Chapter 3
Vaccination with Live Vaccines

3.1 Introduction

When vaccinating immunocompromised individuals, the most important safety issue concerns live-attenuated vaccines. They consist of live pathogens that have been 'weakened' so that they can still replicate but with difficulty and without having the capacity to cause the disease in an immunocompetent host. Given the fear of a theoretical uncontrolled replication that could lead to severe vaccine-induced disease, live-attenuated vaccines are mostly contraindicated in immune compromised children. In patients with severe primary immunodeficiency disease (e.g. severe combined immunodeficiency), live-attenuated vaccines carry a significant risk of vaccine-strain infections. These have been reported following oral rotavirus or poliovirus vaccines, measles-mumps-rubella (MMR) vaccine and bacille Calmette-Guérin (BCG) vaccine [1, 2]. Given the severe outcome of wild-strain measles disease in immunocompromised patients and the ability of the measles vaccine strain to bind to a receptor ubiquitely expressed on nucleated cells (CD46; compared to the wild-strain which binds mainly to CD150 expressed only on activated lymphocytes and antigen-presenting cells), safety is one of the main concerns when giving measles-containing vaccine to immunocompromised individuals. However, there is

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growing evidence documenting the safety of immunizing immunocompromised hosts with different types of live-attenuated vaccines in carefully selected settings.

Previous studies that have assessed the safety and immunogenicity of live-attenuated vaccines in children on immunosuppressive treatment are summarized in Table 3.1. There are almost no data on primary vaccination with MMR in children with dysimmune disorders as the first dose of this vaccine is typically given before the onset of most of these disorders. By contrast, primary vaccination with MMR or varicella vaccine have been studied in solid organ recipients, mostly after liver transplantation. Indeed, as liver transplantation often occurs at an early age, live-attenuated vaccines cannot always be given before transplantation and, in some individuals, primary vaccination can only be considered after transplantation.

3.2 Safety and Immunogenicity Data

3.2.1 Measles, Mumps, Rubella (MMR)

In a prospective, nested, case-control study, the immune response following a booster dose of MMR was comparable in both healthy controls and 15 children with JIA treated with low-dose MTX, more or less anti-TNFα (etanercept) [4]. A Dutch randomized, multicentre, open-label clinical equivalence trial assessed the effect of a MMR booster dose in 137 JIA patients aged between 4 and 9 years (60, MTX; 15, bDMARDs) in which patients were randomly assigned to receive MMR booster or placebo. Among patients taking bDMARDs, treatments were interrupted at five times their half-lives prior to vaccination. The authors observed a good immunogenicity of the booster dose of MMR in JIA patients and no increase in disease flares in the year following vaccination [7]. A retrospective, single-centre Dutch study compared the long-term persistence of antibody to MMR, diphtheria and tetanus toxoids in 400 JIA patients compared

Table 3.1 Summary of previous studies on live-attenuated vaccines in immunocompromised children

Author, year, country	Vaccine	Study design	Disease	No. of patients and treatment/dosage	Safety	Immunogenicity
MMR vaccine						
Dysimmune disorders						
Heijstek 2007 Netherlands [3]	MMR	Retrospective questionnaire to patients	207 patients with JIA	207 JIA patients – 49 treated with MTX – 158 without MTX MTX: median dose 11 mg/m^2/week	– No increase in disease activity – No overt measles infection	NA
Borte 2009 Germany [4]	MMR booster	Prospective	15 patients with JIA	15 JIA patients – 5 MTX alone – 5 MTX + etanercept – 5 patients on MTX 4 years post-MMR MTX 10 mg/m^2/week Etanercept 0.4 mg/kg 2× per week	– No increase in disease activity – No overt MMR infections in ten patients vaccinated under MTX alone or MTX + etanercept	– No impact of both MTX alone or combined with etanercept on antibody and T-cell responses – Trend towards lower antibody titres in JIA-patients treated with MTX compared to healthy children in the long-term, but higher virus-specific IFNgamma-producing T cells

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Table 3.1 (continued)

Author, year, country	Vaccine	Study design	Disease	No. of patients and treatment/dosage	Safety	Immunogenicity
Miyamoto 2011 Brazil [5]	MMR	Retrospective	30 patients with SLE	30 SLE on various treatments (25 HCQ, 19 oral GCs, 14 AZA, 9 intravenous GC, 2 CYC pulse, 2 CSA, 2 MTX, 1 MMF)		At 7–16 years post-immunization, good maintenance of antibodies for measles
Heljstek 2012 Netherlands [6]	MMR booster	Retrospective	400 patients with JIA	400 JIA (246 nonsteroidal anti-inflammatory drugs, 93 MTX, 28 oral GC, 24 DMARD, 8 anti-TNF)		Long-term antibody levels lower for rubella and mumps up to 10 years' post-vaccination, but normal for measles
Heijstek 2013 Netherlands [7]	MMR booster	Randomized controlled trial	137 patients with JIA	137 JIA patients – 63 were vaccinated (29 patients on low-dose MTX, 9 patients on anti-TNF or anti-IL1, briefly interrupted at the time of immunization) – 68 patients not vaccinated	No increase in disease activity or disease flares in the 12 months following vaccination	– Higher antibody titres in patients vaccinated – Seroprotection rates between 97 and 100%, even 12 months post-vaccination. – No patients developed overt vaccine strain viral infection

Uziel 2020 [8] Ten countries	Booster of MMR/MMRV	Retrospective, multicentre	234 patients with rheumatic disease (90% JIA)	124 MTX 71 MTX+biologics 39 biologics only Biologics included anti-TNFa [9], anti-IL1 [10] and anti-IL-6 [6].	MMR/VZV was safe 13 mild adverse events (skin reaction, local pain, mild fever, flu-like symptoms)	NA
Maritsi 2019 [11]	Two doses of MMR	Prospective study on long-term persistence of antibodies after MMR	41 with enthesitis JIA	41 anti-TNF		Measles and rubella antibody loss is accelerated, but seroprotection is retained
Solid organ transplantation						
Rand 1993 USA [12]	One dose of MMR or measles vaccine (primary dose)	Retrospective study	18 patients 1.5–65 months post liver transplantation	13 patients on CSA and prednisone 3 patients on CSA, AZA and prednisone 1 patient on CSA, prednisone and OKT3 1 patient on TAC	One rejection episode 3 weeks after vaccine, no clinical sign of measles	39% seroconversion rate

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Author, year, country	Vaccine	Study design	Disease	No. of patients and treatment/dosage	Safety	Immunogenicity
Kano 2002 Japan [13]	One dose of measles vaccine (revaccination)	Prospective study	13 patients >1 year post liver transplantation	13 patients on TAC (level <5 ng/mL) or CSA (level <50 mg/mL)	No complication	85% seroconversion 64% seroprotected 6 months after vaccination Three breakthrough diseases: two primary vaccine failure, one secondary vaccine failure
Khan 2006 USA [14]	One to three doses MMR (primary dose)	Retrospective study	31 patients 4–20 months post liver transplantation	22 patients on TAC (level 3–10 ng/mL) 9 patients on CSA (level 30–120 μg/L)	No complication	73% seroconversion rate
Shinjoh 2008, 2015 Japan [15, 16]	One to two doses of measles vaccine (primary and revaccination)	Prospective	48 patients >2 years post liver transplantation	26 patients on TAC (level <5 ng/mL) 20 patients on CSA (level <100 ng/mL) 2 patients on TAC and CSA	No complication, two cases of fever without focus 2–3 weeks after vaccination	100% seroconversion rate
Gerner 2009 Germany [17]	One to four doses of MMR (primary dose)	Retrospective	34 patients >1 year post liver transplantation	34 patients, medication NA	No complication	68% seroconversion rate

Kawano 2015 Japan [18]	One to two doses of measles vaccine	Prospective	26 patients >1 year post liver transplantation	26 patients on TAC (level 0–4.9 ng/mL)	No complication	76% seroconversion rate
Pittet 2018 Switzerland [19]	One to three doses of MMR (primary and revaccination)	Prospective	44 patients >1 year post liver transplantation	41 patients on TAC (level <8 ng/mL), including 3 patients on TAC and MMF 1 patient on CSA, 1 patient on CSA and MMF 1 patient on everolimus	No complication	98% seroconversion rate
Hematopoietic stem cell transplantation						
Pauksen 1992 Sweden [20]	One dose of MMR (primary after BMT)	Prospective	7 patients 1–2 years post BMT for ALL	Seven patients without treatment; BMT conditioning regimen included cyclophosphamide 80 mg/kg, vincristine 1.5 mg/m^2, daunorubicin 30 mg/m^2, teniposide 200 mg/m^2, cytosine arabinoside 2500 mg/m^2, prednisone 200 mg/m^2, and total body irradiation	No complication	33% seroconversion rate to measles

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Author, year, country	Vaccine	Study design	Disease	No. of patients and treatment/dosage	Safety	Immunogenicity
Shaw 2002 Australia [21]	One dose of MMR	Retrospective	79 patients >1 year post BMT (underlying condition NA)	No immunosuppressive treatment for >3 months	One patient vaccinated 24 months after allogeneic BMT reported a transient rash and fever 1 week after vaccination	46% seroconversion rate to measles Seroconversion more likely to occur in patients vaccinated >15 months post-BMT (78%) compared with those vaccinated <15 months post-BMT (35%)

Machado 2005 Brazil [22]	One dose of MMR (primary after BMT or booster)	Prospective	61 patients 9–18 months post-BMT for severe aplastic anaemia [23], chronic myelogenous leukaemia [24], ALL [6], acute myelogenous leukaemia [8], non-Hodgkin lymphoma [2], Hodgkin lymphoma [2], or other conditions [23]	27 patients were on immunosuppressive drugs at vaccination for GvHD: – 12 patients on CSA – 11 patients on CSA and prednisone – 2 patients on prednisone alone – 2 patients on MMF	Five patients reported myalgia One patient reported low-grade fever No moderate or severe adverse reactions reported	Primary vaccination: 100% seroconverted 78% maintained seroprotection after 1 year

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Table 3.1 (continued)

Author, year, country	Vaccine	Study design	Disease	No. of patients and treatment/dosage	Safety	Immunogenicity
Small 2010 USA [25]	One dose of MMR (revaccination after BMT)	Prospective	7 patients 1.5–3.6 years post cord blood transplantation for ALL or lymphoma/ chronic lymphocytic leukaemia	GvHD prophylaxis with calcineurin inhibitor and MMF	No complication	43% seroconversion rate to measles

VZV vaccine

Dysimmune disorders

Pileggi 2010 Brazil [26]	Primary dose of VZV	Prospective	25 patients with rheumatic disease	25 patients (17 JIA, 4 juvenile dermatomyositis, 4 other rheumatic diseases) – 5 MTX+DMARDs – 13 MTX+GCs GC 0.1–0.7 mg/kg/day MTX 12–25 mg/m^2/week CSA 3–3.5 mg/kg/day Leflunomide 10 mg/day Penicillamine 13 mg/kg/day	– No increase in disease activity – No severe VZV infection – Three patients with mild self-limited VZV-like rash	– Slight decrease in seroresponse in patients compared to controls – Two of eight patients exposed to VZV developed chickenpox, one was on anti-TNFα – At 1 year, 80% patients maintained VZV antibodies
Lu 2010 North America [27]	VZV	Case series	6 patients with IBD	Six 6-MP Two anti-TNF	No serious adverse events after primary/booster VZV, despite anti-TNFα	Seroprotection in five of six patients

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Author, year, country	Vaccine	Study design	Disease	No. of patients and treatment/dosage	Safety	Immunogenicity
Barbosa 2012 Brazil [28]	VZV booster	Randomized controlled trial	54 patients with SLE	28 SLE vaccinated – 27 HCQ – 18 GCs low-dose – 9 AZA – 2 MTX 26 SLE non-vaccinated – 22 HCQ – 18 GC low-dose – 12 AZA – 2 CSA	No increase in disease flare among vaccinated patients	– Similar antibody response at short term – Over 35.6 months after vaccination, four cases of HZ in the non-vaccinated group compared to none in the vaccinated group

Toplak 2015 Slovenia [29]	Primary dose of VZV	Prospective	6 patients with JIA	Six patients on biologics (three on etanercept, two on tocilizumab, one on infliximab) Four patients received first dose of VZV	Vaccine was safe: no severe adverse events and no varicella infection Stable disease activity	– Five of six patients produced protective antibodies after the second dose – One of six did not and had a mild varicella infection 4 months after the second vaccination. – Production of antibodies higher in children on tocilizumab than in those on etanercept – In the long term, antibodies declined in children on tocilizumab

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Author, year, country	Vaccine	Study design	Disease	No. of patients and treatment/dosage	Safety	Immunogenicity
Groot 2017 Brazil/Netherlands [30]	VZV booster	Prospective	49 patients with various rheumatic diseases	49 patients (39 JIA, 5 juvenile dermatomyositis, 5 juvenile systemic sclerosis) and 18 healthy controls All patients were on MTX, 16 on GC and 3 on biologics (adalimumab, etanercept and abatacept)	Vaccination was safe No disease flare	– Good antibody response and cellular response – No effect of various immunosuppressive treatments. – Second dose (n = 21) increased VZV antibodies

Speth 2018 Germany [31]	VZV (booster and primary dose)	Prospective Based on a pre-vaccination checklist	23 patients with rheumatic disease	23 patients with rheumatic disease 9 on biologics (4 anti-TNF, 2 anti-IL-1, 2 anti-IL-6, 1 abatacept) (9 of 23 had already received one dose of VZV) 9 on low immunosuppressive treatment 14 on high IS	Mild adverse events, no severe adverse events, no rash or vaccine-induced VZV, no disease flare	– Good antibody response, even for the low and high immunosuppressive treatments – 21 of 23 responded after first dose. – 2 of 23 patients failed to respond

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Author, year, country	Vaccine	Study design	Disease	No. of patients and treatment/dosage	Safety	Immunogenicity
Jeyaratnam 2018 [32]	Various live-attenuated vaccine	Retrospective multicentre survey	17 patients with auto-inflammatory disorders	17 patients with auto-inflammatory disorder systemic JIA, 5 CAPS, 4 MKD, 1 FMF 14 on anti-IL-1, 3 on anti-IL-6 7 received MMR boost 1 received first dose of MMR/VZV while on canakinumab, which was stopped at time of vaccination 1 received first dose of VZV while on tocilizumab 4 received first yellow fever vaccine 1 received oral polio while on tocilizumab	Two patients had severe adverse events: varicella infection after VZV booster (in a child on anakinra, low-dose GCs and several DMARDs), and a pneumonia after MMR booster (in a child on canakinumab, low-dose GCs and MTX). Seven patients had a mild disease flare Eight patients had no disease flare	NA

Solid organ transplantation

Zamora 1994 Spain [33]	One dose of VZV (primary dose)	Prospective	17 patients post kidney transplantation	17 patients on prednisone, CSA, and AZA	One patient developed a mild form of varicella 15 days post-vaccination	85% seroconversion rate. Three patients had an attenuated form of varicella 2–4 years post-vaccination, protection 82%
Kano 2002 Japan [13]	One dose of VZV (revaccination)	Observational	7 patients >1 year post liver transplantation	Seven patients on TAC or CSA	No complication	71% seroconversion rate 57% seropositive 6 months after vaccination Five breakthrough diseases: one primary vaccine failure, four secondary vaccine failure
Levitsky 2002 USA [34]	One dose of VZV (primary vaccination post exposure)	Case-report	One patient 11 months after liver transplantation	One patient on TAC, sirolimus and prednisone	Rash 3 weeks later, treated with acyclovir, unclear whether it was due to the vaccine- or the wild-strain of VZV	NA

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Author, year, country	Vaccine	Study design	Disease	No. of patients and treatment/dosage	Safety	Immunogenicity
Chaves 2005 Brazil [35]	One or two doses of VZV (revaccination)	Observational	6 patients after kidney transplantation	3 patients on MMF, prednisone and CSA 2 patients on MMF, prednisone and TAC 1 patient on AZA, prednisone, and TAC	One patient had fever 15 days after immunization (in the setting of an otitis media)	67% seroconversion rate
Khan 2006 USA [14]	One or two doses of VZV (primary doses)	Retrospective	35 patients, 4–173 months post liver transplantation	23 patients on TAC (level 3–10 ng/mL) 11 patients on CSA (level 30–120 µg/L) 1 patient on sirolimus	Three patients had a vesicular rash at the site of the injection and fever within 24 h of immunization	64% seroconversion rate

Weinberg 2006 USA [36]	One dose of VZV (primary dose)	Observational	16 patients, 8–67 months post liver transplantation and/or small bowel transplantation	14 patients on TAC (level ≤10 ng/mL for >1 month), including 1 patient also on sirolimus (level of 7.7 ng/mL) 2 patients on CSA (mean level 93.5 ng/mL) 9 patients also on 1–2.5 mg (0.3 mg/kg) of prednisone on alternate days	Five patients (31%) reported pain and/or erythema and induration at injection site 24 h after vaccination; four patients reported fever. Four patients (25%) reported a vesicular rash 1–24 days after vaccination, three of four (75%) received treatment with oral acyclovir	87% seroconversion rate 86% (12 of 14) had positive cellular responses
Kraft 2006 Canada [37]	One dose of VZV (primary dose)	Case report	One patient, 2 years after heart transplantation	One adult on MMF (500 mg twice daily) and oral CSA (100 mg twice daily)	On day 24 after vaccination, the patient developed a vesicular rash on his face, trunk and limbs and was treated with oral famiclovir and intravenous acyclovir	NA

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Author, year, country	Vaccine	Study design	Disease	No. of patients and treatment/dosage	Safety	Immunogenicity
Shinjoh 2008, 2015 Japan [15, 16]	One or two doses of VZV (primary and revaccination)	Prospective	48 patients, 27–133 months post liver transplantation	26 patients on TAC (level <5 ng/mL) 20 patients on CSA (level <100 ng/mL) 2 patients on TAC and CSA	One patient developed varicella 2 weeks after the first dose of vaccination	70% seroconversion rate after the first dose 81% seroconversion rate after 1–2 doses Three patients developed mild varicella 11 months to 11.5 years after vaccination

Posfay-Barbe 2012 Verolet 2019 Switzerland [38, 39]	One to three doses of VZV (primary and revaccination)	Prospective	49 patients >1 year post liver transplantation	49 patients on TAC, CSA, or MMF	55% reported a local adverse reaction after vaccination 65% reported at least one a systemic reaction after vaccination. Three patients experienced a transient generalized nonvesicular rash, within 1 week (two patients) or 2 weeks (one patient) of vaccination Five patients reported vesicles within 8 weeks after vaccination, which disappeared spontaneously in less than 48 h	100% seroprotection after 1, 2 or 3 vaccinations 96% maintained protective antibody concentrations at a median of 5.5 years after vaccination In 20 patients, VZV-specific $CD4^+$ T cell responses were compared pre- and postimmunization and they showed a significant increase One breakthrough disease reported

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Author, year, country	Vaccine	Study design	Disease	No. of patients and treatment/dosage	Safety	Immunogenicity
Kawano 2015 Japan [18]	One to three doses of VZV (primary and revaccination)	Prospective	19 patients 12–180 months post liver transplantation	19 patients on TAC	One patient developed varicella 30 days after vaccination.	32% seroprotected after first dose (6 of 19) 50% seroprotected after second dose (5 of 10) 25% seroprotected after third dose (1 of 4)
Hematopoietic stem cell transplantation						
Sauerbrei 1997 Germany [40]	One to two doses of VZV (revaccination or booster)	Prospective	15 patients 12–23 months post BMT (underlying condition NA)	No immunosuppressive treatment for >3 months	No complication	100% seroconversion rate (one patient required two doses)
Ljungman 2003 Sweden [41]	One dose of VZV (booster)	Prospective	9 patients 3–4 months after hematopoietic stem cell transplantation	NA	Two patients reported a vesicular rash at the injection site	One patient reported a mild herpes zoster episode 3 months after vaccination and was treated with oral acyclovir

Kussmaul 2010 USA [42]	One to three doses of VZV (primary or revaccination)	Retrospective	68 patients 16–144 months after hematopoietic stem cell transplantation	No immunosuppressive treatment	One patient reported zoster rash 7 days after vaccination (and discontinuation of prophylactic acyclovir). Two patients reported a rash (one diagnosed as impetigo) after VZV and MMR vaccination	64% seroconversion rate (after one to three doses)
Small 2010 USA [25]	One dose of VZV (revaccination)	Prospective	3 patients 1.5–3.6 years post cord blood transplantation for ALL or lymphoma/ chronic lymphocytic leukaemia	GvHD prophylaxis with calcineurin inhibitor and MMF	No complication	33% seroconversion rate

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Table 3.1 (continued)

Author, year, country	Vaccine	Study design	Disease	No. of patients and treatment/dosage	Safety	Immunogenicity
Chou 2011 USA [43]	One to two doses of VZV (revaccination or booster)	Retrospective	44 patients 0.9–14 years post BMT for hematologic malignancy [18], immunodeficiency [44] or other diseases [11]	NA	Three patients reported a mild disseminated rash within 2.5 weeks of vaccination, self-resolved	64% seroconversion rate to one dose

6-MP 6-mercaptopurine, *ALL* acute lymphocytic leukaemia, *AZA* azathioprine, *BMT* bone marrow transplantation, *CAPS* cryopyrin-associated periodic fever syndrome, *CSA* cyclosporine, *CYC* cyclophosphamide, *DMARD* disease-modifying antirheumatic drug, *FMF* familial Mediterranean fever, *GC* glucocorticoid, *GvHD* graft-versus-host disease, *HCQ* hydroxychloroquine, *IFN* interferon, *IL* interleukin, *JIA* juvenile idiopathic arthritis, *MKD* mevalonate kinase deficiency, *MMF* mycophenolate mofetil, *MTX* methotrexate, *NA* not available, *OKT3* muromonab-CD3, *SLE* systemic lupus erythematous, *SOT* solid organ transplantation, *TAC* tacrolimus, *TNF* tumor necrosis factor, *VZV* varicella vaccine

to 2176 healthy controls. They reported lower levels of antigen-specific antibodies in JIA patients for all antigens, except measles, although seroprotection rates were similar in JIA patients and controls. Furthermore, the use of MTX and GCs had no effect on antibody persistence [6]. Other studies have reported that revaccination with MMR in patients treated with various immunosuppressive treatment was safe and immunogenic, although the antibody response was lower in the short- and longer-term [3, 5, 8, 11] (Table 3.1).

In SOT recipients, measles-containing vaccines have been contraindicated after transplantation due to the lack of safety data and the fear of instigating immune-mediated organ rejection or complications following uncontrolled viral replication [44, 45]. Ideally, transplant candidates are encouraged to be vaccinated before transplantation [44, 46] using an accelerated schedule if feasible (starting at the age of 6 months) [47]. Nevertheless, in practice, pre-transplant vaccination is not always performed because patients are either too young or considered too ill, or because of insufficient time before the planned transplantation [24]. In children vaccinated before transplantation, antibodies may wane over time, in particular under the influence of immunosuppressive drugs [23, 46]. In a Swiss cohort of liver transplant recipients, 70% of patients immunized before transplantation were seroprotected post-transplantation and therefore did not require further vaccination. Furthermore, most of these patients were protected against measles during transplantation, as well as during the first year after transplantation when immunosuppression is too high to allow the administration of any live-attenuated vaccine. Unsurprisingly, in this same cohort, patients immunized and transplanted at an older age had a higher chance of being seroprotected against measles compared with those transplanted at a younger age. However, the authors reported that five patients who had been immunized before 9 months of age remained seroprotected after liver transplantation, highlighting the rationale behind the administration of MMR as early as possible before transplantation by using an accelerated schedule if needed [47]. In this same

study, the authors reported that one-third of patients immunized before transplantation were not seroprotected after transplantation, which is a much higher rate of seroprotection loss than that observed in healthy subjects [48]. Similar observations have been made in HIV-infected patients [10, 49], thus indicating the impact of immune deficiency/immunosuppression on the persistence of measles antibodies. Remarkably, all of these patients responded to re-immunization in the context of the study and maintained high seroprotection rates during follow-up.

Although measles-containing vaccines have been administered to transplant recipients for decades, it has been mainly limited to a few outbreak settings (mostly unpublished) [50]. So far, seven retrospective and prospective studies in Japan, the USA, Germany and Switzerland have been performed for a total of 214 transplant recipients (Table 3.1) [12–19]. Overall, the authors of these reports observed a good immunogenicity of primary vaccination or revaccination with measles-containing vaccines in liver transplant recipients, with a 39–100% seroconversion rate, although many patients required further doses to maintain seroprotection during follow-up. The authors did not report any serious adverse events, but the total number of vaccinees is too small to draw any definite conclusion. In one study, a unique multimodal approach was used to closely monitor MMR safety in liver transplant recipients after each vaccination. This included the completion of a vaccine diary for 8 weeks, active surveillance through serial phone calls, and screening of prolonged vaccine-strain replication through the monitoring of viral shedding in urine by polymerase chain reaction [19]. Reassuringly, all studies conclude that measles vaccine appears to be safe after liver transplantation, with no occurrence of serious adverse events attributable to the vaccine, but the overall safety of MMR cannot yet be fully assessed given the limited size of the study population and the low frequency of severe adverse events.

In hematopoietic stem cell transplant recipients, both the Children's Cancer and Leukaemia Group (CCLG) [51] and

the Infectious Diseases Society of America (IDSA) [52] recommend the administration of MMR vaccination at 18 (CCLG) or 24 months (IDSA) after transplantation, if the patient fulfils specific safety criteria. However, there are only a few studies assessing the safety and immunogenicity of MMR revaccination in this context (Table 3.1). Among the four reports [20–22, 25], the seroconversion rate to measles was between 33% and 100% after one to two doses. There was no safety concern. In one study, the authors reported that 27 patients were receiving immunosuppressive treatment for GvHD at the time they received the vaccine [22].

Varicella (Chickenpox) Vaccine (VZV)

In a prospective controlled study, 25 children with various rheumatic diseases (17 JIA, 4 juvenile dermatomyositis, 3 juvenile scleroderma, 1 vasculitis) treated with MTX alone or with prednisone (maximum 10 mg/day) or other csDMARDs received a single primary dose of VZV vaccine. Three patients with JIA presented a mild, self-limited, varicella-like rash in the first 2 weeks post-vaccination, without any other symptoms, and the rash spontaneously resolved after 5–7 days. More importantly, the number of active joints in JIA patients significantly decreased at month 3 after vaccination [26]. In another prospective controlled study, 54 children with SLE treated with various csDMARDs and immune for varicella were randomly assigned to receive a single booster dose of VZV vaccine or placebo. There was no difference in the rates of adverse events or frequency of SLE flares between the vaccinated and non-vaccinated children [28]. A case series reported the administration of a first dose of VZV vaccine in four of six children with JIA treated with bDMARDs. They reported that the vaccine was safe, but not efficacious in all children as one patient did not respond and presented a mild varicella infection 4 months later. Although it is a very small sample size, it appears that patients treated with anti-TNFα (etanercept) responded less well [29]. Another case-control study assessed the immune response to a booster dose of VZV vaccine in 49 children with diverse rheumatic diseases

(three of whom were treated with bDMARDs) compared to 18 healthy controls. They reported good safety data and similar humoral responses in patients compared to healthy controls [30]. Similarly, another prospective study assessed the immune response to primary and booster doses of VZV vaccine in children on immunosuppressive treatments, nine of whom were on bDMARDs. They used a pre-vaccination checklist with basic laboratory tests: white blood cell count $\geq$3000/mm^3; lymphocytes $\geq$1200/mm^3; serum IgG $\geq$500 mg/dL; IgM $\geq$20 mg/dL; and tetanus toxoid antibody $\geq$0.1 IU/mL. In the case of high immunosuppression, additional specifications included a CD4+ lymphocyte count $\geq$200/mm^3 and a positive T cell function (via the analysable positive control of a standard tuberculosis interferon-gamma-release-assay indicating mitogen-induced T cell proliferation). Patients who met the criteria of the pre-vaccination checklist received the first and/or second VZV vaccination, with good safety and immunogenicity results [31].

A retrospective multicentric survey in which physicians treating children with auto-inflammatory diseases on anti-IL-1 and anti-IL-6 were contacted and asked to report safety data concerning the vaccination with live-attenuated vaccines. Good safety data were reported concerning 17 children (7 with sJIA and 10 with periodic fever syndromes), apart from two serious adverse effects: a VZV infection after a VZV booster in a child on anti-IL-1 (anakinra), low GCs and several csDMARDs and a pneumonia after a MMR booster in a child on anti-IL-1 (canakinumab), low GCs and MTX [32]. Finally, a retrospective study from the Paediatric Rheumatology European Society (PRES) Vaccinations Working Group reported good safety data of 234 patients with various rheumatic diseases receiving booster doses of MMR or MMR and varicella (MMRV) combination vaccine while treated with various immunosuppressive treatments [8].

In SOT recipients, there are a dozen publications consisting of case reports, and observational and prospective studies discussing varicella vaccination after transplantation (Table 3.1). These include both primary vaccination and

revaccination, following renal, liver, intestinal or heart transplantation, with varicella vaccine. The MMRV has not yet been studied in solid organ recipients. The authors report a 32–100% seroconversion rate following one to three doses of varicella vaccine. Although many report a high degree of waning immunity during follow up, in one of the largest studies, 96% of patients maintained protective antibody concentrations at a median of 5.5 years of follow up after vaccination [38]. T cell responses were assessed in a total of 34 transplant recipients across two studies and had significantly increased following transplantation [36, 39].

In hematopoietic stem cell transplant recipients, the CCLG does not recommend the administration of varicella vaccination after transplantation [51], whereas the IDSA recommends varicella vaccine only in seronegative patients ≥24 months after hematopoietic stem cell transplantation, provided that there is no GvHD and that the patient is not receiving any immunosuppressive medication [52]. There is limited evidence in the literature suggesting the safety and immunogenicity of varicella vaccine after hematopoietic stem cell transplantation (Table 3.1). Among the five reports, there was a 33–100% seroconversion rate following one to three doses of varicella vaccine [25, 40–43].

In contrast to the measles vaccine studies, several breakthrough diseases have been reported following vaccination due to primary or secondary vaccine failure (Table 3.1). All cases presented with an attenuated form of chickenpox disease and recovered well, with some requiring treatment. There was also a higher rate of rashes reported after vaccination, likely induced by the vaccine given their vesicular nature, although never confirmed by polymerase chain reaction. However, all rashes were self-limited with uneventful recoveries. Overall, the authors had no safety concern following varicella vaccination after solid organ or hematopoietic stem cell transplantation.

3.2.2 Other Vaccines

There are no studies on vaccine responses to yellow fever vaccine in immunocompromised children. However, a survey-based study in Brazil reported that a total of 19 transplant recipients aged 11–69 years old had inadvertently received the yellow fever vaccine 3–340 months after kidney (14 patients), heart (3 patients) or liver (2 patients) transplantation while under various combination of immunosuppressive treatment including prednisone (11 patients), mycophenolate mofetil (10 patients), cyclosporine (8 patients), azathioprine (7 patients), tacrolimus (4 patients), sirolimus (3 patients), and deflazacort (1 patient); none had serious adverse event [53]. Another case series assessing the immune response to a booster dose of yellow fever vaccine in 15 adults with various rheumatic diseases treated with MTX and anti-TNFα reported a similar antibody response to healthy controls and no adverse events, although there was a trend towards a lower immune response in patients, but due to the small sample size, no formal statistics could be performed [54].

3.2.3 Conclusions

There is increasing evidence to suggest that MMR and varicella vaccines are well tolerated in individuals with mild immunosuppression, such as in children with DiGeorge syndrome (if lymphocyte count is >500 cells/μL) [1], HIV-infected individuals (if $CD4^+$ count is >200 cells/μL) [55, 56], liver or kidney transplant recipients (strict conditions [57]), after hematopoietic stem cell transplantation [51, 58], or in individuals with dysimmune disorders on low/no immune suppression [59, 60], including children with nephrotic syndrome [61]. MMR and varicella vaccine have indeed the potential to protect patients against threatening pathogen that are endemic or linked to epidemics in many places around the world.

In children with dysimmune disorders, studies show that those treated with low-dose csDMARDs and GCs who received booster doses of MMR, VZV or primary vaccination against VZV, had no severe adverse reactions and no cases of vaccine-derived viral infections or worsening of disease activity [3, 4, 26, 54]. Therefore, even if larger studies are necessary, it appears that booster vaccinations with live vaccines can be considered in patients with dysimmune disorders treated with various csDMARDs at low dose or GCs, or even some bDMARDs [62] (Table 3.2). However, more data are needed for these new treatments as they are more specific and they could affect a pathway required for vaccine responses. An immunology work-up can also be done before vaccination with live vaccines by looking at the total lymphocyte count, IgG levels, vaccine antibody levels, and possibly CD4 and CD8 counts and a T cell stimulation test.

Concerning immunogenicity, all these results show that live vaccines induce a good immune response in the short term in children with various dysimmune disorders on GCs, csDMARDs or bDMARDs (anti-TNF, anti-IL-1, anti-IL-6) [4, 6–8, 26, 28–31] as summarized in Table 3.1. However, a rapid loss of antibodies can be expected in the longer-term under immunosuppression, although persistence may be maintained with some csDMARDs. Results also suggest that responses are lower in children on bDMARDs. These findings are very important in the context of measles outbreaks occurring worldwide as immunosuppressed children not up to date with their vaccines are particularly at risk of infection. Booster doses may be needed, but it is difficult to establish common guidelines as to when boosters should be given as the long-term effect may depend on the complexity of therapy.

Table 3.2 Definitions of low immunosuppression and restriction on the use of live vaccines, based on expert opinion and recommendations for adults according to [60, 63–65]

Family of treatment	Molecule	Dosage	Live vaccines
Steroids (GCs)			
	Systemic	<0.2–0.5 mg/kg/day or >0.5 mg/kg/day for <2 weeks (delay of 2 weeks [64, 66, 67]	No restriction
	Substitutive treatment or non-systemic		No restriction
csDMARDs			

Inhibitors of DNA synthesis	MTX	≤15 mg/m^2 per week [63]	May be considered for booster immunization with VZV, MMR and yellow fever [63]
	Leflunomide	≤0.5 mg/kg/day [64]	May be considered for booster immunization with VZV (and MMR) off-label according to expert consensus, depending on the individual risk of exposure [60, 63, 64]
	AZA (Imurek®)	≤3 mg/kg/day [64]	May be considered for booster immunization with VZV (and MMR) off-label according to expert consensus, depending on the individual risk of exposure [60, 63, 64]
	6-MP	≤1.5 mg/kg/day [68]	May be considered for booster immunization with VZV (and MMR) off-label according to expert consensus, depending on the individual risk of exposure [60, 63, 64]
	MMF	≤1200 mg/m^2/day	May be considered for booster immunization with VZV (and MMR) off-label according to expert consensus, depending on the individual risk of exposure [60, 63, 64]

(continued)

Table 3.2 (continued)

Family of treatment	Molecule	Dosage	Live vaccines
Intracellular signal transduction	CSA	≤2.5 mg/kg/day	May be considered for booster immunization with VZV (and MMR) off-label according to expert consensus, depending on the individual risk of exposure [60, 63, 64]
PGL inhibitors	5-ASA (Sulphasalazine)	40 mg/kg/day up to 2 g/day	May be considered for booster immunization with VZV/MMR off-label according to expert consensus, depending on the individual risk of exposure [60, 63, 64]
Diverse	Antimalarials, colchicine, thalidomide	Standard dose	No restriction
bDMARDs			
Anti-intestinal integrins	Vedolizumab	Standard dose	No restriction
Anti-IL-5	Mepolizumab	Standard dose	No restriction
Anti-IgE	Omalizumab	Standard dose	No restriction

Anti-receptor activator of nuclear factor kappa-B ligand	Denosumab	Standard dose	No restriction
Inhibitors of VCAM-1 and integrins α4β1	Natalizumab	Standard dose	No restriction

6-MP 6-mercaptopurine, *AZA* azathioprine, *CSA* cyclosporine, *DMARD* disease-modifying antirheumatic drug, *GC* glucocorticoid, *IL* interleukin, *MMF* mycophenolate mofetil, *MMR* measles-mumps-rubella vaccine, *MTX* methotrexate, *PGL* prostaglandin, *VZV* varicella vaccine

3.3 Recommendations

3.3.1 VZV and MMR

Child Immunization Schedules Worldwide
Vaccination schedules for MMR and VZV vaccines differ among countries. While the first MMR vaccine dose is given around 9–15 months of age in all countries, the timing of the second dose varies greatly. It is recommended before the age of 2 years in Switzerland and Australia, or between 4 and 6 years in countries such as France, Spain, the United Kingdom, USA and Canada, or even as late as at 9 years old in Hungary, The Netherlands, Estonia, Norway, Poland and the Slovak Republic [69–72]. Most European countries do not vaccinate against varicella, while VZV vaccine is part of the routine vaccination schedule in Australia, Canada and the USA. Hence, depending on the age at onset of the dysimmune disease or organ failure, the child might not be immune against measles and varicella at the time of diagnosis.

Challenges
The risk of measles and varicella infections in immunocompromised children is even more important at the current time of increasing vaccine hesitancy and measles outbreaks worldwide. Therefore, assuring a protective immunity against measles and varicella in immunocompromised children can be very challenging. Once the immunosuppressive treatment has been introduced, it is no longer possible to vaccinate against these diseases as only live vaccines are available. Furthermore, vaccinating children during the acute phase of disease with a live vaccine is often difficult as a time interval of minimum 4 weeks is necessary between vaccination and the beginning of the immunosuppression or transplantation, and even more if two doses are needed.

Current Recommendations
The recommendations of the PRES concerning live vaccines in children with rheumatic disease were published in 2011

[63] and updated in 2015 [62]. According to PRES, live-attenuated vaccines against MMR and VZV can be given safely in children with rheumatic disease without immunosuppression according to national guidelines [62, 63]. As soon as a dysimmune disorder is suspected, screening for VZV and measles should be done systematically through infection and vaccine history and, if possible, confirmation by vaccine serology [68]. If the surrogate marker is below the threshold considered protective, seronegative patients for VZV and measles should be vaccinated before the start of immunosuppressive/immunomodulatory therapy. Two vaccine doses, at least 1 month apart, should be administered and the last dose should be given ≥1 month before the start of immunosuppressive therapy [63, 68, 73, 74].

In general, live viral vaccines are contraindicated under immunosuppressive therapy. However, as the replication potential of varicella vaccine is low and antivirals are available, varicella vaccine can be considered in any stable child under low-dose therapy with MTX, AZA or 6-MP [60, 68], while MMR and yellow fever vaccinations can be considered in clinically stable patients during low-dosage GCs and MTX therapy ≤15 mg/m^2/week [62, 63]. According to other recommendations, booster vaccinations against VZV, MMR and yellow fever, can also be considered in patients on low-dose csDMARDs [64, 68], as defined in Table 3.2.

Live vaccines should be avoided in children on high-dose immunosuppression [62, 63] as summarized in Table 3.3. Indeed, the replication of the live-attenuated vaccine may not be sufficiently controlled under strong immunosuppression and attenuated vaccines have the theoretical risk of a reversion to the virulent form, thereby inducing overt disease [32, 76]. In the healthy population, this presentation is extremely rare, generally mild and self-limited [77].

In general, it is recommended to wait for at least 4 weeks after discontinuation of high-dose GCs, at least 3 months after discontinuation of csDMARDs, and at least 3 months after discontinuation of a bDMARDs [74].

Table 3.3 Definitions of high-dose immunosuppression and delay necessary between interruption of immunosuppression and live vaccine administration [65, 75]

Family of treatment	Molecule	Dosage	Delay between last dose of treatment and live-vaccines
Steroids	Systemic	Prednisone ≥0.2 mg/kg/day or ≥10 mg/day for >2 weeks or intravenous pulse therapy of methylprednisone [64] >1 mg/kg/day prednisone, >14 days for others [67]	1 month
csDMARDs			
Inhibitors of DNA synthesis	MTX	>15 mg/m^2/week [63]	1–2 months [64, 67]
	Leflunomide	>0.5 mg/kg/day [63]	6 months [64] to 2 years [66–68]
	AZA	>1–3 mg/kg/day [63]	2 months [67] to 3 months [64, 66–68]
	6-MP	>1.5 mg/kg/day [63]	3 months [64, 66, 68]
	MMF	>1200 mg/m^2/day [64]	1 month [67], 2 months [64], 3 months [66]
	CYC	>0.5–2 mg/kg/day [63]	3 months [64, 66, 68]

Intracellular signal transduction	CSA	>2.5 mg/kg/day [63]	3 months [64, 66, 68]
	Tacrolimus	≥0.3 mg/kg/day tacrolimus (blood level >8 ng/mL)	1 month [67], 3 months [66, 68]
	Sirolimus	Standard dose	6 weeks [67], 3 months and verify CD4 and CD19 [65, 66, 68]
	Everolimus	Standard dose	6 weeks [67], 3 months and verify CD4 and CD19 [65, 66, 68]
bDMARDs			
Anti-TNFα	Etanercept	Standard dose	1 month [67] to 2 months [64–66, 68]
Anti-TNFα	Adalimumab, Golimumab, Certolizumab	Standard dose	3 months [64, 66–68]
	Infliximab	Standard dose	3 months [66], 4 months [67]

(continued)

Table 3.3 (continued)

Family of treatment	Molecule	Dosage	Delay between last dose of treatment and live-vaccines
Anti-IL-1	Anakinra	Standard dose	2 weeks [67] to 4 weeks [64, 65]
	Canakinumab	Standard dose	3 months after last dose and before next dose [64], 5 months after last dose [67], 7 months after last dose [65]
Anti-IL-6R	Tocilizumab	Standard dose	2 months [64], 3 months [64, 66, 67]
CTLA4-analogue	Abatacept	Standard dose	3–4 months [67], 3 months [66, 68]
Anti-CD20	Rituximab, Ocrelizumab	Standard dose	12 months + verify reconstitution of B and T cells before [64, 66–68]
Anti-Blys	Belimumab	Standard dose	3 months [64], 4 months [67]
Anti-CD52	Alemtuzumab	Standard dose	6 months [67], >12 months+ verify reconstitution of B and T cells [64, 66, 68]
Anti-C5	Eculizumab	Standard dose	6 months [67]

Anti-IL-17A	Sekukinumab, Ixekizumab	Standard dose	2 months [64], 3 months [66], 9 months [67]
Anti-IL-12 and IL-23	Usterkinumab	Standard dose	3 months [66], 4 months [67], 4.5 months [64]
tsDMARDS			
Anti-JAK	Tofacitinib, Baricitinib, Ruxolitinib	Standard dose	1 month [67], 2 months [64]
Anti-phosphodiesterase 4	Apremilast	Standard dose	2 weeks [67], 1 month [64]

6-MP 6-mercaptopurine, *AZA* azathioprine, *CSA* cyclosporine, *CYC* cyclophosphamide, *DMARD* disease modifying antirheumatic drug, *GC* glucocorticoid, *IL* interleukin, *MMF* mycophenolate mofetil, *MTX* methotrexate, *TAC* tacrolimus, *TNF* tumor necrosis factor

Table 3.2 summarizes the list of low immunosuppressive drugs, while Table 3.3 summarizes the list of high immunosuppressive drugs with the delay necessary between the interruption of the immunosuppressive treatment and immunization with live vaccines. Table 2.2 in Chap. 2 summarizes the effects of each immunosuppressive drug, the half-life, the definition of low and high dose, and the ideal delay between treatment and vaccination with a non-live and live vaccine. Table 3.4 summarizes the recommendations for administration of live-attenuated vaccines in children with rheumatic disease, and Table 3.5 gives recommendations for serological monitoring. These tables should be taken as indicative and not as strict guidelines according to expert consensus [64, 68, 74] based on [65, 66, 68, 75]. Delays were calculated according to the half-lives of the drugs (usually five half-lives) and the expected duration of the immunosuppressive effect after interruption. The various delays can be followed before planning any live vaccines in children on immunosuppressive treatments, while considering the risk and benefit of vaccination in each situation.

In solid organ recipients, live-attenuated vaccines can often not be given before transplantation due to their young age or unstable medical condition [14, 24, 47]. While post-exposure management with non-specific intravenous immunoglobulins may be effective to prevent death [78], it is a costly intervention requiring hospitalization and is 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.

However, extra caution should be taken and close safety monitoring is highly recommended following the administration of live-attenuated vaccines in any situation when the immune system is affected [52, 57]. In the setting of solid organ transplantation, a consensus of worldwide experts meeting in 2018 considered both measles and varicella vaccines to be safe in patients who are clinically well, more than 1 year after liver or kidney transplantation and more than 2 months after an acute rejection episode, and who meet spe-

Table 3.4 Proposed recommendations for live vaccines in children with rheumatic disease

Vaccine	Patient population	Dose and timing	Control of serology – short term – long term	Comments
Varicella	Seronegative for VZV[b]	Two doses	Check serology after first dose if booster vaccination or after second dose if primary vaccination	– 4 weeks before starting immunosuppression – booster doses may be considered under low-dose immunosuppression[a] if personal risk of exposure is high (Table 3.2) [60, 63, 66]
MMR	Seronegative for measles[b]	Two doses	Check serology after first dose if booster vaccination or after second dose if primary vaccination	– 4 weeks before starting immunosuppression. – Booster doses may be considered under low-dose immunosuppression[a] if personal risk of exposure is high (Table 3.2) [63, 66]

(continued)

Table 3.4 (continued)

Vaccine	Patient population	Dose and timing	Control of serology – short term – long term	Comments
Live typhoid vaccine	Only for travel in endemic regions, but use non-live vaccine			Contraindicated for immunosuppressed children, consider non-live polysaccharide vaccine (Typhim Vi®) [66]
BCG vaccine	Only for children returning definitively to endemic countries for tuberculosis			Contraindicated in immunosuppressed children
Yellow fever	Only for travel in endemic regions			– No data in children – Booster doses may be considered under low-dose immunosuppression[a] if the personal risk of exposure is high (Table 3.2) [63, 66]
Rotavirus	Follow local guidelines			Usually not applicable as should not be given after the age of 6 months [67]

MMR measles-mumps-rubella vaccine, *VZV* varicella vaccine
[a]Low-dose immunosuppression as defined in Table 3.2
[b]Correlate of protection as defined in Table 3.5 [65, 68]

Table 3.5 Summary of recommendation for serological monitoring

Pathogen	Rationale for monitoring	Test used	Unit	Susceptible	Short-term protection	Long-term protection	Mechanism prevented
Diphtheria	Monitor vaccine response and guide for booster indication	Toxin neutralisation	IU/L	<100	100–999	≥1000	Toxin production
Tetanus		Toxin neutralisation	IU/L	<100	100–999	≥1000	Toxin production
Pertussis	No indication	ELISA					Mucosal replication
Polio	Not routinely indicated	Serum neutralisation					Viremia
Haemophilus influenzae b	Could be used to document protection in high-risk situations	ELISA	mg/L	<0.15		≥1	Bacteraemia
Hepatitis A	Not routinely indicated	ELISA	IU/L	<20	≥20	≥20	Viremia
Hepatitis B	Monitor vaccine response as poorly immunogenic in immunocompromised individuals	ELISA	IU/L	<10	10–99	≥100	Viremia

(continued)

Table 3.5 (continued)

Pathogen	Rationale for monitoring	Test used	Unit	Susceptible	Short-term protection	Long-term protection	Mechanism prevented
Human papillomavirus	No indication	ELISA					Mucosal replication
Influenza	No indication	HAI					Mucosal replication
Pneumococcus	Could be used to guide for booster indication	Serotype-specific ELISA Serotype-specific OPA	mg/L Dilution	<0.3 <1/8 (differ across serotypes)	0.3–0.9 >1/8 (differ across serotypes)	≥1 >1/8 (differ across serotypes)	Bacteraemia
Meningococcus	No indication	ELISA Bactericidal test					Bacteraemia
Measles	Could be used to document protection in high-risk situations	Microneutralization assay ELISA	IU/L IU/L	<120 <150–200	120–499 200–499	≥500 ≥500	Viremia
Mumps	No indication	Serum neutralisation					Viremia
Rubella	Could be used to document protection prior to pregnancy	Immunoprecipitation	IU/L	<10	≥20	≥20	Viremia
Varicella	Could be used to document protection in high-risk situations	Serum neutralization Glycoprotein ELISA	Dilution IU/L	<1/64 <50	≥1/64 50–200	≥1/64 ≥200	Viremia

Yellow fever	No indication	ELISA					Viremia
Tick-borne encephalitis	Could be used to document protection in high-risk situations	ELISA (Enzygnost) ELISA (VIE-ELISA)	IU/L VIEU/mL	<6.98 <63	≥10.32 ≥127	≥10.32 ≥127	Viremia
Rabies	Could be used to document protection in high-risk situations	Serum neutralisation	IU/L	<0.5	≥0.5	≥0.5	Neuronal invasion

Adapted from [68, 81–83]

ELISA enzyme-linked immunosorbent assay, *HAI* hemagglutination inhibition assay, *HIV* human immunodeficiency virus, *HSCT* hematopoietic stem cell transplantation, *OPA* opsonophagocytic assay, *SOT* solid organ transplant

cific criteria of 'low-level' immunosuppression. The latter is defined as tacrolimus levels of <8 ng/mL or cyclosporine levels of <100 ng/mL (each for two consecutive readings), and a prednisone dose equivalent of <20 mg/day (or <2 mg/kg/day 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. Furthermore, in areas with a low incidence of measles, MMR vaccination is only considered during an outbreak or travel to endemic risk areas [57]. This same group of experts has also recommended to perform an immunological workup before administering measles or varicella vaccines after transplantation, including measurement of the total IgG level, total lymphocytes and CD4 counts [57]. They recommend further caution and in-depth immunologic evaluation for patients with a 'higher level' of immunosuppression, defined as those who have received MMF, T cell-depleting agents (e.g. anti-thymocyte globulin, rituximab, alemtuzumab), or have persistently elevated viral loads of Epstein-Barr virus, which is 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') [57].

Despite the publication of the consensus, clinicians should keep in mind that administration of live-attenuated vaccine in transplant recipients is still 'off-label' in all countries, and it is recommended to clearly document obtainment of informed consent after evaluating the risk-benefit of the intervention with the patient, their family and physicians. The consortium of experts also recommends a combination of both passive and active surveillance following vaccination [57]. It includes education of patients and families to seek medical attention promptly for any 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 3–4 weeks

after vaccination to identify any adverse event that might have occurred (active surveillance) [57].

A recent survey has revealed that several paediatric centres around the world are already administering live-attenuated vaccine after transplantation outside the context of clinical trials, in off-label settings [79]. Most respondents believed that these vaccines should be offered to solid organ recipients, especially in selected patients and situations (e.g. outbreak). However, this same survey showed a great variability in strategies for the prevention and management of varicella and measles in solid organ recipients and has revealed that the majority of the respondents did not perform any immunological workup before vaccination, and that close monitoring for adverse events was not done routinely in the majority of centres [79]. The data provided in this survey, coming from diverse caregivers worldwide, helped to identify knowledge gaps and practitioners' concerns, and could be used as a starting point for the creation of educational materials that would inform intervention methods and promote safe administration of live-attenuated vaccine in solid organ recipients. There is an increasing number of practitioners willing to administer live-attenuated vaccine in immunocompromised individuals 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 various disease societies.

In hematopoietic stem cell recipients, the CCLG recommends the administration of MMR vaccination as of 18 months after transplantation, provided that there is an absence of active chronic GvHD, as well as being off immunosuppressive treatment for at least 1 year and off IVIg for at least 3 months [51]. A second dose of MMR is recommended 6 months after the first dose, but can be given as early as 1 month after in outbreak situations. Varicella vaccine is not routinely recommended. IDSA guidelines differ slightly with the recommendation of varicella vaccine (only if seronegative) and MMR (regardless of serology) in patients ≥24 months after hematopoietic stem cell transplantation, pro-

vided that there is no GvHD and that the patient is not receiving any immunosuppressive medication [52].

For all immunocompromised conditions, it is also recommended to verify the vaccination status of the household and other close contacts and vaccinate them if indicated so as to minimize the risk for immunocompromised children through a 'cocooning strategy' [74]. In addition, if there is no time to administer live vaccines before starting immunosuppression, patients should be informed of their risk in the case of known exposure and advised to consult rapidly to receive prophylactic treatment antivirals/Igs [68].

Under immunosuppression, it is recommended to first give a non-live vaccine (preferably following a novel antigen, such as hepatitis A) and assess the antibody response 1 month after vaccination, as well as to measure the number of CD4/CD8 cells. If the antibody response is good, including the T cell numbers, a live vaccine can be considered [68].

3.3.2 Other Live Vaccines

Other live vaccines are usually contraindicated in patients on immunosuppression and the same recommendations should be followed as for VZV and MMR vaccines (Tables 3.2, 3.3, and 3.4). If travel is planned to an endemic country for yellow fever soon after the diagnosis, this vaccine should be administered before starting immunosuppression. In general, families should be discouraged from travelling to countries endemic for yellow fever and other diseases for which only live vaccines are available. Yellow fever vaccination can be given in clinically stable patients during low dosage MTX [68]. If yellow fever vaccine has been already administered previously, an antibody measurement should be performed. Seropositivity indicates past immunity and enables travel to yellow fever endemic areas, regardless of the time elapsed since immunization. As a precaution, oral typhoid vaccination (Vivotif®) and BCG vaccine should generally be avoided in all patients under immunosuppression [68].

3.3.3 *Treatment with Intravenous Immunoglobulin (IVIg)*

In the case of treatment with IVIg, the immune response to live vaccines may be reduced if the vaccine is administered immediately before or after the infusion. Live-vaccines should be given either 2 weeks before or should be delayed for 3–11 months after IVIg, depending on the dose. In the case of treatment with IVIG within 14 days of a live vaccine, the vaccine should be verified after 3–11 months of IVIg treatment and the vaccine re-administered if necessary.

3.3.4 *Infants Born to Mothers Who Received Immunosuppressive Treatment During Pregnancy*

As some immunosuppressive drugs pass the placental barrier, they can be found in newborns for 6–8 months, especially if they were taken by mothers at the end of pregnancy. These drugs can affect the development of the immune system of the newborn and also affect the response to vaccination. For example, a case of fatal 'BCGitis' has been reported in a 3-month-old infant whose mother had been treated with infliximab during pregnancy [80]. Drugs such as MTX, MMF, leflunomide and cyclophosphamide are teratogenous and contraindicated during pregnancy [9]. Other medications such as antimalarials, sulfasalazine, AZA, cyclosporine, tacrolimus and colchicine are not immunosuppressive and can be administered during pregnancy [9]. COX2 selective nonsteroidal antiinflammatory drugs (NSAIDs) and corticosteroids can be given until 28 gestational weeks [9]. In severe refractory maternal disease during pregnancy, pulses of methylprednisolone and IVIg can also be given until the end of pregnancy if necessary. It should be noted that biological monoclonal antibodies are transferred through the placenta, like other Igs, from week 13 until the end of pregnancy, with a peak during the last 4 weeks of pregnancy, resulting in a

blood level 120–130% higher than the mother's blood levels. Then, it appears that the half-life of the biological molecules is prolonged in newborns (infliximab can be measured for up to 6–12 months in babies, adalimumab for 3–6 months). Concerning anti-TNFα, they can be given during the two first trimesters and it seems that etanercept and certolizumab can also be given until the end of pregnancy due to a low rate of transplacental passage. Other bDMARDs should not be used during pregnancy [9].

EULAR recommends vaccinating infants according to the normal schedule if biological agents have been discontinued before week 22 of gestation. However, if immunosuppressive treatment is continued past 22 weeks in the mother, live vaccines (including BCG, rotavirus, oral polio, MMR and VZV) should be given after the age of 6 months. It is also possible to measure the metabolite levels in the blood of the infant. By contrast, inactivated vaccines can be given according to the normal schedule [9].

Most csDMARDs, bDMARDs and tsDMARDs are contraindicated during breastfeeding, except for antimalarials, sulfasalazine, AZA, cyclosporine, tacrolimus, colchicine, prednisone, Ig and also anti-TNF because of a low transfer to breast milk. Therefore, children who are only exposed to those immunosuppressive drugs during breastfeeding can be vaccinated normally [9].

References

1. Sobh A, Bonilla FA. Vaccination in primary immunodeficiency disorders. J Allergy Clin Immunol Pract. 2016;4(6):1066–75.
2. Fekrvand S, Yazdani R, Olbrich P, Gennery A, Rosenzweig SD, Condino-Neto A, et al. Primary immunodeficiency diseases and Bacillus Calmette-Guerin (BCG)-vaccine-derived complications: a systematic review. J Allergy Clin Immunol Pract. 2020.
3. Heijstek MW, Pileggi GC, Zonneveld-Huijssoon E, Armbrust W, Hoppenreijs EP, Uiterwaal CS, et al. Safety of measles, mumps and rubella vaccination in juvenile idiopathic arthritis. Ann Rheum Dis. 2007;66(10):1384–7.

4. Borte S, Liebert UG, Borte M, Sack U. Efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept. Rheumatology (Oxford). 2009;48(2):144–8.
5. Miyamoto M, Ono E, Barbosa C, Terreri M, Hilario M, Salomao R, et al. Vaccine antibodies and T- and B-cell interaction in juvenile systemic lupus erythematosus. Lupus. 2011;20(7):736–44.
6. Heijstek MW, van Gageldonk PG, Berbers GA, Wulffraat NM. Differences in persistence of measles, mumps, rubella, diphtheria and tetanus antibodies between children with rheumatic disease and healthy controls: a retrospective cross-sectional study. Ann Rheum Dis. 2012;71(6):948–54.
7. Heijstek MW, Kamphuis S, Armbrust W, Swart J, Gorter S, de Vries LD, et al. Effects of the live attenuated measles-mumps-rubella booster vaccination on disease activity in patients with juvenile idiopathic arthritis: a randomized trial. JAMA. 2013;309(23):2449–56.
8. Uziel Y, Moshe V, Onozo B, Kulcsar A, Trobert-Sipos D, Akikusa JD, et al. Live attenuated MMR/V booster vaccines in children with rheumatic diseases on immunosuppressive therapy are safe: multicenter, retrospective data collection. Vaccine. 2020;38(9):2198–201.
9. Gotestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016;75(5):795–810.
10. Bekker V, Scherpbier H, Pajkrt D, Jurriaans S, Zaaijer H, Kuijpers TW. Persistent humoral immune defect in highly active antiretroviral therapy-treated children with HIV-1 infection: loss of specific antibodies against attenuated vaccine strains and natural viral infection. Pediatrics. 2006;118(2):e315–22.
11. Maritsi DN, Kopsidas I, Vartzelis G, Spyridis N, Tsolia MN. Long-term preservation of measles and rubella specific-IgG antibodies in children with enthesitis related arthritis on anti-TNFalpha treatment: a prospective controlled study. Rheumatology (Oxford). 2019;58(9):1686–8.
12. Rand EB, McCarthy CA, Whitington PF. Measles vaccination after orthotopic liver transplantation. J Pediatr. 1993;123(1):87–9.
13. Kano H, Mizuta K, Sakakihara Y, Kato H, Miki Y, Shibuya N, et al. Efficacy and safety of immunization for pre- and post- liver transplant children. Transplantation. 2002;74(4):543–50.

14. Khan S, Erlichman J, Rand EB. Live virus immunization after orthotopic liver transplantation. Pediatr Transplant. 2006;10(1):78–82.
15. Shinjoh M, Miyairi I, Hoshino K, Takahashi T, Nakayama T. Effective and safe immunizations with live-attenuated vaccines for children after living donor liver transplantation. Vaccine. 2008;26(52):6859–63.
16. Shinjoh M, Hoshino K, Takahashi T, Nakayama T. Updated data on effective and safe immunizations with live-attenuated vaccines for children after living donor liver transplantation. Vaccine. 2015;33(5):701–7.
17. Gerner P, Lainka E, Ballauff A, Gierenz N, Hoyer P. Immunization with the measles-mumps-rubella vaccine in children before and after liver transplantation. Z Gastroenterol. 2009;47(09):P098.
18. Kawano Y, Suzuki M, Kawada J, Kimura H, Kamei H, Ohnishi Y, et al. Effectiveness and safety of immunization with live-attenuated and inactivated vaccines for pediatric liver transplantation recipients. Vaccine. 2015;33(12):1440–5.
19. Pittet LF, Verolet CM, McLin VA, Wildhaber BE, Rodriguez M, Cherpillod P, et al. Multimodal safety assessment of measles-mumps-rubella vaccination after pediatric liver transplantation. Am J Transplant. 2018.
20. Pauksen K, Duraj V, Ljungman P, Sjolin J, Oberg G, Lonnerholm G, et al. Immunity to and immunization against measles, rubella and mumps in patients after autologous bone marrow transplantation. Bone Marrow Transplant. 1992;9(6):427–32.
21. Shaw PJ, Bleakley M, Burgess M. Safety of early immunization against measles/mumps/rubella after bone marrow transplantation. Blood. 2002;99(9):3486.
22. Machado CM, de Souza VA, Sumita LM, da Rocha IF, Dulley FL, Pannuti CS. Early measles vaccination in bone marrow transplant recipients. Bone Marrow Transplant. 2005;35(8):787–91.
23. Eckerle I, Rosenberger KD, Zwahlen M, Junghanss T. Serologic vaccination response after solid organ transplantation: a systematic review. PLoS One. 2013;8(2):e56974.
24. Verma A, Wade JJ. Immunization issues before and after solid organ transplantation in children. Pediatr Transplant. 2006;10(5):536–48.
25. Small TN, Iovino CS, Abboud M, Lubin M, Papadopoulos E, Scaradavou A, et al. Vaccine response in recipients of HLA mismatched unrelated double unit cord blood transplantation (CBT). Am Soc Hematol. 2010.

26. Pileggi GS, de Souza CB, Ferriani VP. Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. Arthritis Care Res. 2010;62(7):1034–9.
27. Lu Y, Bousvaros A. Varicella vaccination in children with inflammatory bowel disease receiving immunosuppressive therapy. J Pediatr Gastroenterol Nutr. 2010;50(5):562–5.
28. Barbosa CM, Terreri MT, Rosario PO, de Moraes-Pinto MI, Silva CA, Hilario MO. Immune response and tolerability of varicella vaccine in children and adolescents with systemic lupus erythematosus previously exposed to varicella-zoster virus. Clin Exp Rheumatol. 2012;30(5):791–8.
29. Toplak N, Avcin T. Long-term safety and efficacy of varicella vaccination in children with juvenile idiopathic arthritis treated with biologic therapy. Vaccine. 2015;33(33):4056–9.
30. Groot N, Pileggi G, Sandoval CB, Grein I, Berbers G, Ferriani VPL, et al. Varicella vaccination elicits a humoral and cellular response in children with rheumatic diseases using immune suppressive treatment. Vaccine. 2017;35(21):2818–22.
31. Speth F, Hinze CH, Andel S, Mertens T, Haas JP. Varicella-zoster-virus vaccination in immunosuppressed children with rheumatic diseases using a pre-vaccination check list. Pediatr Rheumatol Online J. 2018;16(1):15.
32. Jeyaratnam J, Ter Haar NM, Lachmann HJ, Kasapcopur O, Ombrello AK, Rigante D, et al. The safety of live-attenuated vaccines in patients using IL-1 or IL-6 blockade: an international survey. Pediatr Rheumatol Online J. 2018;16(1):19.
33. Zamora I, Simon JM, Da Silva ME, Piqueras AI. Attenuated varicella virus vaccine in children with renal transplants. Pediatr Nephrol. 1994;8(2):190–2.
34. Levitsky J, Te HS, Faust TW, Cohen SM. Varicella infection following varicella vaccination in a liver transplant recipient. Am J Transplant. 2002;2(9):880–2.
35. Chaves Tdo S, Lopes MH, de Souza VA, Dos Santos SS, Pereira LM, Reis AD, et al. Seroprevalence of antibodies against varicella-zoster virus and response to the varicella vaccine in pediatric renal transplant patients. Pediatr Transplant. 2005;9(2):192–6.
36. Weinberg A, Horslen SP, Kaufman SS, Jesser R, Devoll-Zabrocki A, Fleckten BL, et al. Safety and immunogenicity of varicella-zoster virus vaccine in pediatric liver and intestine transplant recipients. Am J Transplant. 2006;6(3):565–8.

37. Kraft JN, Shaw JC. Varicella infection caused by Oka strain vaccine in a heart transplant recipient. Arch Dermatol. 2006;142(7):943–5.
38. Verolet CM, Pittet LF, Wildhaber BE, McLin VA, Rodriguez M, Grillet S, et al. Long-term seroprotection of varicella-zoster immunization in pediatric liver transplant recipients. Transplantation. 2019;103(11):e355–e64.
39. Posfay-Barbe KM, Pittet LF, Sottas C, Grillet S, Wildhaber BE, Rodriguez M, et al. Varicella-zoster immunization in pediatric liver transplant recipients: safe and immunogenic. Am J Transplant. 2012;12(11):2974–85.
40. Sauerbrei A, Prager J, Hengst U, Zintl F, Wutzler P. Varicella vaccination in children after bone marrow transplantation. Bone Marrow Transplant. 1997;20(5):381–3.
41. Ljungman P, Wang FZ, Nilsson C, Solheim V, Linde A. Vaccination of autologous stem cell transplant recipients with live varicella vaccine: a pilot study. Support Care Cancer. 2003;11:739–41.
42. Kussmaul SC, Horn BN, Dvorak CC, Abramovitz L, Cowan MJ, Weintrub PS. Safety of the live, attenuated varicella vaccine in pediatric recipients of hematopoietic SCTs. Bone Marrow Transplant. 2010;45(11):1602–6.
43. Chou JF, Kernan NA, Prockop S, Heller G, Scaradavou A, Kobos R, et al. Safety and immunogenicity of the live attenuated varicella vaccine following T replete or T cell-depleted related and unrelated allogeneic hematopoietic cell transplantation (allo-HCT). Biol Blood Marrow Transplant. 2011;17(11):1708–13.
44. Kelly DA, Bucuvalas JC, Alonso EM, Karpen SJ, Allen U, Green M, et al. Long-term medical management of the pediatric patient after liver transplantation: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transpl. 2013;19(8):798–825.
45. McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2013;62(RR-04):1–34.
46. Chow J, Golan Y. Vaccination of solid-organ transplantation candidates. Clin Infect Dis. 2009;49(10):1550–6.
47. Danzinger-Isakov L, Kumar D. Guidelines for vaccination of solid organ transplant candidates and recipients. Am J Transplant. 2009;9(Suppl 4):S258–62.

48. Davidkin I, Jokinen S, Broman M, Leinikki P, Peltola H. Persistence of measles, mumps, and rubella antibodies in an MMR-vaccinated cohort: a 20-year follow-up. J Infect Dis. 2008;197(7):950–6.
49. Belaunzaran-Zamudio PF, Garcia-Leon ML, Wong-Chew RM, Villasis-Keever A, Cuellar-Rodriguez J, Mosqueda-Gomez JL, et al. Early loss of measles antibodies after MMR vaccine among HIV-infected adults receiving HAART. Vaccine. 2009;27(50):7059–64.
50. Feldman AG, Kempe A, Beaty BL, Sundaram SS. Immunization practices among pediatric transplant hepatologists. Pediatr Transplant. 2016;20(8):1038–44.
51. Patel S, Heath P, Skinner R. Vaccinations for paediatric patients treated with standard-dose chemotherapy and hematopoietic stem cell transplantation recipients. UK: Children's Cancer and Leukaemia Group; 2016 [updated Sep 2017]. https://www.cclg.org.uk/write/MediaUploads/Member%20area/Treatment%20guidelines/Vaccinations_for_Children_treated_with_Standard-dose_Chemotherapy_and_HSCT_Recipients-Sept_2014-FINAL_CCLG.pdf
52. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58(3):309–18.
53. Azevedo LS, Lasmar EP, Contieri FL, Boin I, Percegona L, Saber LT, et al. Yellow fever vaccination in organ transplanted patients: is it safe? A multicenter study. Transpl Infect Dis. 2012;14(3):237–41.
54. Scheinberg M, Guedes-Barbosa LS, Mangueira C, Rosseto EA, Mota L, Oliveira AC, et al. Yellow fever revaccination during infliximab therapy. Arthritis Care Res. 2010;62(6):896–8.
55. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Recommended immunization schedule for adults and adolescents with HIV infection [updated 13 Sep 2017, 17 May 2020]. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf
56. Scott P, Moss WJ, Gilani Z, Low N. Measles vaccination in HIV-infected children: systematic review and meta-analysis of safety and immunogenicity. J Infect Dis. 2011;204(Suppl 1):S164–78.
57. Suresh S, Upton J, Green M, Pham-Huy A, Posfay-Barbe KM, Michaels MG, et al. Live vaccines after pediatric solid organ

transplant: proceedings of a consensus meeting, 2018. Pediatr Transplant. 2019;9:e13571.
58. Ljungman P, Cordonnier C, Einsele H, Englund J, Machado CM, Storek J, et al. Vaccination of hematopoietic cell transplant recipients. Bone Marrow Transplant. 2009;44(8):521–6.
59. Papp KA, Haraoui B, Kumar D, Marshall JK, Bissonnette R, Bitton A, et al. Vaccination guidelines for patients with immune-mediated disorders on immunosuppressive therapies. J Cutan Med Surg. 2019;23(1):50–74.
60. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58(3):e44–100.
61. Kamei K, Miyairi I, Ishikura K, Ogura M, Shoji K, Funaki T, et al. Prospective study of live attenuated vaccines for patients with nephrotic syndrome receiving immunosuppressive agents. J Pediatr. 2018;196:217–22.e1.
62. Groot N, Heijstek MW, Wulffraat NM. Vaccinations in paediatric rheumatology: an update on current developments. Curr Rheumatol Rep. 2015;17(7):46.
63. Heijstek MW, Ott de Bruin LM, Bijl M, Borrow R, van der Klis F, Kone-Paut I, et al. EULAR recommendations for vaccination in paediatric patients with rheumatic diseases. Ann Rheum Dis. 2011;70(10):1704–12.
64. Wagner N, Assmus F, Arendt G, Baum E, Baumann U, Bogdan C, et al. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2019;62(4):494–515.
65. Eperon G, Buhler S, Enriquez N, Vaudaux B. The immunosuppressed traveler: vaccination guidelines. Rev Med Suisse. 2018;14(605):922–33.
66. Wiedermann U, Sitte HH, Burgmann H, Eser A, Falb P, Holzmann H, et al. Guidelines for vaccination of immunocompromised individuals. Wien Klin Wochenschr. 2016;128(Suppl 4):337–76.
67. Belgium SHCo. Vaccination of immunocompromised or chronically ill children and/or adults. In: Food Chain Safety and Environment SHC, editor. Belgium; 2019.
68. Bühler S, Hatz C. Background document on immune-mediated inflammatory diseases (IMID), module 2: vaccination in patients with inflammatory bowel diseases and other gastroenterological (auto)immune conditions. In: Immunisation SFACo, editor. 2017.

69. Toplak N, Uziel Y. Vaccination for children on biologics. Curr Rheumatol Rep. 2020;22(7):26.
70. European Centre for Disease Control and Prevention. Vaccine schedules in European countries. 2020. https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId
71. Centers for Disease Control and Prevention. US immunization guide. 2021. https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html
72. Government of Canada. Canadian Immunization guide. 2020. https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-1-key-immunization-information/page-13-recommended-immunization-schedules.html
73. Akikusa JD, Crawford NW. Vaccination in paediatric rheumatology. Curr Rheumatol Rep. 2014;16(8):432.
74. Rheumatology BSaHCobotFACoIaebtSSfAaIatSSf. Background document on immune-mediated inflammatory diseases (IMID), module 1: vaccination in patients with autoimmune inflammatory rheumatic diseases (AIIRD). 2013.
75. Bühler S, Eperon G, Ribi C, Kyburz D, van Gompel F, Visser LG, et al. Vaccination recommendations for adult patients with autoimmune inflammatory rheumatic diseases. Swiss Med Wkly. 2015;145:w14159.
76. Leung J, Siegel S, Jones JF, Schulte C, Blog D, Schmid DS, et al. Fatal varicella due to the vaccine-strain varicella-zoster virus. Hum Vaccin Immunother. 2014;10(1):146–9.
77. Morin MP, Quach C, Fortin E, Chedeville G. Vaccination coverage in children with juvenile idiopathic arthritis followed at a paediatric tertiary care centre. Rheumatology (Oxford). 2012;51(11):2046–50.
78. Young MK, Nimmo GR, Cripps AW, Jones MA. Post-exposure passive immunisation for preventing measles. Cochrane Database Syst Rev. 2014;4:CD010056.
79. Pittet LF, Danziger-Isakov L, Allen UD, Ardura MI, Chaudhuri A, Goddard E, et al. Management and prevention of varicella and measles infections in pediatric solid organ transplant candidates and recipients: an IPTA survey of current practice. Pediatr Transplant. 2020;24(8):e13830.

80. Cheent K, Nolan J, Shariq S, Kiho L, Pal A, Arnold J. Case report: fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. J Crohns Colitis. 2010;4(5):603–5.
81. Plotkin SA. Correlates of protection induced by vaccination. Clin Vaccine Immunol. 2010;17(7):1055–65.
82. Plotkin SA. Vaccines: correlates of vaccine-induced immunity. Clin Infect Dis. 2008;47(3):401–9.
83. Plotkin SA. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. 6th ed. Philadelphia, PA: Elsevier; 2012. 1576 p.