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BRIEF COMMUNICATION

# Management and prevention of varicella and measles infections in pediatric solid organ transplant candidates and recipients: An IPTA survey of current practice

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## Abstract

**Background:** Varicella and measles infections can be life-threatening after solid organ transplantation (SOT) but may be preventable with live-attenuated vaccines (LAV).

**Methods:** This survey conducted in January 2019 among subscribers of the International Pediatric Transplantation Association listserv aimed to explore the current strategies to prevent and manage both infections in the pediatric SOT population, including recommending LAV after SOT.

**Results:** The answers given by 95 pediatric SOT healthcare workers show that these strategies are not yet optimal and call for further education. In particular, 59% of respondents are unnecessarily waiting for a SOT candidate to be >1 year of age to start administrating LAV before SOT. Interestingly, most respondents are willing to administer LAV after SOT (57%), and a fifth (21%) are already doing so, off-label. The survey queried the precautions taken to improve safety evaluations after LAV, and identified knowledge gaps and practitioners' concerns.

**Conclusion:** The results of this survey could be used as a starting point for education and promotion of the safe administration of LAV in carefully selected SOT recipients; in turn, this would increase available data that would contribute to the development of evidence-based guidelines by the transplant societies and ultimately prevent these infections after SOT.

**Abbreviations:** AST ID COP, American Society of Transplantation Infectious Diseases Community of Practice; IPTA, International Pediatric Transplant Association; IVIG, intravenous immunoglobulin; LAV, live-attenuated vaccine; MMR, measles-mumps-rubella; SOT, solid organ transplantation.

  

## 1 | INTRODUCTION

Varicella and measles infections cause serious complications in SOT recipients.[1-3] Although both diseases are vaccine-preventable, outbreaks continue to occur.[4] All non-seroprotected SOT recipients are at risk of acquiring these infections, during local outbreaks or while traveling to at risk areas. The AST ID COP has published guidelines to help physicians in preventing and managing varicella infection.[3,5] To date, there is no similar document available for measles infection, due to a lack of a specific antiviral agent and therefore mostly supportive care.[6]

Although both diseases are vaccine-preventable, vaccinations are not always optimally provided before SOT. Indeed, since the varicella and the measles-mumps-rubella (MMR) formulations are live-attenuated vaccines (LAV), the SOT candidate needs to be at least 6 months old in order to avoid vaccine-strain neutralization by circulating maternal antibodies. It is recommended that children receive LAV ≥4 weeks prior to the projected SOT.[7] Until recently, LAV were not recommended after SOT, due to lack of sufficient safety data and fear of complications secondary to uncontrolled viral replication.[7,8] However, LAV have been safely administered to SOT recipients, in the context of small clinical studies, off-label, or outbreak settings.[9-20] There is increasing evidence describing the use of varicella,[9-17] measles,[13-19] and yellow fever[20] vaccines after transplant that add to the knowledge that selected LAV can be safely administered to carefully selected SOT recipients. An international consensus document was recently published, describing the minimal standards that should be followed if considering the administration of LAV after SOT.[21]

Beyond the existing literature, it is likely that most of the off-label use of LAV post-SOT has not been reported nor published. Further it is suspected that a practitioner's approach and opinion regarding the use of LAV post-SOT varies around the world. The aim of this survey was to explore the strategies and local guidelines of caregivers on prevention and treatment of varicella and measles among SOT candidates and recipients in the pediatric transplant community, including use of varicella and measles vaccines before and after SOT. This survey was distributed before the publication of the consensus guideline and also aimed to gauge current medical staff opinions on recommending LAV after pediatric SOT.[21]

## 2 | METHODS

A 62-item survey was distributed electronically to the 651 subscribers of the IPTA listserv in January 2019. The survey was developed by the authors and explored management and prevention of varicella and measles infections in pediatric SOT candidates and recipients (detailed in the appendix). The introductory e-mail indicated that the completion of the survey implied informed consent from the participants to subsequent anonymous publication of their answers. A reminder was sent once.

Questions were asked on the following topics, for both varicella and measles: prevention in SOT candidates and recipients, treatment in SOT recipients, and off-label vaccination after SOT. It was clearly stated that the questions only pertained to SOT candidates and recipients; the management of patients following hematopoietic cell transplantation was not explored. Respondents' demographic and hospital data were collected, as well as local guidelines when available. Given the range of expertise and experience of those surveyed, the options of "do not know," "unsure," and "not applicable" were also provided, and completion of all questions was not mandatory for a survey to be included in analysis.

The answers of the 95 respondents included are described using standard descriptive statistics. Rates are expressed according to the number of answers available for each question (which is not always 95). When appropriate, rates are calculated among subgroups; these subgroups are defined by respondents' answer to previous questions (such as whether or not they administer LAV after SOT). Respondents were classified as "routinely administering LAV post-SOT" if they reported administrating on a routine basis at least one LAV (varicella and/or measles) to their SOT recipients, as "occasionally administering LAV post-SOT" if they administered at least one LAV occasionally (and none routinely), and as "never giving LAV after SOT" if they reported never administrating any LAV in transplant recipients. All analyses were performed using Stata software, version 13 (StataCorp).

## 3 | RESULTS

### 3.1 | Respondents' characteristics

A total of 100 subscribers responded. Most respondents (80%) completed at least 90% of questions. Five respondents completed only the first demographic questions and were removed from analysis leaving 95 respondents. Over 75% of the remaining 95 respondents answered all questions. Demographic data are available in Table S1 (appendix). Briefly, responders came from 27 different countries, including 46% from the United States; they were predominantly transplant physicians (68%). Most respondents were managing kidney (78%) or liver (54%) transplantation, and fewer were involved in heart (37%), lung (19%), pancreas (12%), small bowel (20%), or multivisceral (18%) transplantations. Half of the respondents were working in centers that performed only one type of organ transplant.

### 3.2 | Prevention of varicella and measles before transplantation

Nearly all respondents obtained varicella serology before SOT (92%, 88/95) and 97% (91/94) recommend varicella vaccination for seronegative SOT candidates and to those with no documented history of

varicella disease or vaccination. Only two respondents (2%) neither checked serology nor vaccinated before SOT. The frequencies were lower with measles: 81% (77/95) of respondents checked measles serology, and 90% (84/93) recommend vaccination if indicated; nine respondents (9%) neither checked nor vaccinated.

Regarding the minimum age required to start vaccination, about half of the respondents wait for the SOT candidate to be at least one year of age before giving varicella (53%, 48/90) and measles (44%, 40/90) vaccines (Table S2). Most respondents (89%, 82/92) required a minimum of 4 weeks between vaccination and transplantation, 4% (4/92) use a minimum of 2 weeks, 1% (1/92) of 3 weeks, and 1% (1/92) of 6 weeks. Five respondents did not report planning any delay between vaccination and transplantation (5%). If either varicella or measles vaccines were given within 4 weeks of organ availability, half of the respondents would always defer transplantation (51% [47/93] and 49% [46/93], respectively). Some would personalize the management (32% [30/93] and 42% [39/93], respectively), based on the patient's situation. In particular, some respondents would give immunoglobulins (6% [6/93] and 8% [7/93], respectively) or an intravenous antiviral (12% [11/93] and 1% [1/93], respectively) after vaccination in order to be able to proceed with transplantation without a delay.

### 3.3 | Use of varicella and measles vaccines after transplantation

Overall, 20 respondents (21%, 20/95) have given at least one LAV after transplantation (Table S3), including two doing so in the context of a research protocol (10%, 2/20). Eight respondents (8%, 8/95) routinely recommend the administration of LAV after transplantation, including seven who routinely administer varicella vaccine (7%, 7/95) and five who routinely administer measles vaccine (5%, 5/95). These vaccinations are then administered by the patient's primary care physician (4%, 4/95) or at the transplantation center (4%, 4/95). Another twelve respondents (13%, 12/95) sometimes recommend varicella and/or measles vaccines after transplantation, in certain patients or situations, such as an outbreak setting. The remaining 75 respondents have never given LAV after SOT.

Before administrating LAV, most respondents would ensure that their patient fulfills certain safety criteria, such as being out a minimum time from transplantation and on "low immunosuppression." Some respondents also order laboratory testing before vaccination. These are detailed below and in Table 1.

Regarding the delay in time from transplant, most wait for patients to be at least one or two years post-SOT. Two respondents did not wait for a specific period after transplantation as they were vaccinating patients in outbreak settings only. Ten responders provided information on how they would vaccinate patients in the setting of increased immune suppression for active treatment of rejection. The specific durations to delay included: delay three months (50%, 5/10), six months (40%, 4/10) or 12 months (10%, 1/10), and used the same delays for both varicella and measles vaccines.

Respondents were then asked whether they required (or would require) any evaluation of immune function prior to providing varicella or measles vaccine after SOT (such as functional assay, lymphocyte and/or CD4 count). Among the eight respondents that routinely give LAV after SOT, most (88%, 7/8) did not order any specific laboratory testing before vaccinating their patients, and only one reviewed the lymphocyte count. Among the 12 respondents that sometimes gave LAV after SOT, a quarter did not order any specific laboratory testing before vaccinating their patients, and half of them reviewed the lymphocyte count, including one respondent evaluating CD4 count, and another one performing a CD4 count as well as a lymphocyte functional assays. The remaining three respondents answered they did not know whether immune testing was obtained prior to vaccination at their institution. Among those who are currently not administrating LAV after SOT, a few would order tests, and one proposed to seek advice from the infectious disease team.

Among the 20 respondents who routinely or occasionally administer LAV post-SOT, most offer "passive" follow-up after vaccination (65%, 13/20), meaning that families are asked to call their transplant team in case of fever or cutaneous rash. A minority of respondents (25%, 5/20) do "active" follow-ups such as direct clinical evaluation (20%, 4/20), and/or medical team performing systematic phone/electronic communication with the family (15%, 3/20). One respondent did not do any particular follow-up after either vaccine. Assessment of vaccine seroresponse using serological testing is done by 74% (14/19) of the respondents after varicella vaccine, 60% (9/15) after measles vaccine.

Respondents' theoretical recommendations for the management of rash or unexplained fever after varicella or measles vaccines are detailed in Table S4. In brief, the majority of the respondents would treat in case of rash following varicella (74%, 14/19) or measles vaccination (60%, 9/15). Among those who would treat following varicella vaccine, all would prescribe an antiviral (100%, 14/14) and a fifth would administer varicella-specific IVIG as well (21%, 3/14). Following measles vaccine, 78% would prescribe an antiviral (7/9), but only one respondent provided information on which antiviral ("ribavirin"). Half would give IVIG (56%, 5/9), including two respondents reporting having access to measles-specific immunoglobulins (40%, 2/5). There was no agreement on neither indication for giving therapy nor treatment duration after either of the vaccines.

### 3.4 | Respondents' personal opinion on recommending live-attenuated vaccines after transplantation

Overall 57% of respondents (44/78) think that transplant practitioners should give LAV to SOT recipients, 24% (19/78) believe vaccine should not be administered, and 19% (15/78) are "unsure" (Figure 1). The remaining 17 respondents did not provide any answer to this question. Among the 44 respondents who think that LAV should be given post-SOT, most (89%, 39/44) would restrict their use to selected patients (68%, 30/44), organs (7%, 3/44), or situation (eg,

**TABLE 1** Responses to practice patterns regarding the administration of varicella or measles vaccine after pediatric solid organ transplantation

| | Varicella vaccine | | | Measles vaccine | | |
|---|---|---|---|---|---|---|
| | Vaccinate routinely post-SOT (n = 7) | Vaccinate occasionally post-SOT (n = 12) | Don't vaccinate post-SOT (n = 76) | Vaccinate routinely post-SOT (n = 5) | Vaccinate occasionally post-SOT (n = 12) | Don't vaccinate post-SOT (n = 78) |
| Transplantation center | | | | | | |
| Multiple organ | 5/7 (71%) | 8/12 (67%) | 35/76 (46%) | 3/5 (60%) | 8/12 (67%) | 37/78 (47%) |
| Single organ | 2/7 (29%) | 4/12 (33%) | 41/76 (54%) | 2/5 (40%) | 4/12 (33%) | 41/78 (53%) |
| Delay post-transplantation | | | | | | |
| No delay | 0 | 2/12 (17%) | 0 | 0 | 2/12 (17%) | 0 |
| 6 mo | 1/7 (14%) | 0 | 0 | 0 | 1/12 (8%) | 0 |
| 12 mo | 4/7 (57%) | 5/12 (42%) | 0 | 3/5 (60%) | 4/12 (33%) | 0 |
| 2 y | 2/7 (29%) | 2/12 (17%) | 1/72 (1%) | 2/5 (40%) | 2/12 (17%) | 1/74 (1%) |
| Other | 0 | 1/12 (8%)[a] | 1/72 (1%)[b] | 0 | 1/12 (8%)[a] | 0 |
| Don't know/not applicable | 0 | 2/12 (17%) | 70/72 (97%) | 0 | 2/12 (17%) | 73/74 (99%) |
| Delay after increased immunosuppression for active treatment of rejection | | | | | | |
| No delay | 1/7 (14%) | 0 | 0 | 1/5 (20%) | 0 | 0 |
| 3 mo | 1/7 (14%) | 4/12 (33%) | 0 | 2/5 (40%) | 3/12 (25%) | 0 |
| 6 mo | 2/7 (29%) | 2/12 (17%) | 0 | 0 | 3/12 (25%) | 0 |
| Other | 3/7 (43%)[c] | 1/12 (8%)[a] | 0 | 2/5 (40%)[d] | 2/12 (17%)[e] | 0 |
| Don't know/not applicable | 0 | 5/12 (42%) | 71/71 (100%) | 0 | 4/12 (33%) | 73/73 (100%) |
| Prevaccination workup[f] | | | | | | |
| No | 6/7 (86%) | 4/12 (33%) | 42/71 (59%) | 4/5 (80%) | 5/12 (42%) | 42/73 (58%) |
| Lymphocyte count | 1/7 (14%) | 6/12 (50%) | 9/71 (13%) | 1/5 (20%) | 4/12 (33%) | 10/73 (14%) |
| CD4 count | 0 | 2/12 (17%) | 2/71 (3%) | 0 | 1/12 (8%) | 2/73 (3%) |
| Lymphocyte functional assay | 0 | 0 | 1/71 (1%) | 0 | 0 | 2/73 (3%) |
| Don't know/ not applicable | 0 | 2/12 (17%) | 20/71 (28%) | 0 | 3/12 (25%) | 21/73 (29%) |
| Follow-up after vaccination[f,g] | | | | | | |
| No specific follow-up | 1/7 (14%) | 0 | 29/57 (51%) | 1/4 (25%) | 1/11 (9%) | 26/51 (51%) |
| Passive follow-up: phone call | 4/7 (57%) | 8/12 (67%) | 23/57 (40%) | 3/4 (75%) | 8/11 (73%) | 18/51 (35%) |
| Active follow-up: phone call | 0 | 3/12 (25%) | 1/57 (2%) | 0 | 2/11 (18%) | 3/51 (6%) |
| Active follow-up: physical examination | 2/7 (29%) | 2/12 (17%) | 3/57 (5%) | 0 | 1/11 (9%) | 5/51 (10%) |
| Other, as per research protocol | 1/7 (14%) | 1/12 (8%) | 1/57 (2%) | 1/4 (25%) | 0 | 0 |

(Continues)

**TABLE 1** (Continued)

| | Varicella vaccine | | | Measles vaccine | | |
|---|---|---|---|---|---|---|
| | Vaccinate routinely post-SOT (n = 7) | Vaccinate occasionally post-SOT (n = 12) | Don't vaccinate post-SOT (n = 76) | Vaccinate routinely post-SOT (n = 5) | Vaccinate occasionally post-SOT (n = 12) | Don't vaccinate post-SOT (n = 78) |
| Serological evaluation after vaccination | | | | | | |
| Yes | 4/7 (57%) | 10/12 (83%) | 40/63 (63%) | 2/4 (50%) | 7/11 (64%) | 37/55 (67%) |

*Note:* Data are number (%) of respondents that answered the question. Mo: month, y: year.

[a]"For liver transplant patients who are on reduced immunosuppression (eg, tacrolimus monotherapy)."

[b]"Greater than 5 y."

[c]"As soon as they get back to tacrolimus monotherapy," "Shall be on low immunosuppression for at least 1 y," "Individualized."

[d]"Shall be on low immunosuppression for at least 1 y," "Individualized."

[e]"As soon as they get back to tacrolimus monotherapy," "Only for liver transplant patients who are on reduced immunosuppression (eg, tacrolimus monotherapy)."

[f]Respondents were allowed to give multiple answers.

[g]"Passive follow-up: phone call": Families are asked to call in case of adverse events, such as fever and rash; "Active follow-up: phone call": The transplant team specifically call at a given time after vaccination for evaluation of adverse events; and "Active follow-up: physical examination": The patient is seen physically by the transplant team for evaluation of adverse events.

outbreaks; 14%, 6/44), and only few respondents (11%, 5/44) would recommend it to all SOT recipients. These percentages vary depending on respondents' role, experience, type of organ, and country (Figures 1 and 2). Overall, respondents from the United States, Canada, Central Europe, New Zealand, South Africa, and Japan were the most favorable regarding administration of LAV post-SOT.

### 3.5 | Management of varicella and measles exposure after transplantation

Nearly 80% of respondents have a protocol for management of SOT recipients following varicella exposure (78%, 62/79), but fewer have one after measles exposure (35%, 28/79); Table S5 details differences in management. Sixteen respondents did not provide any answer to this question. In centers with a protocol available, most respondents recommend empiric treatment for SOT recipients after a contact with either varicella (90%, 56/62) or measles (96%, 27/28) with IVIG (84% [47/56] and 100% [27/27], respectively) and/or oral antiviral therapy (70% [39/56] and 11% [3/27], respectively). In centers with no protocol available, a surprisingly high proportion of respondents (41%, 21/51) would not give any prophylactic treatment to SOT recipients after exposure to measles. Overall, there are important variations among respondents' answers for the acceptable delay between identified exposure and start of antiviral prophylaxis and the duration of prophylaxis (Table S5).

### 3.6 | Management of chickenpox, zoster, and measles infection after transplantation

Most of the respondents have a protocol for management of SOT recipients in case of chickenpox (70%, 54/77) or zoster (64%, 49/76), but less than a third have a protocol for measles infection (30%, 23/76). A total of 18 to 19 respondents did not answer these questions. Centers with a protocol available are more likely to provide treatment than those without protocol: 81% vs 57%, 86% vs 41%, and 61% vs 25%, for chickenpox, zoster, and measles infections, respectively (Table S6). A surprisingly high proportion of respondents (26%, 20/76) would not recommend any treatment in case of measles infection after SOT. However, the survey did not ask whether the respondent would decrease the SOT recipient's immunosuppressive treatment or not.

## 4 | DISCUSSION

Varicella and measles are both life-threatening infections after SOT, with reported mortality rates among immunocompromised patients of up to 25% and 70%, respectively.[1,22,23] Whereas both the AST ID COP and the Infectious Diseases Society of America provide guidelines to help manage varicella exposure and infection,[3,8] guidance for prevention and treatment of measles infection outside of pretransplant vaccination is lacking. The results of

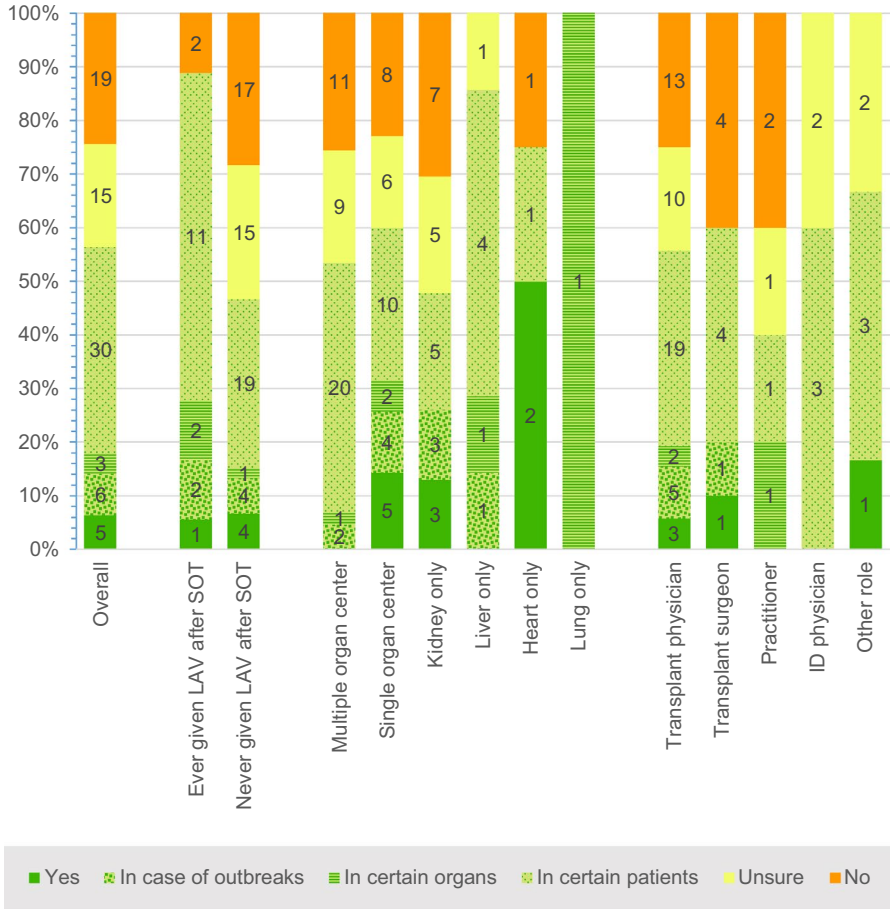


**FIGURE 1** Respondents' personal opinion on recommendation of LAV after SOT, by previous experience, type of organ, and role. Data represent number of unique respondents who answer the question "Do you think we should give live-attenuated vaccines to transplant recipients?" ID: infectious diseases

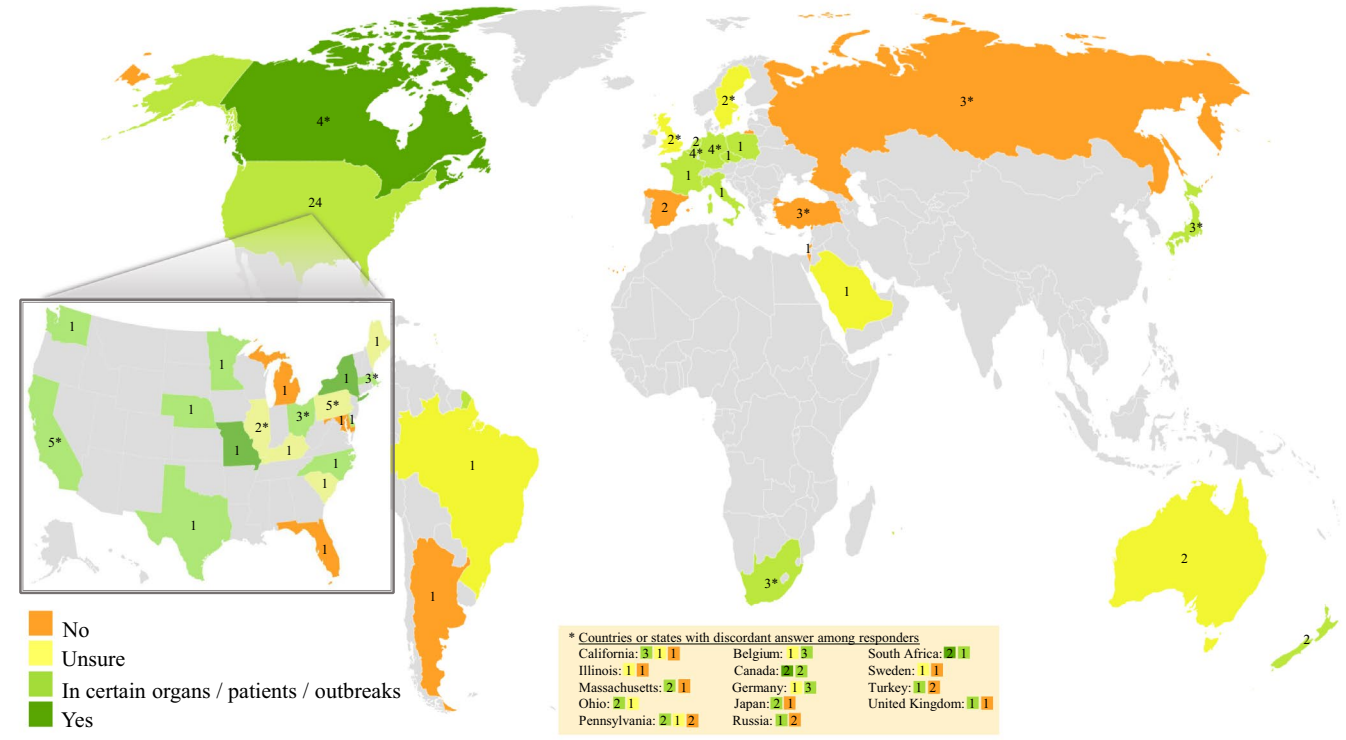


**FIGURE 2** Respondents' leading opinion on recommendation of LAV after SOT, by country. Data represent number of unique respondents who answer the question "Do you think we should give live-attenuated vaccines in transplant recipients?" The color code represents the most frequent answer given by the respondents coming from the same country/state

this survey—although somewhat limited by a small sample size—show that there are still many gaps in practitioner awareness of the potential severities of both infections and highlight the need for further education.

The survey also demonstrates that efforts should be made to increase LAV vaccination rates before SOT. The majority of respondents (59%) wait for the SOT candidate to be at least one year old before giving LAV. However, both varicella and measles vaccination can be administered as early as six months of age without harm and potential benefit.[8] Studies show that a high number of patients immunized before SOT continue to be seroprotected after SOT and do not require further vaccination.[11,14,19,24] Recently, a study reported 50% of patients (5/10) immunized with MMR before 9 months of age had sustained seroprotection against measles up to 15 years after liver transplantation.[19] Application of accelerated vaccine schedules (starting at 6 months of age) in SOT candidates should therefore be promoted. However, as antibodies may wane over time, in particular under the influence of immunosuppression,[12,17,19] routine monitoring of serology should be considered after SOT, as well as consideration for revaccination in selected populations.

Despite published reports demonstrating limited numbers of patients receiving LAV after SOT, this survey shows that several centers around the world are already administrating LAV after SOT. Most respondents (57%) believe that LAV should be offered to SOT recipients, especially in selected patients and situations (eg, outbreak). Given the lack of consensus guidelines, a collaborative initiative was held in February 2018 assembling worldwide experts in pediatric transplantation, vaccinology, immunology, and infectious diseases.[21] The aim of this 2-day consortium was to review the evidence and develop an international consensus on the minimal standards that should be followed when administrating LAV after SOT. These recommendations were published in mid-2019, several months after the completion of this survey.

Briefly, the consensus considered both LAV to be safe in patients who are more than one year after liver or kidney transplantation and more than two months after an acute rejection episode, clinically well, and meet specific criteria of "low-level" immunosuppression. The latter was defined as tacrolimus levels of <8 ng/mL or cyclosporine levels of <100 ng/mL (each for two consecutive readings), and prednisone dose equivalent of <20 mg/d (or <2 mg/kg/d for those <10 kg). Recommendations for use of both vaccines are restricted to liver and kidney transplant recipients only, pending the availability of further evidence in other graft types. In areas with a low incidence of measles, MMR vaccination is only considered during outbreak or travel to endemic risk areas.[21]

Whereas in the survey the majority of the respondents do not perform any immunologic workup before administrating LAV after SOT, the newly published consensus recommends it systematically, including measurement of total immunoglobulin G level, total lymphocytes and CD4 counts.[21] Further caution and in-depth immunologic evaluation are recommended for patients with a "higher-level" of immunosuppression, such those who have received mycophenolate mofetil, lymphocyte-depleting agents (eg, anti-thymocyte globulin, rituximab, alemtuzumab), or have persistently elevated viral loads of Epstein-Barr virus (suggestive of potential T-cell dysfunction). Also included in this group are patients with complete thymectomy in the neonatal period, as well as liver transplant recipients who are undergoing immune suppression withdrawal with the goal of cessation (achievement of "functional tolerance").[21]

The current survey suggests that close monitoring for adverse events is not done routinely in the majority of centers providing LAV administration in SOT recipients. However, the consortium now recommends a combination of both passive and active surveillance.[21] It includes education of patients and families to seek medical attention promptly for new onset of rash or fever within 4 weeks following vaccination (passive surveillance), and at least one telephone contact with the patient's caregiver at three to four week after LAV to identify any adverse event that might have occurred (active surveillance). Clinicians should keep in mind that even with the publication of the consensus recommendations, administration of LAV after SOT is still "off-label" in all countries, and it is recommended to clearly document obtainment of informed consent.

In summary, the survey shows great variability in strategies for the prevention and management of varicella and measles in SOT recipients. This may be partly explained by the heterogeneity in respondents' background, with only 6% being infectious disease physicians. Further education and studies could hence assist in optimizing prevention and management. The data provided in this survey, coming from diverse caregivers worldwide, help to identify knowledge gaps and practitioners' concerns. It could be used as a starting point for the creation of educational materials that would inform intervention methods and promote safe administration of LAV after SOT. There is an increasing number of practitioners willing to administer LAV after SOT, and safety reports on this practice should be promoted, in order to increase the available data and to help with the elaboration of further detailed guidelines by the transplant societies.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## AUTHOR CONTRIBUTION

KMPB, LDI, UDA, MIA, AC, EG, BH, MGM, DVL, and MG: Conceived the study. KMPB and LFP: Designed the questionnaire. LFP: Analyzed the data and drafted the manuscript. KMPB, LDI, UDA, MIA, AC, EG, BH, MGM, DVL, MG, and LFP: Critically revised the intellectual content and finally approved the version to be published.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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