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Multimodal safety assessment of measles-mumps-rubella vaccination after pediatric liver transplantation

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Live-attenuated vaccines are currently contraindicated in solid-organ transplant recipients. However, the risk of vaccine-preventable infections is lifelong, and can be particularly severe after transplantation. In this prospective interventional national cohort study, 44 pediatric liver transplant recipients with measles IgG antibodies <150 IU/L (below seroprotection threshold) received measles-mumps-rubella vaccine (MMR) at a median of 6.3 years posttransplantation (interquartile range, 4.0 to 10.9). A maximum of two additional doses were administered in nonresponders or when seroprotection was lost. Vaccine responses occurred in 98% (95% confidence interval [CI], 88-100) of patients. Seroprotection at 1-, 2-, and 3-year follow-up reached 62% (95% CI, 45-78), 86% (95% CI, 70-95), and 89% (95% CI, 67-99), respectively. All patients responded appropriately to the booster dose(s). Vaccinations were well tolerated and no serious adverse event attributable to vaccination was identified during the 8-week follow-up period (or later), using a multimodal approach including standardized telephone interviews, diarized side effect reporting, and monitoring of vaccinal virus shedding. We conclude that live attenuated MMR vaccine can be administered in liver transplant recipients fulfilling specific eligibility criteria (>1 year posttransplantation, low immunosuppression, lymphocyte count ≥0.75 G/L), inducing seroprotection in most subjects. (Clinicaltrials.gov number NCT01770119).

KEYWORDS
clinical research/practice, clinical trial, infection and infectious agents—viral, infectious disease, liver transplantation/hepatology, pediatrics, vaccine

1 | INTRODUCTION

Solid-organ transplantation (SOT) recipients are at high risk of severe infection due to their immunosuppressive therapy.[1] Measles is a particular threat for the immunocompromised host, with serious complications occurring in approximately 80%, of which 40% to 70% are fatal.[2,3] These patients often have atypical clinical manifestations and up to 30% do not present with the pathognomonic measles rash.[3] As no specific treatment exists, care is mostly supportive.[4]

A live attenuated vaccine is recommended for the prevention of measles worldwide. It is usually administered from the age of 9 to 12 months and is frequently distributed as a combined preparation against measles-mumps-rubella (MMR). Measles-containing vaccines are currently contraindicated after SOT due to the lack of safety data and the fear of instigating immune-mediated organ rejection or complications following uncontrolled viral replication.[5,6] Ideally, transplant candidates should be vaccinated before transplantation[5,7]

Abbreviations: 95% CI, 95% confidence interval; ELISA, enzyme-linked immunosorbent assays; IQR, interquartile range; LT, liver transplantation; MMR, measles-mumps-rubella; OR, odds ratio; SOT, solid-organ transplantation; TCID50, tissue culture infective dose.

using an accelerated schedule if needed (starting at the age of 6 months).[8] Nevertheless, in practice, pretransplant vaccination may not be performed because patients are either too young or considered too ill, or because of insufficient time before the planned SOT.[9] Indeed, we have previously reported that between 1990 and 2002 only 40% of patients older than 12 months were up-to-date for their MMR immunization at the pretransplantation visit.[10] Furthermore, in children vaccinated before SOT, antibodies may wane over time, in particular under the influence of immunosuppression.[7,11]

We previously reported excellent immunogenicity and tolerance for the live-attenuated varicella zoster vaccine in pediatric liver transplant (LT) recipients, to whom it is now offered as they meet specific eligibility criteria.[12] However, not all live viral vaccines are equally attenuated, and the replication pattern of measles containing vaccines exceeds that of the varicella zoster vaccine.[13] In addition, effective antivirals are not available in the event of disease resulting from measles immunization. Although measles-containing vaccines have been administered to LT recipients, it has been mainly limited to a few epidemic settings (mostly unpublished). So far, only five retrospective and prospective studies based in Japan and the United States have been performed (Table S1 in the Appendix S1), and no consensus yet exists on the safety of this practice.[14-19]

In the present study, we assessed the safety and immunogenicity of the MMR vaccine post-LT with a special emphasis on measles immunogenicity, given its consequences in immunosuppressed patients.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This interventional, prospective, national cohort study was conducted at Geneva University Hospitals (Geneva, Switzerland), the Swiss national center for pediatric LT. All LT recipients were approached at least 1 year posttransplantation. A total of 90 patients less than 18 years of age were enrolled between April 2013 and December 2016. Written informed consent was obtained from parents/legal guardians. Further details are provided in the Appendix S1.

The study was performed in accordance with the principles of the Declaration of Helsinki and the study protocol was approved by the regional ethics committee (approval number CE12-226) and by the Swiss Agency for Therapeutic Products (Swissmedic, approval number 2013DR4003). All authors vouch for the accuracy and completeness of the data presented.

2.2 | Antigen-specific antibody titer

Measles specific IgG antibodies were assessed using automated enzyme-linked immunosorbent assays (ELISA) at baseline, 4 weeks after each MMR dose, and annually. Seroprotection was set at a concentration of >150 IU/L, a threshold previously determined experimentally as correlating with the presence of neutralizing antibodies. Seroconversion was defined as a rise in measles-specific IgG concentration above the seropositivity threshold in a previously nonseroprotected patient (see Appendix S1 for further details, as well as mumps and rubella serology).

2.3 | Measles-mumps-rubella vaccine administration

Patients without measles seroprotection who fulfilled all safety criteria, including low immunosuppression (steroids <2 mg^{-1} kg d^{-1}, tacrolimus <0.3 mg^{-1} kg d^{-1}, and tacrolimus level <8 ng/mL for >1 month) and a sufficient lymphocyte count (≥0.75 G/L) were eligible for MMR immunization. Participants received a standard dose (0.5 mL) of Priorix (GlaxoSmithKline, Switzerland) including at least 10^3 50% tissue culture infective dose (TCID50) of measles (Schwarz strain), $10^{3.7}$ TCID50 of mumps (RIT 4385 strain), and $10^{3.0}$ TCID50 of rubella (Wistar RA 27/3 strain). A second dose was administered at least 4 weeks after the first one to patients who did not seroconvert after the first dose, if the safety criteria were fulfilled. According to the authorization of Swissmedic, a maximum of two additional MMR doses was administered to these nonresponders or if antibodies waned below seroprotection levels during follow-up, irrespective of the number of doses received before study inclusion.

2.4 | Vaccine safety and breakthrough disease monitoring

Patients were closely monitored for 8 weeks after each immunization, using at least three standardized telephone interviews (7 to 10 days, 20 days, and 1 month after each immunization) and diary cards. Urinary vaccine virus shedding was screened using an in-house polymerase chain reaction targeting the measles nucleoprotein gene as previously described.[20] Parents were requested to consult immediately if a skin rash appeared. In this case, biological swabs were collected to distinguish measles wild strain from vaccine strain or other viruses by polymerase chain reaction. A history of breakthrough disease or serious adverse events was sought at annual visits.

2.5 | Statistical analysis

The sociodemographic and clinical characteristics of patients were described using standard descriptive statistics, ie, frequencies, median, and interquartile range (IQR) if the variable was not normally distributed. Patients with no previous history of MMR vaccination (before and/or after transplantation) were considered as "MMR-naïve," and were described separately from the "nonnaïve" patients. Rates of local and systemic adverse events were expressed after each dose according to the number of patients returning symptom diaries. The occurrence of each adverse event in the MMR-naïve group was compared to the nonnaïve group using Chi-squared or Fischer's exact tests depending on the sample size. The seroprotection rate was calculated by dividing the number of seroprotected

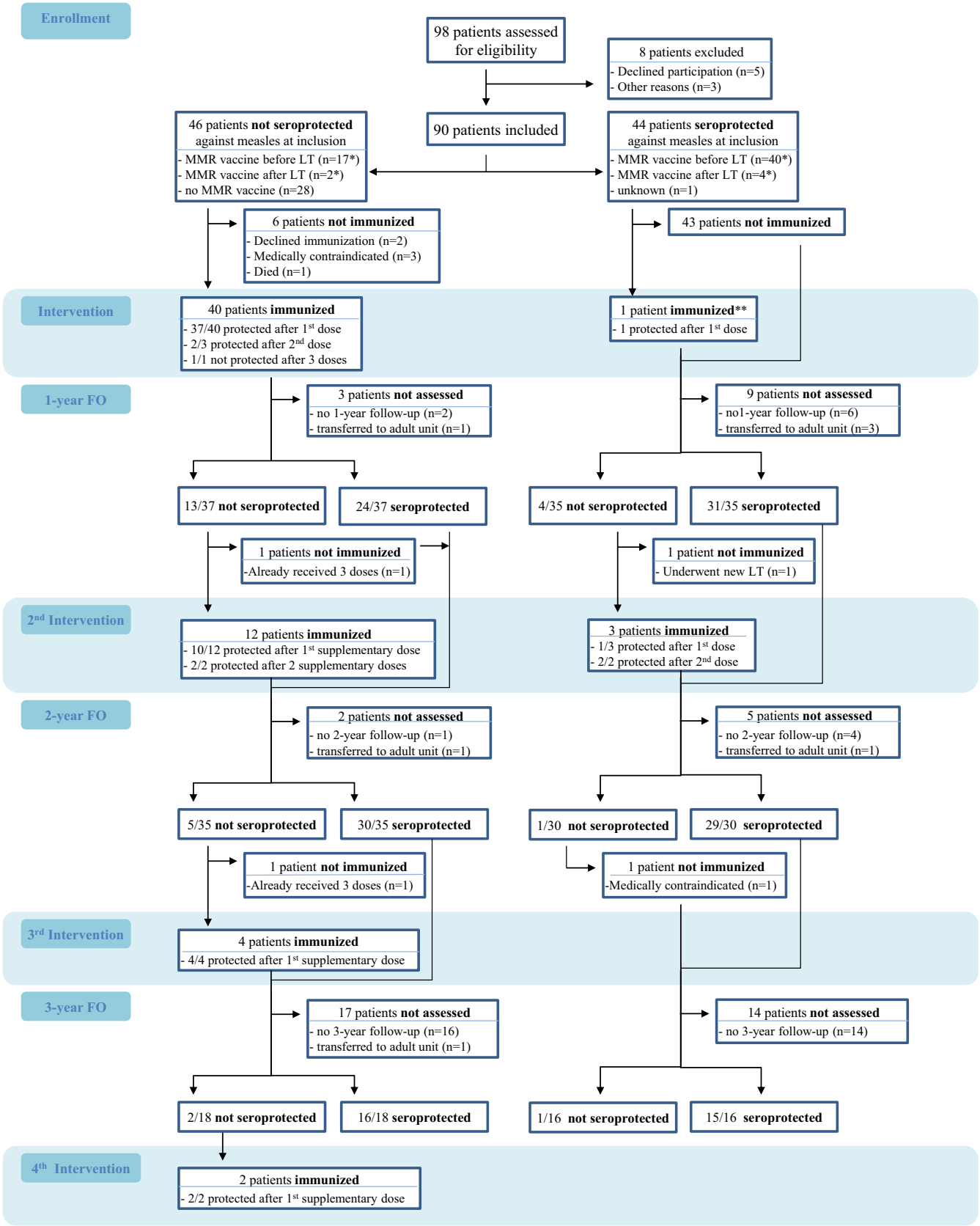

FIGURE 1 Flowchart of study participants. *Some patients received MMR vaccine both before and after transplantation (before study inclusion). **One patient received a MMR dose when it was not indicated (see Appendix S1). MMR, measles-mumps-rubella; FO, follow-up; LT, liver transplantation; n, number of patients [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Factors predicting measles seroprotection at inclusion

	Seroprotection at inclusion		Adjusted for age at first LT	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Diagnosis of biliary atresia	0.40 (0.17-0.95)	.04	2.15 (0.51-9.04)	.3
No. MMR doses before inclusion		<.001 (overall)		<.001 (overall)
None	Reference	Reference	Reference	Reference
1 dose	31.5 (3.45-287)	.002	116 (1.97-6809)	.02
≥2 doses	95.2 (11.5-790)	<.001	153 (2.92-7988)	.01
No. MMR doses before inclusion		<.001 (overall)		<.001 (overall)
None	0.03 (0-0.29)	.002	0.01 (0-0.51)	.02
1 dose	Reference	Reference	Reference	Reference
≥2 doses	3.02 (0.92-9.88)	.07	1.31 (0.35-5.01)	.7
Age at first MMR vaccination before LT (mo)		.01 (overall)		<.001 (overall)
<9	Reference	Reference	Reference	Reference
9-12	3.20 (0.54-19.0)	.2	1.64 (0.23-11.5)	0.6
>12	7.73 (1.87-32.0)	.005	1.39 (0.24-8.21)	.7
Age at first MMR vaccination before LT (years, continuous variable)	7.99 (1.17-54.6)	.007	0.70 (0.12-4.16)	.7
Age at last MMR vaccination before LT (years, continuous variable)	4.06 (1.27-13.0)	<.001	0.79 (0.18-3.44)	.8
Time between last MMR vaccination and LT		<.001 (overall)		<.001 (overall)
<4 months	Reference	Reference	Reference	Reference
4-12 months	2.51 (0.58-10.9)	.2	2.19 (0.45-10.6)	.3
>12 months	37.7 (4.12-345)	.001	5.02 (0.24-103)	.3
Time between last MMR vaccination and LT (year, continuous variable)	2.56 (1.05-6.28)	<.001	1.26 (0.29-5.55)	.8
Age at first LT (y)		<.001 (overall)	—	—
<1	0.16 (0.05-0.60)	.006		
1-3	Reference	Reference		
>3	10.4 (2.55-42.3)	.001		
Age at first LT (years, continuous variable)	2.41 (1.48-3.94)	<.001	—	—
Previous history of rejection	0.58 (0.25-1.35)	.2	2.08 (0.64-6.81)	.2
No. rejection episodes		.3 (overall)		<.001 (overall)
None	Reference	Reference	Reference	Reference
1 episode	0.72 (0.30-1.73)	.5	2.61 (0.75-9.06)	.1
2 episodes	0.16 (0.02-1.48)	.1	0.49 (0.04-6.81)	.6
3 episodes	0.40 (0.03-4.74)	.5	1.79 (0.11-28.9)	.7
Time between last rejection episode and inclusion (years, continuous variable)	0.90 (0.78-1.04)	.1	0.90 (0.77-1.05)	.2

CI, confidence interval; LT, liver transplantation; MMR, measles-mumps-rubella; OR, odds ratio.

patients by the total number of patients receiving the vaccine with exact binomial 95% CI. Factors associated with measles seroprotection at inclusion and at 1-year follow-up were identified using univariate logistic regression adjusted for age at first LT (see Appendix S1). All tests were two-tailed and a *P*-value <.05 was considered statistically significant. Nonparametric tests were used when variables were not normally distributed. All tests were performed with Stata software, version 13 (StataCorp, College Station, TX).

3 | RESULTS

3.1 | Patient characteristics

Of 98 pediatric LT recipients, 90 were included in the study (Figure 1; participation rate, 92%; 43 females, 48%). Patients were transplanted at a median age of 1.4 years of age (IQR, 0.8-4.1), most frequently (57%, 51/90) for biliary atresia (Table S2). Median age at study inclusion was 10.3 years (IQR, 5.7-13.6), approximately 5 years

TABLE 2 Patients immunized during the study

Subject number	Diagnosis	Treatment	Age at LT [years]	Previous history of MMR vaccination	Time from LT to first MMR study dose [year]
3	Biliary atresia	CSA	1.2	No MMR vaccine	14.1
4	Biliary atresia	TAC	0.8	1 dose after LT	8
5	Biliary atresia	TAC	0.8	1 dose before LT	2.4
6	Hemochromatosis	TAC	0.3	No MMR vaccine	2.9
7	Biliary atresia	TAC	0.8	1 dose after LT	14.3
10	CHIC	TAC	0.9	No MMR vaccine	9.2
12	ALF of IC	TAC	3.8	2 doses before LT	2.1
14	Biliary atresia	TAC	0.9	No MMR vaccine	4.9
15	Biliary atresia	TAC	1.8	1 dose before LT	14.1
18	Biliary atresia	TAC	0.9	No MMR vaccine	12.2
20	Cryptogenic cirrhosis	TAC	1.3	2 doses before LT	6.3
23	PFIC type 3	TAC	0.6	No MMR vaccine	5
26	Biliary atresia	TAC+MMF	1.0	2 doses prior LT	6.3
28	Biliary atresia	TAC	1.1	No MMR vaccine	3.1
29	Biliary atresia	TAC	1.8	No MMR vaccine	5.6
30	Biliary atresia	TAC	0.9	No MMR vaccine	6.2
31	Hepatic VOD	TAC	0.9	No MMR vaccine	10
32	Hepatoblastoma	TAC	2.0	1 dose before LT	3.6
35	Biliary atresia	TAC	1.0	1 dose before LT	3.1
38	Biliary atresia	TAC	0.8	1 dose before LT	2.1
39	Biliary atresia	TAC	0.5	No MMR vaccine	9.2
40	Biliary atresia	TAC	1.1	No MMR vaccine	4.2
41	Biliary atresia	TAC	0.7	No MMR vaccine	6.1
42	Biliary atresia	TAC	1.4	1 dose before LT	13
43	Biliary atresia	TAC	0.8	No MMR vaccine	12
44	Biliary atresia	TAC	0.6	No MMR vaccine	7
45	Biliary atresia	CSA+MMF	0.4	No MMR vaccine	10
46	Biliary atresia	TAC+MMF	0.7	No MMR vaccine	15.7
47	Biliary atresia	TAC	0.8	No MMR vaccine	3.9
49	Alpha1-antitrypsin deficiency	TAC	1.8	2 doses before LT	7.3
51	Biliary atresia	TAC+SCS	0.7	1 dose before LT	4.3
52	ALF of IC	TAC	0.6	No MMR vaccine	13
54	OTC	TAC	4.2	2 doses before LT	11.8
56	Biliary atresia	TAC+MMF	0.7	No MMR vaccine	17.1
57	Biliary atresia	TAC	0.8	1 dose before +1 dose after LT	7.9
59	Biliary atresia	TAC	0.7	No MMR vaccine	4
62	PFIC type 3	TAC	3.8	No MMR vaccine	8.1
67	Biliary atresia	TAC	2.7	2 doses before LT	6.2
69	Biliary atresia	TAC	0.9	No MMR vaccine	12.4
70	Biliary atresia	TAC	1.6	2 doses before LT	2.5
71	Biliary atresia	EVR	1.3	2 doses before LT	5.6
73	Biliary atresia	TAC	0.8	2 doses prior LT	2.8

No. MMR study doses	Immunogenicity of MMR study dose	Seropositivity at last follow-up	Time from last MMR study dose to last follow-up [month]	Duration of follow-up [year]
1	Protected after 1 dose	Seroprotected	36.1	3.0
1	Protected after 1 dose	Seroprotected	36.0	3.0
1+1	Needed booster at 1 year FO	Seroprotected	17.6	3.2
1	Protected after 1 dose	Seroprotected	37.6	3.2
1	Protected after 1 dose	Seroprotected	38.4	3.2
1	Protected after 1 dose	Seroprotected	33.8	2.9
1+1+1	Needed booster at 1 and 3 years FO	Seroprotected	1.1	3.2
1+1+1	Needed booster at 1 and 2 years FO	Seroprotected	11.6	3.0
1	Protected after 1 dose	Seroprotected	10.6	2.1
1	Protected after 1 dose	Seroprotected	35.4	3.0
1+1+1	Needed booster at 1 and 2 years FO	Seroprotected	2.3	2.2
1	Protected after 1 dose	Seroprotected	23.0	1.9
1	Protected after 1 dose	Seroprotected	1.1	1.6
1	Protected after 1 dose	Seroprotected	22.5	3.2
1	Protected after 1 dose	Seroprotected[a]	25.9	2.2
1+1	Needed booster at 1 year FO	Seroprotected	5.7	3.0
1	Protected after 1 dose	Seroprotected	35.8	3.0
1+2	Needed 2 boosters at 1 year FO	Seroprotected	5.0	2.6
1+1	Needed booster at 1 year FO	Seroprotected	19.5	3.0
1+1	Needed booster at 1 year FO	Seroprotected	4.1	2.1
3	Primary vaccine failure	Seroprotected	30.5	3.0
1	Protected after 1 dose	Seroprotected	34.2	3.0
1+1+1	Needed booster at 1 and 2 years FO	Seroprotected	1.3	2.2
1+1+1	Needed booster at 1 and 3 years FO	Seroprotected	0.9	2.9
1	Protected after 1 dose	Seroprotected	25.1	2.1
2	Protected after 2 doses	Seroprotected	26.4	3.1
1	Protected after 1 dose	Seroprotected	36.2	3.0
1	Protected after 1 dose	Seroprotected	15.4	2.9
1	Protected after 1 dose	Seroprotected	36.4	3.0
1	Protected after 1 dose	Seroprotected	30.0	2.9
1	Protected after 1 dose	Seroprotected	1.3	2.4
1	Protected after 1 dose	Seroprotected	24.1	2.0
1	Protected after 1 dose	Seroprotected	12.9	1.1
2	Protected after 2 doses	Seroprotected	1.3	1.5
1	Protected after 1 dose	Seroprotected	23.9	2.0
1	Protected after 1 dose	Seroprotected	23.8	2.0
1+2	Needed 2 boosters at 1 year FO	Seroprotected	5.3	1.9
1+1+1	Needed booster at 1 and 2 years FO	Seroprotected	1.1	2.4
1	Protected after 1 dose	Seroprotected	23.8	2.0
1[b]	Lost protection at 1-year follow-up	Seroprotected[a]	16.5	2.4
1	Protected after 1 dose	Seroprotected	16.8	1.8
2	Protected after 2 doses	Seroprotected	0.8	1.7

(Continues)

TABLE 2 (Continued)

Subject number	Diagnosis	Treatment	Age at LT [years]	Previous history of MMR vaccination	Time from LT to first MMR study dose [year]
74	Cryptogenic cirrhosis	TAC	0.9	No MMR vaccine	6.7
80	Biliary atresia	TAC	1.1	2 doses prior LT	3.2

ALF, acute liver failure; CSA, cyclosporin; EVR, everolimus; FO, follow-up; CHIC, Cholestatic hepatopathy of indeterminate cause; LT, liver transplantation; MMF, mycophenolate mofetil; MMR study dose, any dose of measles-mumps-rubella administered at inclusion if seronegative or during follow-up; OTC, ornithine transcarbamylase deficiency; PFIC, progressive familial intrahepatic cholestasis; SCS, systemic corticosteroids; TAC, tacrolimus; VOD, veno-occlusive disease.

[a]These two patients (numbers 29 and 70) received intravenous immunoglobulin during follow-up, secondary to rituximab administration for the management of posttransplantation lymphoproliferative disorder.

[b]Booster dose was contraindicated at 1-year follow-up because of posttransplantation lymphoproliferative disorder.

(IQR, 1.8-9.9) after their last transplant and 5.7 years (IQR, 1.9-9.9) after the last rejection episode (among the 45 patients [50%] with a previous history of acute cellular rejection). Most patients (94%) were receiving tacrolimus and 24% were receiving two different antirejection drugs.

3.2 | Measles seroprotection at inclusion

Fifty-one percent (46/90) of children were not seroprotected against measles at inclusion, although 39% of these unprotected patients (18/46) had previously been immunized. Overall, six patients were immunized on an off-label basis after LT (median, 3.9 years; range, 0.8–13.7) before inclusion (Table S3). None had a history of overt measles disease before inclusion. Most of the patients who were not immunized before inclusion (22/28; 79%) were transplanted before the age of 12 months (43% before 9 months). Among children immunized before LT, 40 of 57 (70%; 95% CI, 57–82%) were seroprotected at inclusion (Figure 1, Table S3 and Figure S1 in Appendix S1). The 44 children seroprotected against measles at inclusion had been transplanted at an older age (median age, 4.0 years; IQR, 1.7–10.5) and immunized at a median age of 1.1 years (IQR, 1.0–1.4). Univariate factors associated with seroprotection after LT are shown in Table 1. Patients immunized and transplanted at an older age had a higher chance of being seroprotected against measles at inclusion than younger transplanted children. Multivariate analyses showed that all variables were highly dependent on each other, thus preventing the identification of independent factors.

3.3 | Seroresponse to Measles-Mumps-Rubella immunization

MMR vaccine was given at baseline to 40 of 46 nonseroprotected patients (Figure 1 and Table 2). Thirty-seven of the 40 patients (93%; 95% CI, 80–98%) reached seroprotection 4 weeks after the first dose; 2 of 40 were protected only after the second dose (Figures 1 and 2; Figure S2 in Appendix S1). The seroresponse to a two-dose schedule thus reached 98% (39/40; 95% CI, 87–100%) as is expected in nonimmunocompromised patients.[6,21] Among the 28 LT patients who had never received a measles containing vaccine before inclusion, 24 were vaccinated (Figure 3). Primary response rates reached 88% (21/24; 95% CI, 68–97%) and 96% (23/24; 95% CI, 79–100%) after one and two doses, respectively. MMR vaccine was also administered during follow-up to 3 of 44 previously immunized patients who lost seroprotection during follow-up. All responded to one or two doses of MMR (Figure 1). One patient received the MMR vaccine at inclusion while it was not indicated as he was retrospectively identified as seroprotected before vaccination (see Appendix S1). Vaccine responses to the rubella and mumps components followed similar trends (see Appendix S1).

3.4 | Maintenance of seroprotection against measles at 1-year follow-up

At 1-year follow-up, seroprotection was maintained in 62% (95% CI, 45–78%) of patients that had previously responded to immunization (MMR-naïve: 81%; 95% CI 58–95%; nonnaïve: 44%; 95% CI, 20–70%). Fourteen patients had measles serology below the seroprotection-associated threshold (Figure 2). Factors associated with the maintenance of seroprotection at 1-year follow-up are shown in Table S4. Briefly, patients that were MMR-naïve at inclusion were more likely to maintain seroprotection 1 year later (Figure 3; OR, 6.8; 95% CI, 1.7–27.5). Similarly, a stronger response 4 weeks after the first dose of MMR (concentration >400 IU/L) significantly increased the chance of remaining seroprotected (OR, 4.1; 95% CI, 1.0–16.0). Among patients who lost seroprotection 1 year after vaccination, 12 received booster doses and 10 (83%; 95% CI, 52–98%) reached seroprotection after one supplementary dose, while two patients required two supplementary doses. Therefore, the seroprotection rate was 100% (one-sided 97.5% CI, 74–100%) after boosting.

3.5 | Maintenance of seroprotection against measles at 2- and 3-year follow-up

Among the 35 immunized patients for whom a 2-year follow-up serology was available, 30 remained seroprotected (86% maintenance of protection; 95% CI, 70–95%; MMR-naïve: 90%; 95% CI 70–99%; nonnaïve: 79%; 95% CI, 49–95%). Four required a third

No. MMR study doses	Immunogenicity of MMR study dose	Seropositivity at last follow-up	Time from last MMR study dose to last follow-up [month]	Duration of follow-up [year]
1	Protected after 1 dose	Seroprotected	2.5	0.8
2	Protected after 2 doses	Seroprotected	0.9	1.6

dose (Figure 2) and the remaining patient had already received three doses. All five patients who lost seroprotection had successfully responded to the first dose, but required a 1-year follow-up booster dose. All four were seroprotected after this supplementary dose. At 3-year follow-up, 16 of 18 were still seroprotected (89% maintenance of protection; 95% CI, 65–99%; MMR-naïve: 100%; 97.5% CI 72–100%; nonnaïve: 75%; 95% CI, 35–97%); the two patients who lost seroprotection responded well to a third dose. The evolution of seroprotection against rubella and mumps is detailed in the Appendix S1.

3.6 | Vaccine safety monitoring

All patients were closely monitored during 8 weeks after each immunization. Among the 70 total doses of MMR administered, the standardized diary card was only answered for 49 injections (70%; Table S5). However, each patient was contacted by telephone at least three times after each dose, thus enabling individualized safety monitoring (Table S6). There was an 18% rate of self-reported overall injection site reaction during the first week following vaccination, mostly local redness/induration (6%) and pain (8%). Almost half of the patients (41%) experienced a systemic side effect during the first 2 weeks. There were some differences in adverse event rates in the MMR-naïve group compared to the nonnaïve group, but none was statistically significant (Table S5). Particular attention was paid around day 10 after MMR administration as it represents the peak of measles replication (Table S7). Four patients reported fever, three patients increased tiredness, and two headache around day 10. One patient had fever at day 20 including headache, irritability, myalgia, arthralgia, and gastrointestinal symptoms. Another patient reported afebrile coryza and conjunctivitis at day 21 and 4 patients experienced a localized rash starting between days 11 and 21. All these events are possibly attributable to viral replication. However, measles RNA was not identified in urine at days 7 to 10, 20, or 30, nor in the biological samples of two patients with fever around day 10 (Appendix S1). All patients with side effects received supportive care and amoxicillin was prescribed to two patients with acute otitis media starting at days 3 and 8, respectively. All cases improved clinically within a few days. No serious adverse event attributable to vaccination was detected during the 4 weeks following any dose of MMR.

Severe adverse events included one alloimmune hepatitis 4.5 months after vaccination in a patient with slightly abnormal liver function tests before immunization. He was successfully treated with steroids. Three other patients had a rejection episode at 6 months, 9 months, and 3 years after vaccination. Each patient was successfully treated by transiently increasing immunosuppression. Posttransplant lymphoproliferative disorder was diagnosed at 4 and 18 months after immunization in two patients. One patient was hospitalized 7 weeks after his second dose of MMR because of intestinal obstruction (Table S8). Causality assessment indicated these severe adverse events as unlikely to be related to MMR immunization. Among the enrolled, but nonimmunized patients, there were nine serious adverse events, including one posttransplant lymphoproliferative disorder and eight cases of graft dysfunction (abnormal liver tests). One patient required retransplantation and another, unfortunately, died. As safety is a major concern when considering MMR immunization of immunosuppressed patients, all relevant side effects reported are presented individually as narratives in the Appendix S1.

4 | DISCUSSION

In this cohort of 44 pediatric LT recipients that fulfilled our vaccination criteria, we did not observe any serious adverse events related to MMR vaccination and we demonstrated that the vaccine is immunogenic reaching a high seroprotection rate (98%), similar to previous studies in both healthy individuals and transplant recipients.[6,11,22] One dose was sufficient to elicit seroprotection in 89% of our patients. While 38% lost this protection within 1 year, all responded to booster dose(s), which emphasizes the importance of annual serological monitoring to evaluate the need for subsequent booster dose(s) in immunocompromised patients.

Although exposure is more frequent in countries with low MMR-immunization coverage, measles may be imported and outbreaks can occur if the overall measles immunity of the population is less than 95%.[23,24] Recent large outbreaks have been observed in

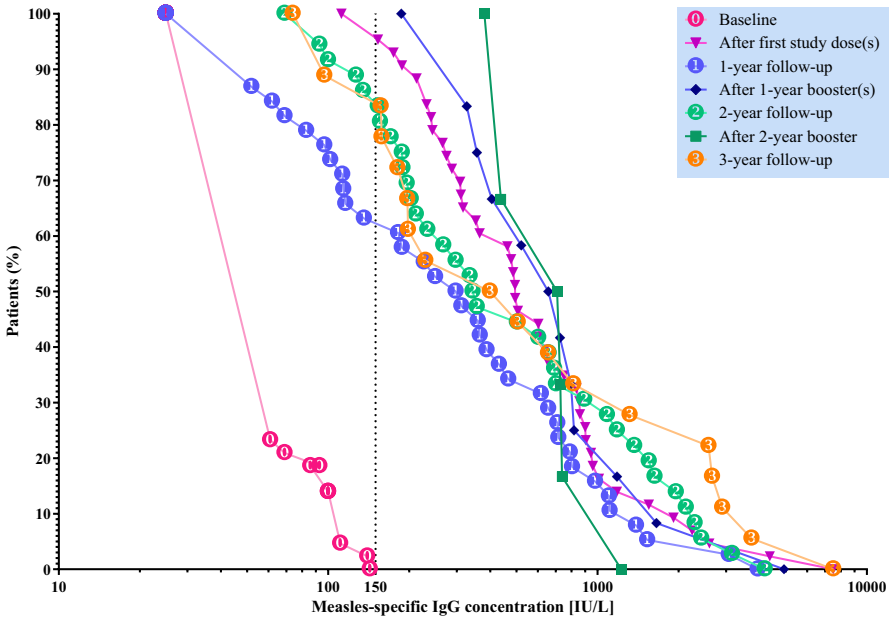

FIGURE 2 Reverse cumulative distribution curves of measles IgG concentration following MMR immunization after transplantation. MMR, measles-mumps-rubella; IU/L, international unit per liter; IgG, immunoglobulin G [Color figure can be viewed at wileyonlinelibrary.com]

Europe and elsewhere. In Switzerland, vaccination coverage is only 86%, leading to sporadic outbreaks.[25] In 2016, measles incidence was 0.81 cases per 100,000 inhabitants.[26] For many children, the MMR vaccine cannot be given before transplantation due to their young age or unstable medical condition.[8,9,16] While postexposure management with nonspecific intravenous immunoglobulins may be effective to prevent death,[27] it is a costly intervention requiring hospitalization and not readily available in routine care. As measles is highly contagious, contact is not always recognized and diagnosis can be further complicated by atypical presentations in these immunocompromised patients. Thus, revising recommendations for measles immunization after transplantation may be warranted.

A unique multimodal approach was used to closely monitor MMR safety in LT patients after each immunization. The overall safety of MMR could not be fully assessed given the limited size of our study population and the low frequency of severe adverse events. However, this study adds much-needed data on the safe use of live vaccines in carefully selected SOT recipients.[12,14-19,28-33] By contrast with previous reports, measles RNA shedding was not detected after MMR vaccination in LT recipients, despite sensitive molecular assays.[34-36]

Measles vaccination should be encouraged before SOT. In our cohort, 70% of patients immunized before transplantation were seroprotected at inclusion and did not require further vaccination despite immunosuppression. Not surprisingly, patients immunized and transplanted at an older age had a higher chance of being seroprotected against measles at inclusion than those transplanted at a younger age. However, we identified five seroprotected patients

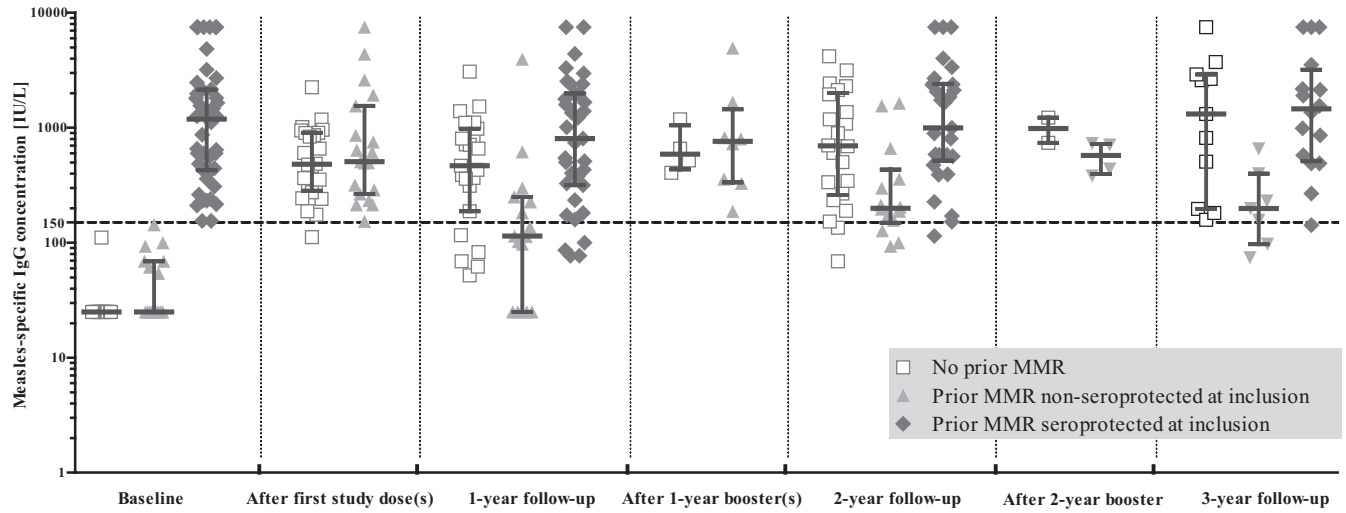

FIGURE 3 Evolution of seroprotection against measles throughout the study and seroresponse to MMR vaccine in patients with or without prior MMR immunization. MMR, measles-mumps-rubella vaccine; IU/L, international unit per liter; IgG, immunoglobulin G

who had been immunized before 9 months of age. This should encourage practitioners to administer MMR before transplantation by using an accelerated schedule if needed.[8] Nevertheless, one-third of our patients immunized before LT were not seroprotected at inclusion, a much higher rate of antibody loss than in healthy subjects. Similar observations have been made in HIV-infected patients,[37,38] indicating the impact of immune deficiency/immunosuppression on the persistence of measles antibodies. Remarkably, all patients responded to re-immunization, retaining high seroprotection rates during follow-up. Thus, regular serological monitoring after LT should be used to identify the need for booster doses.

While this study is somewhat limited by the small number of immunized patients, it is the largest cohort reported to date with the longest follow-up period that also presents detailed, individualized, multimodal safety monitoring. Measles-specific antibody concentrations were assessed using an ELISA (instead of the gold standard plaque reduction neutralization assay), not only because its correlation with protection was established in our laboratory conditions as elsewhere, but also because ELISA is used in routine practice and enables generalizability to clinical settings.[39] In healthy subjects, T cell-mediated immunity is considered a key factor in controlling measles virus replication and disease severity.[4,40] However, as its assessment is not standardized and the role of T cells in immunosuppressed patients is undefined, we consider serology as a more appropriate measure of immunogenicity in this population at present. We only monitored measles shedding, whereas the systemic adverse events observed after vaccination could possibly be partly due to rubella or mumps vaccine virus replication. Finally, while our study was limited to selected pediatric LT recipients, its results could be cautiously extrapolated to the adult LT population and perhaps also to other SOT recipients with similar immunosuppressive regimens.[41]

In summary, we demonstrated that the live attenuated MMR vaccine can be administered after LT, being well tolerated and inducing measles seroprotection in most children after a single dose. Yearly monitoring of measles serology identified patients requiring subsequent boosters, which also were immunogenic and safe.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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