vaccinated pDGS patients had mild side effects, but no severe reactions were reported.[70] A sporadic case report has linked varicella vaccine to death in pDGS patient with CD4+ count of <500 cells/mm.[3,71] This evidence supports the use of CD4+ >500 cells/μL as a safety threshold for consideration of live vaccination.[68-71]

In settings where evidence has not evaluated safety of live viral vaccination, the immune evaluation is suggested to be expert driven and to consider the clinical history of the patient, the prior immunosuppression, and the use of alternative protective strategies such as passive immunity. For example, given the potential for long-term effects following rituximab, documentation of the return to normal B-cell counts is recommended prior to consideration of live viral vaccines, in addition to the suggested minimum evaluation of ALC, CD4+ T-cell count, and IgG. In addition, consideration could be given to demonstrating the ability to produce protective antibodies to inactivated vaccines prior to administration of live viral vaccines.

*5. Informed consent prior to administration of live vaccines*

*Recommendations*:

(i) Consent should be consistent with standard of practice for consent for vaccination at the local institution.

(ii) Additional documentation both for primary care provider and for families should be given to provide education and indication for "off-label" use of live vaccines in SOT recipients.

*Supporting information or evidence*:

Clinicians should follow approaches that are consistent with practices in their jurisdictions. However, it seems prudent to have in place a mechanism of informed consent, the documentation of which would vary across jurisdictions. Informed consent is obtained prior to use of non-live vaccines in most, if not all jurisdictions. However, there is variability in the extent to which documentation of this consent occurs and the nature of the documentation. An informal survey during the consortium meeting indicated that consent ranged from formal written informed consent for each administered vaccination to general discussion and verbal consent with chart documentation of the process and parent's or guardian's agreement.

*6. Monitoring for adverse events following immunization*

*Recommendations*:

(i) A combination of active and passive surveillance should be in place to monitor for adverse events.

(ii) Patients and families should be advised to seek medical attention promptly for new onset of rash or high fever (T > 38°C) within 4 weeks following vaccination. If active varicella-zoster virus infection is suspected, detection of the virus and strain typing should be attempted and initiation of antiviral therapy should be considered

(iii) We recommend a minimum of one telephone contact with the patient's caregivers at 3-4 weeks after vaccination to inquire about symptoms including fever, rash, injection-site reactions, and/or any symptoms that required medical attention or affected daily activities

(iv) Practitioners should conform to local requirements to report adverse events after vaccination. This includes passive vaccine safety surveillance systems (eg, US Vaccine Adverse Event Reporting System[72]), quality improvement bodies, and research ethics boards/institutional review boards if applicable. Practitioners should make themselves aware of ongoing surveillance studies of live vaccination post-SOT in their jurisdictions.

*Supporting information or evidence*:

Patients and families should be counseled to monitor for the appearance of rash and/or fever, particularly in the second week after vaccination, and to seek medical attention promptly. If skin lesions are suspicious for varicella, virologic samples should be collected for VZV PCR or culture where testing is available. Strain typing should also be attempted to discern vaccine vs wild-type strain. If VV-associated disease is suspected, consider prompt initiation of antiviral therapy. Likewise, for all suspicious rashes or symptoms, appropriate isolation precautions should be undertaken by the patient and healthcare facility. Transplant teams may also consider monitoring for signs of acute rejection that occur within a certain time frame (eg,

30 days) post-vaccination. To facilitate monitoring and management of patients post-vaccination, referral to a specialized immunization clinic, where such services exist, or an infectious disease specialist should be considered.[73]

Different mechanisms exist to monitor for adverse events following immunization, including active as well as passive surveillance. Most countries have passive surveillance systems to capture spontaneous reports of adverse events reported by clinicians, patients, and vaccine manufacturers.[72,74] In some jurisdictions, certain events have mandated reporting. Healthcare providers should be aware of the reporting requirements in their jurisdiction.

Active surveillance systems include hospital-based sentinel surveillance (eg, Canadian Immunization Monitoring Program Active [IMPACT][75]), participant-based active surveillance (eg, Canadian National Vaccine Safety Network[76]), and analysis of linked health administrative databases (eg, Vaccine Safety Datalink[77]). Participant-based active surveillance systems use online surveys or text messaging to capture the occurrence of new health events within a specific interval post-vaccination.[78] Severe adverse events are confirmed by a nurse. This approach could be adapted to monitor for adverse events after live vaccines across several transplant centers. At a minimum, centers implementing live vaccination for SOT recipients should consider contacting patients and/or caregivers 3-4 weeks after live vaccination to capture adverse events.

The number of SOT recipients who will be eligible for live vaccination in a given jurisdiction is likely to be small, and current active and passive surveillance systems may not be able to detect increases in rare adverse events in this population. An international registry of outcomes of SOT recipients receiving live vaccines would augment existing surveillance systems and help to facilitate earlier detection of changes in the safety profile of live vaccines in this population.

*7. Current knowledge gaps and future research endeavors*

Several knowledge gaps were identified at the consortium. Additional research is needed to address several issues that relate to or influence the role of live vaccines after pediatric SOT. These include, but are not limited to:

- Live vaccination in cardiac, lung, and multivisceral transplant recipients
- Role of the recently approved herpes zoster subunit vaccine in the prevention of primary varicella infection and herpes zoster reactivation post-transplantation.
- Optimal assessment of immune status prior to vaccination
- Specific criteria that define level of immune suppression
- Immunologic consequences of newer immune suppressants, biologic agents, and mTOR inhibitors such as sirolimus.
- Impact of incomplete vaccination series administered prior to transplantation
- Optimal assessment of immune responses post-vaccination, including number of doses required to achieve immune protection, and durability of vaccine response
- International, multicenter registry of patients receiving live vaccines post-SOT to track adverse events and monitor for safety.

## 4 | SUMMARY

This document provides guidance on the use of live viral vaccines after SOT and is the first to guide clinicians with minimum standards for baseline immune evaluations and practical considerations such as the administration of varicella vaccine first. While recommendations are made, the goal is not to be prescriptive but to provide standard principles to follow if live vaccines are being considered in these patients. The development of a structured, color-coded framework assists knowledge translation and allows clinicians to see how these recommendations apply to their patients. As further data emerge, subsequent iterations of these guidelines will incorporate data for other organ groups and vaccine types. In addition, recognizing that care of SOT recipients can occur both in specialized centers and in primary care settings, these guidelines were written such that they could be adapted regardless of primary care vs specialty practice settings. Lastly, the guidelines echo those iterated in the IDSA vaccination in the immunocompromised host guideline as well as other international guidelines.[79-81] We advocate for strategies for live vaccines administration in SOT recipients to be discussed at large expert consensus bodies in addition to national regulatory bodies and advisory committees on vaccination.[19-21]

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### AUTHOR CONTRIBUTIONS

Dr Suresh and Dr Allen: Collated the consortium data and wrote the drafts of the manuscript; Dr Upton, Dr Green, Dr Pham-Huy, Dr Posfay-Barbe, Dr Michaels, and Dr Top: Contributed to the writing of initial drafts of sections of the manuscript; Drs. Green, Pham-Huy, Posfay-Barbe, Michaels, and Top: Jointly share third authorship status; Dr Allen and Dr Upton: Organized the consortium and assembled all contributing authors; all authors: Were members of the consortium and edited drafts of the manuscript.

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## APPENDIX A

**TABLE A1** Search terms used in literature review

| |
|---|
| Transplant |
| Transplantation |
| Vaccine |
| Vaccination |
| Immunization |
| Measles |
| Mumps |
| Rubella |
| Measles-Mumps-Rubella Vaccine |
| Varicella |
| Chickenpox |
| Herpes Zoster Vaccine |
| Herpes Zoster |
| Attenuated |
| Live |

**TABLE A2** Recommended time interval before receipt of MMR or varicella vaccine

| Product | Dose | Advisory Committee on Immunization Practices (CDC) Interval | Canadian Immunization Guide (PHAC) Interval |
|---|---|---|---|
| Blood | | | |
| Red blood cells, washed | 10 mL/kg (negligible IgG/kg) | None | None |
| RBCs, adenine-saline added | 10 mL/kg (10 mg IgG/kg) IV | 3 mo | N/A |
| Reconstituted red blood cells | 10 mL/kg | N/A | 3 mo |
| Packed red blood cells (hematocrit 65%) | 10 mL/kg (60 mg IgG/kg) IV | 6 mo | 6 mo |
| Whole blood (hematocrit 35%-50%) | 10 mL/kg (80-100 mg IgG/kg) IV | 6 mo | 6 mo |

(Continues)

**TABLE A2** (Continued)

| Product | Dose | Advisory Committee on Immunization Practices (CDC) Interval | Canadian Immunization Guide (PHAC) Interval |
|---|---|---|---|
| Plasma/platelet products | 10 mL/kg (160 mg IgG/kg) IV | 7 mo | 7 mo |
| Immunoglobulin | | | |
| IM immunoglobulin | 0.02-0.06 mL/kg IM | N/A | 3 mo |
| IM immunoglobulin | 0.25 mL/kg IM | N/A | 5 mo |
| IM immunoglobulin (measles prophylaxis) | 0.50 mL/kg IM | 6 mo | 6 mo |
| IV immunoglobulin (replacement therapy, ITP, measles or varicella prophylaxis) | 300-400 mg/kg IV | 8 mo | 8 mo |
| IV immunoglobulin (replacement therapy, ITP) | 800-1000 mg/kg IV | 10 mo | 10 mo |
| IV immunoglobulin (Kawasaki disease) | 2000 mg/kg IV | 11 mo | 11 mo |
| Specific immunoglobulin | | | |
| Monoclonal antibody to respiratory syncytial virus (RSV) F protein (Synagis [MedImmune]) | 15 mg/kg/4 wk IM | None | None |
| Rabies prophylaxis (HRIG) | 20 IU/kg (22 mg IgG/kg) IM | 4 mo | 4 mo |
| Rh immune globulin | 300 mcg IM | N/A | 3 mo |
| Tetanus (TIG) | 250 units (10 mg IgG/kg) IM | 3 mo | 3 mo |
| Varicella-zoster immune globulin | 125 units/10 kg (60-200 mg IgG/kg) IM (maximum 625 units) | 5 mo | 5 mo |
| Hepatitis B prophylaxis (HBIG) | 0.06 mL/kg IM | 3 mo | 3 mo |
| Hepatitis A IG, duration of international travel ≤3 mo | 0.02 mL/kg (3.3 mg IgG/kg) IM | 3 mo | N/A |
| Hepatitis A IG, duration of international travel ≥3 mo | 0.06 mL/kg (10 mg IgG/kg) IM | 3 mo | N/A |
| Cytomegalovirus immune globulin (CMVIg) | 150 mg/kg, IV | 6 mo | 6 mo |
| Botulism immune globulin, intravenous | 1.5 mL/kg (75 mg IgG/kg) IV | 6 mo | N/A |

*Note:* Adapted from Tables 3-5 Advisory Committee on Immunization Practices and Chapter 11, Table 1 Canadian Immunization Guide.