In Clinical Practice

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Laure F. Pittet

Vaccination of Immunosuppressed Children in Clinical Practice

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Preface

Immunosuppressed children are particularly at risk of vaccine-preventable diseases; however, vaccine coverage in this population remains too low. This is explained by a fear of possible adverse effects of vaccines under immunosuppression, but also lack of data and clear recommendations, in particular regarding vaccination with live vaccines in this population.

In this book, the latest literature and various recommendations on vaccination in immunosuppressed children are discussed in detail, with the aim to give practical guidelines on vaccination to specialists caring for children who are immunosuppressed for various reasons.

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Geneva, Switzerland — Geraldine Blanchard-Rohner
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Contents

Abbreviations

5-ASA	5-Aminosalicylic acid
6-MP	6-mercaptopurine
AAP	American Academy of Paediatrics
ACIP	Advisory Committee on Immunization Practices
AIEOP	Italian Association Paediatric Haematology Oncology
AIIRD	Auto-immune inflammatory rheumatic disease
ALL	Acute lymphoblastic leukaemia
APC	Antigen-presenting cell
AZA	Azathioprine
BAFF	B-cell activating factor
BCG	Bacille Calmette-Guérin
BCR	B cell receptor
bDMARDs	Biological DMARDs
BLys	B lymphocyte stimulator
BMT	Bone marrow transplantation
cAMP	Cyclic adenosine monophosphate
CAPS	Cryopyrin-associated autoinflammatory syndrome
CCLG	Children's Cancer and Leukaemia Group
CD	Cluster of differentiation
CHIVA	Children's HIV Association
CNS	Central nervous system
CRP	C-reactive protein
CSA	Cyclosporine A
csDMARDs	Conventional synthetic DMARDs
CSF	Cerebrospinal fluid

CTLA4	Cytotoxic T-lymphocyte-associated protein 4
CTX	Chemotherapy
DC	Dendritic cells
DISC	Defective infectious single cycle virus
DMARDs	Disease modifying anti-rheumatic drugs
DTP	Diphtheria-tetanus-pertussis vaccine
DTPa-IPV	Diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine
EBMT	European Society for Blood and Marrow Transplantation
ELISA	Enzyme-linked immunosorbent assay
EPO	Erythropoietin
EULAR	European League Against Rheumatism
FMF	Familial Mediterranean fever
GCs	Glucocorticoids
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GvHD	Graft-versus host disease
HAV	Hepatitis A vaccine
HBV	Hepatitis B vaccine
HCQ	Hydroxychloroquine
Hib	*Haemophilus influenzae* type
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
HSCT	Haematopoietic stem cell transplantation
IBD	Inflammatory bowel disease
IDSA	Infectious Diseases Society of America
Ig	Immunoglobulin
IIV	Inactivated influenza vaccine
IL	Interleukin
INF	Interferon
IPTA	International Paediatric Transplant Association
IPV	Inactivated poliovirus vaccine
IRAK4	Interleukin-1 receptor-associated kinase-4
IVIg	Intravenous immunoglobulin
JAK	Janus kinase

JAK-STAT	Janus kinase-signal transducer and activator of transcription proteins
JDM	Juvenile dermatomyositis
JIA	Juvenile idiopathic arthritis
LAIV	Live-attenuated influenza vaccine
LPAM-1	Lymphocyte Peyer patch adhesion molecule 1
mAB	Monoclonal antibody
MBP	Mannose-binding protein
MCV4	Meningococcal 4-valent conjugate vaccine
MEN B	Meningococcus type B vaccine
MenACWY	Quadrivalent polysaccharide conjugate meningococcal vaccine
MHC	Major histocompatibility complex
MKD	Mevalonate kinase deficiency
MMF	Mycophenolate mofetil
MMPI	Matrix metalloproteinase-1
MMR	Measles-mumps-rubella vaccine
MMRV	Measles-mumps-rubella-varicella vaccine
MTX	Methotrexate
NFAT	Nuclear factor activated T cells
NF-kB	Nuclear factor kappa-B
NK	Natural killer
NOD	Nucleotide-binding oligomerization domain
NSAIDs	Non-steroidal anti-inflammatory drugs
OPA	Opsonophagocytic assay
OPV	Oral polio vaccine
PAMP	Pathogen-associated molecular patterns
PCV13	Pneumococcal 13-valent conjugate vaccine
PCV7	Pneumococcal 7-valent conjugate vaccine
PDE4	Phosphodiesterase-4
PENTA	Paediatric European Network for Treatment of AIDS
PGL/s	Prostaglandins
PPV23	23-valent polysaccharide pneumococcal vaccine

PRES	Paediatric Rheumatology European Society
PRR	Pattern recognition receptors
RAS-MAP	RAS-mitogen-activated protein kinase
RSV	Respiratory syncytial virus
rVSV-ZEBOV	Recombinant vesicular stomatitis virus-Zaire Ebola virus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCD	Sickle cell disease
SLE	Systemic lupus erythematosus
SOT	Solid organ transplant
TAC	Tacrolimus
TCR	T cell receptor
TLR	Toll-like receptor
TNF	Tumour necrosis factor
tsDMARDs	Targeted synthetic DMARDs
VPD	Vaccine-preventable disease
VZV	Varicella zoster virus
WFH	World Federation of Hemophilia

Chapter 1
Importance of Vaccinating Immunocompromised Children

1.1 Overview of the Immune System

The immune system protects the body against "non-self" intruders and prevents infections by microorganisms such as viruses, bacteria, fungi or parasites [1]. Schematically, three levels of defence can be identified: (1) anatomical and physiological barriers; (2) innate immunity; and (3) adaptive immunity [2].

Anatomical and physiological barriers are the primary line of defence to prevent pathogens from entering the host. They consist of intact skin and mucous membranes that maintain a physical barrier, vigorous mucociliary clearance mechanisms, the presence of low pH in the stomach or bacteriolytic lysozyme in tears, saliva and other secretions [1]. The immune response then kicks in with the collaborative efforts of the innate and adaptive immunity pathways.

The **innate immune response** is the oldest component from an evolutionary standpoint and is also found in all animals and plants in a certain form. It is the first line of attack against an invading pathogen and is immediately available. However, the response is not specific to individual microorganisms. Most of the effectors of the innate immune system are derived from myeloid progenitor cells. The main cellular

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mediators are phagocytic cells (monocytes, macrophages and neutrophils), mastocytes and natural killer cells [1]. The innate immune system also includes components of non-hematopoietic origin, such as the complement system, lipopolysaccharide binding proteins, acute-phase reactants (C-reactive protein), antimicrobial peptides (defensins) and mannose-binding lectins [3]. Cells are activated via pattern recognition receptors (PRR) that sense invading pathogens by the recognition of pathogen-associated molecular patterns (PAMP) shared by a large number of pathogens, which are not present in the host. For example, the PRR named "Toll-like" receptors (TLR) recognize PAMP characteristics of bacteria, fungi or viruses (Fig. 1.1; Table 1.1). Mannose receptors and ficolins are also PRR, which recognize carbohydrates present on bacterial cell walls, such as mannose, fucose or N-acetyl-D-glucosamine. Mannose-binding lectin is an example of a soluble receptor that recruits complement upon binding to the bacterial cell wall. Nucleotide-binding oligo-

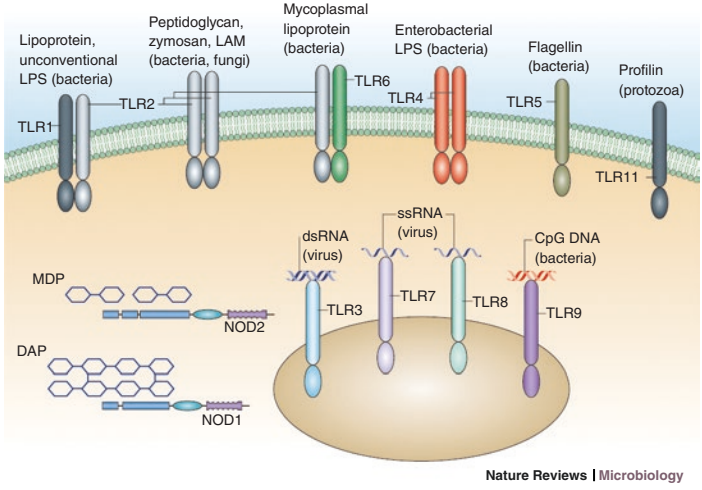

FIGURE 1.1 Pattern-recognition receptors: Toll-like receptors and nucleotide-binding oligomerization domain. Reproduced from [4]

Table 1.1 Innate immune recognition by Toll-like receptors.

Toll-like receptor	Cellular distribution	PAMP	Pathogen
TLR-1, TLR-2, TLR-6	Monocytes, dendritic cells, mast cells, eosinophils, basophils	Peptidoglycan, lipoprotein	Bacteria, mycobacteria, fungi
TLR-3	NK cells	Double-stranded RNA	Virus
TLR-4	Macrophages, dendritic cells, mast cells, eosinophils	Lipopolysaccharide, lipoteichoic acids, mannans	Bacteria, fungi
TLR-5	Intestinal epithelium	Flagellin	Bacteria
TLR-7	Plasmocytoid dendritic cells, NK cells, eosinophils, B cells	Single-stranded RNA	Virus
TLR-8	NK cells	Single-stranded RNA	Virus
TLR-9	Plasmocytoid dendritic cells, eosinophils, B cells, basophils	DNA with unmethylated CpG	Bacteria, herpesvirus
TLR-10	Plasmocytoid dendritic cells, eosinophils, B cells, basophils	Unknown	Unknown

Adapted from [5]
DNA deoxyribonucleic acid, *NK* natural killer, *RNA* ribonucleic acid, *TLR* Toll-like receptor

merization domain (NOD) are intracellular PRR that recognize bacterial peptidoglycan components. As all PRR are expressed broadly on a large number of cells, the system is

able to act promptly after an encounter with the pathogen to elicit a rapid response [6].

The **adaptive immune response** develops throughout life and is mediated by the B and T lymphocytes, which arise from lymphoid progenitor cells (Fig. 1.2). The lymphocytes are mobilized by cues from the innate response, recognize the pathogen via antigen-specific receptors expressed on their surfaces (B- or T-cell receptors, respectively), and eliminate the pathogen by producing specific antibodies (B cells) and/or through various cell activation (T cells). Antibodies produced by **B cells** are effective in binding to the enzymatic active sites of toxins, clearing extracellular pathogens via receptor blockade, promotion of opsonophagocytosis, and complement activation. **T cells** recognize host cells that are infected by viruses, intracellular bacteria or other intracellular parasites. $CD8^+$ T cells kill the infected cells directly (release of perforin, granzyme) or indirectly (cytokine release). $CD4^+$ T cells act indirectly through the secretion of cytokines that support activation and differentiation of the other immune mediators (such as B cells, $CD8^+$ T cells or macrophages) [8]. The immune response elicited by the lymphocytes is more specific to a given pathogen and therefore eliminates it more efficiently than the innate mediators. However, the response takes time to develop and requires a prior exposure to the pathogen. Indeed, there is only a small number of cells specific to a given pathogen. After encountering the antigen derived from the pathogen, these so-called 'antigen-specific' cells need to multiply during a process known as clonal expansion in order to mount an effective response. For these reasons, an effective adaptive response generally occurs after the innate response.

After a first encounter with a pathogen, the adaptive response usually produces memory cells, which are long-lived cells that persist in an apparently dormant state, but can re-express effector functions faster after a subsequent encounter with their specific antigen. The adaptive pathway is therefore responsible for the long-lasting immunity that can follow exposure to disease or vaccination: this is called 'immunological

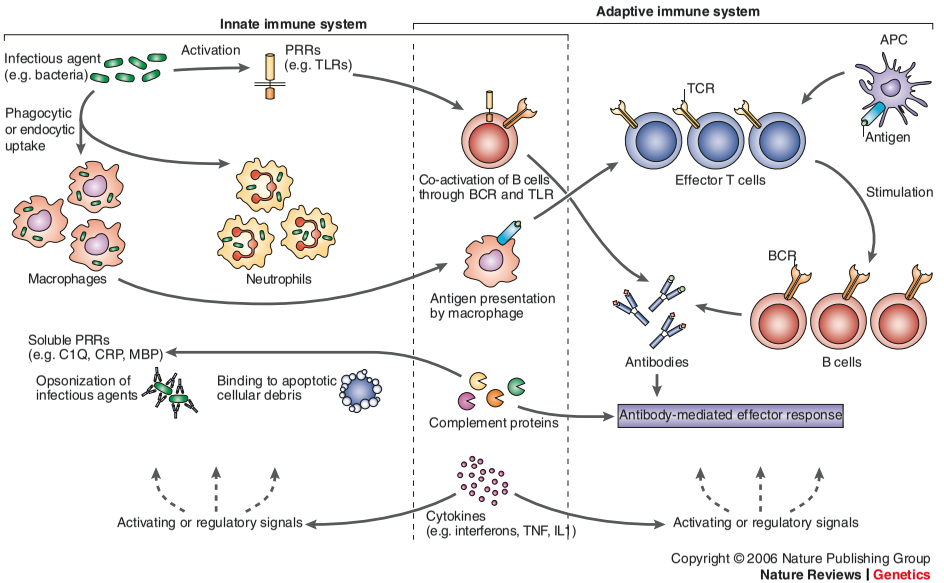

FIGURE 1.2 Presentation of the innate and adaptive immune systems. Reproduced from [7]. *APC* antigen-presenting cell, *BCR* B-cell receptor, *C1Q* complement protein 1Q, *CRP* C-reactive protein, *IL1* interleukin 1, *MBP* mannose-binding protein, *PAMP* pathogen-associated molecular patterns, *PRR* pattern-recognition receptors, *TCR* T-cell receptors, *TLR* Toll-like receptors, *TNF* tumour necrosis factor

memory'. This process contributes to a more effective response against specific pathogens when they are encountered again, even decades after the initial sensitizing encounter.

Immunological memory can be illustrated by the measurement of the antibody response following the first and subsequent encounter to a given antigen (Fig. 1.3). The first encounter with an antigen produces a **primary response**: after a lag phase, specific antibody directed against the antigen appears; its concentration rises to a plateau—usually 4 weeks after exposure—and then declines. Following a second encounter, a very rapid **secondary response** occurs and produces higher concentrations of the specific antibody, thus providing a specific and faster defence against the pathogen [1].

The activity of the immune system is regulated by different mediators, both from the innate and the adaptive system, to prevent **abnormal immune responses,** including inappropriate responses that lead to tissue damage, such as hypersensitivity and allergy or reactivity against self-antigens (called

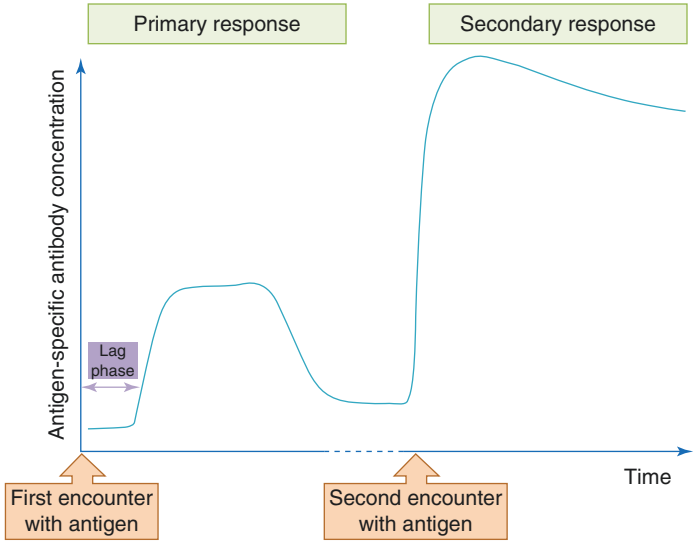

FIGURE 1.3 Primary and secondary immune responses to a given antigen. Adapted from [1]

"autoimmunity"). By contrast, immunodeficiency is defined by the alteration of the normal defence mechanisms, leading to an impaired response to pathogens.

The immune response is also affected by **age**. Indeed, the infant's immune system is "immature" at birth, resulting in a higher risk of infection and poorer vaccine responses [9]. Neonates have limited B-cell responsiveness, inducing a poor ability to respond to T-independent polysaccharide antigens, such as polysaccharidal vaccines, as well as lower and less persistent antibody responses to T-dependent protein antigens [10]. At the other extreme, it has been shown that both the innate and adaptive immune responses are progressively affected by age, a process known as immunosenescence. As a result, elderly people present an increased susceptibility to infection, decreased response to vaccination, poorer responses to known and new antigens, and an impaired immune surveillance function, leading to a higher risk of cancer [11].

1.2 Definitions of Immunodeficiency and Immunosuppressive Regimens

A variety of medical conditions and drugs can affect the immune system. Immunodeficiency can be primary or acquired, secondary to a disease or medication [12]. The most common conditions are discussed below and summarized in Table 1.2.

Primary immunodeficiency disorders result from the alteration of any mediator of the innate or adaptive immune system. They constitute a heterogeneous group of nearly 200 different genetic diseases leading to various degrees of severity of presentation with recurrent infections, autoimmunity and malignancies [2, 14]. Of note, they are rare diseases with an overall prevalence of approximately 1:10,000 live births [15]. The International Union of Immunological Societies Expert Committee for Primary Immunodeficiency classifies them as: combined immunodeficiencies (e.g. severe combined immunodeficiency), well-defined syndromes with immunode-

Table 1.2 Medical conditions associated with a compromised immune system and the most frequent treatment options

Medical condition	How is the immune system affected	Frequently-used drugs
Primary immunodeficiency		
Primary immunodeficiency disorders	Genetic abnormality affecting various pathways of the immune response	GCs, csDMARDs, IVIg
Acquired immunodeficiency		
Underlying state		
Prematurity	Immune cell immaturity Low IgG level (not had time to transfer from the mother)	–
Malnutrition Anorexia nervosa	Immune response impaired due to malnutrition	–
Obesity	Immune response slightly impaired due to overweight (and insulin resistance), higher risk of respiratory infection	–
Underlying infection		
Human immunodeficiency virus infection	Lower $CD4^+$ T-cell	–
Underlying disease		
Diabetes mellitus	Impaired phagocytic and neutrophil function, worsens with inadequate glycaemic control	–

Table 1.2 (continued)

Medical condition	How is the immune system affected	Frequently-used drugs
Asplenia/ hyposplenia Sickle cell disease	Higher risk of fulminant infection with encapsulated bacteria and parasites (highest risk in the first 2 years of asplenia, but persists lifelong)	–
Haemophilia	Historical increased risk of transfusion-related transmission of viral infection	
Coeliac disease	Functional hyposplenism (reversible), impaired immune response	
Renal failure, chronic kidney disease (including dialysis)	Mild defects in T cell function, immune response impaired by malnutrition, increased intracellular calcium, iron overload, and uremic toxins; Ig loss in dialysate	–

(continued)

Table 1.2 (continued)

Medical condition	How is the immune system affected	Frequently-used drugs
Chronic liver disease	Impaired phagocyte function and defects in opsonizing antibody, Ig loss in ascites, hyposplenism (with severe liver disease), higher risk of severe superimposed viral hepatitis	–
Chronic heart disease or malformation	Infections may precipitate cardiac decompensation	–
Chronic lung disease Asthma Cystic fibrosis Bronchopulmonary dysplasia	Increased risk of severe respiratory infections. Severe lung diseases leading to poor mucociliary clearance, bronchiectasis, defects in pulmonary macrophage function, and immunosuppressive treatment in severe asthma	GCs, bDMARDs (anti-IgE)

Table 1.2 (continued)

Medical condition	How is the immune system affected	Frequently-used drugs
Chronic neurological disease and neurodevelopmental disorder	Decreased protection of airways increases the risk of infection and higher risk of complications for some vaccine-preventable diseases (e.g. influenza, pneumococcus, varicella, pertussis)	
CNS anatomic barrier defect (e.g. CSF leak, inner ear dysplasia, or cochlear implant)	Deficient anatomical barrier leads to a higher risk of CNS infection	
Inborn errors of metabolism	Neurological defect, concomitant immunodeficiency, metabolic decompensation	
Transplant recipients		
Hematopoietic stem-cell transplantation	Impaired and immature immune cells, loss of Ig	Conditioning treatment
Solid organ transplantation	Immunosuppressive treatment to prevent graft rejection	csDMARDs

(continued)

Table 1.2 (continued)

Medical condition	How is the immune system affected	Frequently-used drugs
Dysimmune disorders		
Inflammatory bowel diseases	Underlying defect in immune system, immunosuppressive treatment to control disease activity	5-Aminosalicylic acid (5-ASA), GCs, csDMARDs (AZT, 6-MP, MTX, cyclosporin), bDMARDs (anti-TNFα, anti-integrins)
Non-systemic juvenile idiopathic arthritis	Underlying defect in immune system, immunosuppressive treatment to control disease activity	csDMARDs, bDMARDs (anti-TNFα)
Systemic juvenile idiopathic arthritis	Underlying defect in immune system, immunosuppressive treatment to control disease activity	GCs, bDMARDs (anti-IL-1, anti-IL-6)
Vasculitis	Underlying defect in immune system, immunosuppressive treatment to control disease activity	GCs, csDMARDs, bDMARDs (anti-TNFα)
Kawasaki disease	Underlying defect in immune system, immunosuppressive treatment to control disease activity	GCs, IVIg, bDMARDs (anti-TNFα, anti-IL-1)
Juvenile dermatomyositis	Underlying defect in immune system, immunosuppressive treatment to control disease activity	GCs, csDMARDs, bDMARDs (anti-TNFα)

Table 1.2 (continued)

Medical condition	How is the immune system affected	Frequently-used drugs
Systemic lupus erythematosus and other connective tissue diseases	Underlying defect in immune system, immunosuppressive treatment to control disease activity	GCs, csDMARDs, bDMARDs (anti-TNFα)
Nephrotic syndrome	Urinary loss of IgG, oedema, immunosuppressive treatment	GCs, csDMARDs, bDMARDs (anti-CD20)
Hemolytic uremic syndrome	Requires medication inhibiting the deployment of the terminal complement system, high risk of meningococcal disease	bDMARDs (C5)
Auto-inflammatory syndrome (TNF receptor-associated periodic syndrome), familial Mediterranean fever	Underlying defect in immune system, immunosuppressive treatment	Colchicine, csDMARDs, bDMARDs (anti-IL-1, anti-IL-6)
Interferonopathy	Underlying defect in immune system, immunosuppressive treatment	GCs, csDMARDs, bDMARDs, tsDMARDs (JAK inhibitors)
Multiple sclerosis and other autoimmune diseases of the brain (neurosarcoidose, cerebral vasculitis)	Decreased protection of airways increases risk of infection, immunosuppressive treatment	GCs, IVIg, csDMARDs (AZT, MTX, MMF, cyclophosphamide), bDMARDs (anti-CD20, anti-TNF)

(continued)

Table 1.2 (continued)

Medical condition	How is the immune system affected	Frequently-used drugs
Dermatological diseases (psoriasis, severe atopic dermatitis, cutaneous erythematosus lupus, alopecia areata)	Underlying defect in immune system, deficient skin barrier, immunosuppressive treatment. Chickenpox particularly prone to bacterial superinfection; severe dermatologic diseases possibly require immunosuppressive treatment	Topical and systemic GCs, topical anti-calcineurin, csDMARDs (cyclosporin, MTX, bDMARDs (anti-IL-17), tsDMARDs (JAK inhibitors, phosphodiesterase inhibitors)
Undesirable side-effect/s of treatment		
Oncological diseases	Most cancers and their treatment affect the immune system	Chemotherapy
Non-chemotherapy idiosyncratic drug-induced neutropenia	Underlying disease requires a treatment that can induce severe neutropenia	Most frequently due to metamizole, clozapine, sulfasalazine, thiamazole, carbimazole, amoxicillin, cotrimoxazole, ticlopidine and valganciclovir.

Adapted from [13]
6-MP 6-mercaptopurine, *anti-TNF* anti-tumor necrosis factor, *AZT* azathioprine, *CNS* central nervous system, *CSF* cerebrospinal fluid, *GCs* glucocorticoids, *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs), *bDMARDs* biological DMARDs, *tsDMARDs* targeted synthetic DMARDs, *IVIg* intravenous immunoglobulin, *JAK* Janus kinase, *MMF* mycophenolate mofetil, *MTX* methotrexate

ficiency (e.g. Wiskott–Aldrich syndrome, ataxia-telangiectasia disease, DiGeorge syndrome); predominantly antibody deficiencies (e.g. combined variable immunodeficiency disease); diseases of immune dysregulation (e.g. Chediak-Higashi syndrome, familial hemophagocytic lymphohistiocytosis syndromes, lymphoproliferative syndromes or syndromes with auto-immunity); congenital defects of phagocytes (e.g. X-linked chronic granulomatous disease); defects in innate immunity; autoinflammatory disorders; and complement deficiencies [14]. Most of these patients present with infections and primary immune deficiency should be suspected in the case of recurring or chronic infections, especially when caused by unusual or opportunistic organisms, or in the case of recurrent infections due to the same pathogen when disease responds poorly to standard antimicrobial treatment or results in unexpected organ damage (e.g. bronchiectasis). In such patients, infections can usually be prevented by vaccination, regular administration of immunoglobulins, or by prophylactic or pre-emptive antimicrobial therapy, and, sometimes, through hematopoietic stem cell transplantation, or gene therapy [16]. Primary immunodeficiency disorders are beyond the scope of the content presented and not the main focus of this book.

Acquired immunodeficiency can be secondary to different factors. These factors can be an infectious agent (e.g. infection with human immunodeficiency virus (HIV) which causes lifelong immunosuppression, or following infections with measles virus that cause prolonged post-infection immunosuppression), an underlying state (e.g. malnutrition, obesity, young age, prematurity), an underlying disease (e.g. dysimmune disorders, hyposplenia, diabetes mellitus, chronic organ failure), or medications [12]. Medications can affect the immune system either as an undesirable side effect (e.g. chemotherapy, drug-induced neutropenia) or intentionally in conditions in which the immune response has to be restrained (e.g. management of dysimmune disorders, allergic disorders, solid organ transplant (SOT), or induced graft-versus-host disease).

Chemotherapies used in cancer typically cause immunosuppression. The goal of chemotherapy is to eliminate the cancer cells, which are characterized by an uncontrollable multiplication, while sparing normal cells. Treatment targets cells that grow and divide quickly by inhibiting mitosis or cell division. Unfortunately, the host cells involved in immunity also have a high multiplication rate. Therefore, the immune system is frequently adversely affected by chemotherapy.

Dysimmune disorders include children with systemic autoimmune diseases and those with immunological diseases specific to a single organ, such as the digestive tract, eyes, skin or the central nervous system. In these children, the immune system is dysregulated with an uncontrolled, overwhelming or unnecessary immune response, where sometime the self is perceived as non-self, and the immune system attacks itself. These children are treated with immunosuppressive therapy to control the disease and limit self-destruction, which includes traditional immunomodulatory drugs, such as glucocorticoids (GCs), disease-modifying antirheumatic drugs (DMARDs) and biologics. Currently, DMARDs are classified as conventional synthetic (csDMARDs), biological (bDMARDs) and targeted synthetic (tsDMARDs) DMARDs (Table 1.3) [17].

The immune system of **SOT recipients** needs to be permanently suppressed to prevent the rejection of the non-self-transplanted organ as the proteins of the donor constituting the transplanted organ are perceived as an intruder by the recipient's immune system. Unfortunately, there is currently no method or medication available that could selectively suppress the host's immune response to the graft antigens and maintain other immune responses at the same time. The number of transplant recipients increases daily. According to the most recent data of the Global Database on Donation and Transplantation that registers worldwide activity in organ transplantation [18], there were approximately 146,840 SOTs in 2018, representing more than 400 transplantations per day [19]. Kidney (95,479 transplants [65%]) and liver (34,074 transplants [23%]) were the most frequently transplanted organs, followed by heart (8311 [6%]), lung (6475 [4%]), pancreas (2338 [2%]) and small bowel (163 [0.1%]) [19]. Immunosuppressive regimens differ

Table 1.3 List of immunosuppressive agents

Type of immunosuppressive agents	Class	Targets	Molecule
GCs		Various	Prednisolone, prednisone, methyl prednisolone, dexamethasone
csDMARDs	Inhibitors of DNA synthesis	Pyrimidine synthesis	MTX, leflunomide
		Purine synthesis	AZT, 6-MP, MMF
		DNA by alkylation	Cyclophosphamide
	Intracellular signal transduction	Calcineurin	Cvclosporin Tacrolimus
		mTOR	Sirolimus, everolimus
	Phenolic glycolipids		5-ASA derivatives: sulfasalazine, mesalazine
	Diverse		Hydroxychloroquine, colchicine, thalidomide
bDMARDs		TNFα	Adalimumab, golimumab, certolizumab, infliximab, etanercept
		IL-1	Canakinumab, anakinra, rilonacept
		IL-6	Tocilizumab
		Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)	Abatacept
		CD20	Rituximab, ocrelizumab
		Blys	Belimumab
		Integrin $\alpha_4\beta_7$	Vedolizumab
		IL-17A	Sekukinumab, ixekizumab
		IL-12 and IL-23	Usterkinumab
		CD52	Alemtuzumab
		C5	Eculizumab
tsDMARDs		JAK	Tofacitinib, baricitinib, ruxolitinib
		Phosphodiesterase 4	Apremilast

6-MP 6-mercaptopurine, *AZT* azathioprine, *GCs* glucocorticoids, *csDMARDs* conventional synthetic disease modifying anti-rheumatic drugs (DMARDs), *bDMARDs* biological DMARDs, *tsDMARDs* targeted synthetic DMARDs, *IL* interleukin, *MMF* mycophenolate mofetil, *MTX* methotrexate

according to the type of transplanted organ and given that not all organs are equally immunogenic, immune tolerance differs between them [20]. Schematically, the level of immune suppression required to prevent organ rejection ranked in ascending order is the following: renal <liver <intestine <heart <lung transplant, with the latter requiring the most immunosuppressive treatment regimen.

Hematopoietic stem cell transplantation has become the treatment of choice in many haematological conditions or oncological diseases, particularly haematological malignancies and primary immunodeficiency diseases. Sources of hematopoietic stem cells include donor bone marrow, stimulated peripheral blood or umbilical cord blood. Transplantation is preceded by a myeloablative preparation (conditioning treatment), aiming to eradicate cancer and help further engraftment. It usually consists in a combination of total body irradiation and immunosuppressive chemotherapy. Immunosuppressive medications are continued after transplantation to help engraftment (by preventing graft rejection by the recipient's cells) and to prevent graft-versus-host-disease (GvHD (by preventing that donor's cells attack the recipient) [21]. Immunosuppressive treatment can be withheld after successful engraftment if there is no GvHD. By contrast, lifelong immunosuppressive treatment is usually indicated for solid organ recipients. However, a certain state of immunosuppression persists after transplantation, despite successful homing and engraftment of stem cells into host hematopoietic tissues, because donor-derived immune reconstitution in the transplant recipient may not readily achieve functional maturation until months to years, if at all, after transplantation [22].

1.3 Risk of Infections

Immunocompromised children are at an increased risk of infection due to higher exposure through their frequent visits to hospitals and outpatient clinics with the presence of other sick children. They are particularly prone to severe infections

leading to complications or death, as well as chronic infections (e.g. chronic hepatitis E or persistent parvovirus B19 infection). The type of infection to which these conditions predispose depends on the part of the immune system affected and are summarised in Table 1.4. In addition, there is

Table 1.4 Category of immune deficiencies and their clinical presentation

Category	Examples of diseases	Clinical presentation
Lymphocyte B defect	Ig deficiency: Bruton's agammaglobulinemia, hyper-IgM syndrome, selective Ig deficiency, common variable immunodeficiency	**Recurrent bacterial infections**; sinopulmonary and respiratory tract infections, pyogenic organisms, non-enveloped virus, rotavirus, parvovirus B19
Lymphocyte T defect	Thymic aplasia (DiGeorge syndrome), IL12-receptor deficiency, hyper-IgE syndrome (Job's syndrome), chronic mucocutaneous candidiasis, Wiskott-Aldrich syndrome, ataxia telangiectasia	**Opportunistic infections**; *Candida* spp, *Pneumocystis jirovecii*, *Mycobacterium avium*-intracellular complex, herpesviruses
Phagocyte deficiency or dysfunction	Leukocyte adhesion deficiency, Chédiak-Higashi syndrome, chronic granulomatous disease, cyclic neutropenia, myeloperoxidase deficiency	**Bacterial and fungal infections;** *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Serratia* and *Nocardia* species, streptococci, other enteric organisms, *Candida*, *Burkholderia*, *Aspergillus*, *Chromobacterium* species.

(continued)

Table 1.4 (continued)

Category	Examples of diseases	Clinical presentation
Complement deficiency	Deficiencies of the complement classical, alternative or terminal pathway, deficiencies in complement regulatory protein, medication inhibiting the formation of the terminal complement system (eculizumab)	**Recurrent sinopulmonary infections, invasive infections due to encapsulated bacteria** (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*)
Hyposplenia or asplenia	Anatomical or functional, secondary to hematologic, auto-immune or infiltrative disease	**Infection with encapsulated bacteria**, particularly *Streptococcus pneumoniae*

Adapted from [2, 14, 15]
Ig immunoglobulin, *IL* interleukin

the probability that they may be insufficiently vaccinated. Thus, the severity and complications of these infections related to the underlying disease and/or treatment will have a higher impact on the host response to infection. However, the literature does not differentiate between the risk of getting an infection from the occurrence of associated complications.

In a retrospective cohort study of 6980 paediatric solid organ recipients, 1092 (16%) were hospitalised for a vaccine-preventable disease in the first 5 years following transplantation; an 87-fold higher rate compared with the general population. The case fatality rate was approximately 2% and 17% were admitted to critical care [23].

Another study assessing the risk of infection every 2 months for 1 year in children with juvenile idiopathic arthritis (JIA) treated with bDMARDs reported that 57% (n = 175)

of patients developed an infection. Upper respiratory tract infections were among the most frequent infections and mostly treated in ambulatory care. Only three serious infections (two pneumonia, one pleural effusion) were documented. The authors also found that the infection rate was highest in systemic JIA and lowest in enthesitis-related arthritis. Of note, it was higher in children treated with infliximab compared to those treated with etanercept [24].

A systematic literature review on the risk of infection in children with JIA and inflammatory bowel disease (IBD) treated with anti-TNF-α reported that patients presented mostly mild viral infections and, less frequently, severe bacterial and fungal infections associated with intrinsic risk factors and concurrent immunosuppressive therapy [25]. Another systematic literature review comparing the rates of serious infections in children with JIA treated with bDMARDs with controls reported no difference in the risk of serious infection between the two groups (pooled relative risk, 1.13; 95% confidence interval [CI] 0.63–2.03). Several studies have reported similar rates of serious infection in children with JIA receiving bDMARDs or csDMARDs [24, 26]. However, other studies have reported that the highest rates of infection were in children treated with bDMARDs, especially anti-TNFα (such as etanercept and infliximab) [24, 25, 27, 28], or a combined treatment of csDMARDs (such as methotrexate [MTX]) and bDMARDs [29]. Upper respiratory tract infections (including severe influenza) were among the most frequent infections, together with complicated varicella [24, 25, 27–31].

As most patients receive a combined treatment rather than a single molecule, it is particularly challenging to design a clinical study to assess the effect of various immunosuppressive regimen on the risk of infection and to also understand the biology behind the infectious risk.

1.4 Burden of Vaccine-Preventable Diseases in Immunocompromised Children

1.4.1 Viral Diseases

As reported in studies looking at national viral surveillance data in the USA and in England, children with chronic medical conditions are known to be more affected by influenza virus infection [32, 33]. Indeed, influenza is probably the most common vaccine-preventable disease leading to hospitalisation, accounting for 3% of all critical care admissions in the USA during the influenza season [34]. In a retrospective cohort study in paediatric SOT recipients, 40% of hospitalisations for a vaccine-preventable disease were due to influenza infection [23].

In the case of varicella, natural exposure is almost inevitable in countries without a routine immunization policy. Varicella infection carries a higher risk of complications in immunocompromised individuals [35] and studies in HIV-positive children have shown how severe varicella infections can present in this vulnerable population. Indeed, one study reported a hospitalisation rate 150 times higher in HIV-positive children not treated compared to healthy children [36]. Another study reported that children on anti-TNFα had a hospitalisation rate due to shingles and varicella of 32 and 26 cases per 100,000 patients compared to 3.4 and 1.9 cases, respectively, in healthy children [37]. A Swiss study reported that 18% of children with rheumatic disease treated with csDMARDs and/or bDMARDs developed complications with varicella compared to an incidence rate of 0.85 per 100,000 in healthy children [38]. Similar findings were reported in individuals with IBD [39]. Furthermore, most immunocompromised children who are seronegative to varicella are often recommended to receive immunoglobulin and acyclovir prophylaxis after natural exposure to varicella [40], which also complicates their quality of life and has a certain economic cost.

Concerning human papilloma virus (HPV), against which vaccination is widely recommended during adolescence, studies in immunocompromised individuals have shown that the risk of HPV infection and related malignancy is increased up to 100-fold [41] compared to healthy controls, especially among those with systemic lupus erythematosus (SLE), with an increased incidence of high-risk and multiple infections, including cervical dysplasia [42]. There is also an increased risk of HPV-associated neoplasia under immunosuppression [43]. For example, patients with SLE have persistent infections and cervical intraepithelial neoplasia lesions [44].

1.4.2 Bacterial Diseases

Concerning *Neisseria meningitidis* infections [45], children with a complement deficiency have a 5000- to 10,000-fold increased risk of meningococcal disease compared to healthy children, with 40–50% experiencing recurrent meningococcal diseases [46]. Children with acquired complement deficiency are also more at risk of meningococcal infections, such as those treated with a terminal complement pathway inhibitor (eculizumab) used to treat certain autoimmune diseases [47]. Patients receiving an immunosuppressive treatment are also at risk of hyposplenism and therefore more at risk of infections by encapsulated bacteria such as *N. meningitidis*, *Streptococcus pneumoniae* and *Hemophilus influenzae* type b (Hib). Children with chronic medical conditions are also at risk of invasive pneumococcal diseases, which carry a high mortality rate (11–30%) [48]. Ladhani et al. reported that around 30% of English children who developed an invasive pneumococcal disease during 2009–2011 had a comorbidity, with approximately one-third having an immunodeficiency [49, 50]. For example, invasive pneumococcal diseases have been frequently reported in individuals with IBD [51], nephrotic syndrome [52], or an hyposplenic condition [53, 54].

1.4.3 Vaccine-Preventable Diseases

Infectious diseases for which a vaccine is available for children include influenza virus, *S. pneumoniae*, *H. influenzae*, meningococcus, polioviruses, varicella zoster virus (VZV), measles, mumps, rubeola, HPV, hepatitis A (HAV) and B virus (HBV), tick-borne encephalitis, etc. Each vaccine has a specific indication, including the age group, and may vary between countries for healthy children.

1.5 Challenges in the Vaccination of Immunocompromised Children

One of the major achievements in medicine is the development of vaccines, which allow to protect against many potentially fatal infectious diseases, thus decreasing mortality worldwide. However, recent outbreaks of vaccine-preventable diseases, such as measles, show that reaching a sufficient vaccine coverage of the international population remains a challenge [55, 56].

Completion of vaccination series are even more important in immunocompromised children. First, they are more susceptible to infections due to the underlying conditions that affect their immune system and influence their natural defence mechanisms against various infectious agents. Furthermore, in children with dysimmune disorders, they often require a rapid start of immunosuppressive treatment after diagnosis, usually lasting for many months or even years until it can be reduced or interrupted, which renders vaccination even more challenging in this population. Similarly, in children with chronic organ failure, there is sometimes only a limited window of opportunity before transplantation. Indeed, it is expected that most chronic diseases or immunosuppressive drugs will affect the immune capacity of the child to a different degree, depending on the disorder and the agent, thereby reducing their capacity to respond to many vaccines. In addition, only non-live vaccines are recom-

mended during immunosuppressive treatment and the use of live attenuated vaccines should be carefully assessed on a case-by-case basis.

In the specific population of children with dysimmune disorders treated with various immunosuppressive agents, the indication for each vaccine can be even more complicated and it becomes very challenging for the specialists who care for these children to decide upon the best vaccination scheme. Moreover, several concerns, misconceptions and unanswered questions have led to decreased vaccination rates in children with chronic inflammatory and autoimmune diseases [57, 58], who are often less adequately vaccinated than healthy children [59–61]. For example, in Ljublijana, Slovenia, only 65% of 18-year-old young adults with rheumatic diseases were up to date with their vaccines, with the most frequently omitted being HBV and a second dose of measles-mumps-rubella (MMR) [62]. In addition, only 10% had received the seasonal influenza vaccine and 4% the pneumococcal 13-valent conjugate vaccine (PCV13) [62]. Similarly, 40% of children with JIA in Canada had an incomplete vaccination record for their age [58]. Likewise, in adults with autoimmune inflammatory rheumatic disease (AIIRD), it has been reported that over one-half of patients had never received a pneumococcal or influenza vaccination and less than one-third were appropriately vaccinated [63]. A retrospective review of the medical charts of adults in the USA with IBD revealed that vaccination was the least frequently followed quality of care recommendation [64]. In Italy, vaccination rates in children with HIV, cystic fibrosis, liver transplantation or diabetes were low against pneumococcus (<25%) and highly variable for influenza (21–90%) [61].

The reasons described for these decreased rates were that medical specialists caring for immunocompromised patients did not feel responsible for monitoring their vaccination schedules [65]. Additionally, parents—and even specialists—remained uncertain about the safety of some vaccines in the context of children with autoimmune diseases and under immunosuppressive treatment [58]. Safety aspects in terms of

the potential interferences of vaccination on the underlying disease, as well as the question of whether vaccination under immunosuppressive treatment is sufficiently immunogenic/protective, are repeatedly subjects of discussion and debate [66–68]. In addition, current vaccine recommendations for paediatric populations with dysimmune disorders are often based on small sample sizes with low levels of evidence, especially for the use of live vaccines [66–68]. Other reasons for low vaccination rates include the severity of the underlying disease, an absence of specific recommendations or contraindications, clinicians and patients' lack of knowledge, concern about vaccine effectiveness, parent refusal, sporadic contact with primary care physicians, and confusion regarding the role of specialty care providers vs. primary care providers in a patient's overall care [61, 69, 70]. Moreover, as vaccination guidelines change frequently and differ for each different medical condition, it is really challenging for clinicians to stay up-to-date with the most recent, specific recommendations.

The main focus of this book is on children with transplantation, autoimmune and autoinflammatory disorders who are treated with various immunosuppressive molecules as they very often require a rapid start of a long-term immunosuppressive treatment. Current data on vaccination under frequently used immunomodulatory treatments will be discussed in detail, as well as current evidence regarding the immunogenicity and safety of commonly-used vaccines in children treated with different immunosuppressive regimens. Practical guidance is also proposed to help specialists to optimize vaccination strategies in this vulnerable population.

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Chapter 2
Immune Responses to Vaccination

2.1 Antigen-Induced Immune Responses

During natural infection, the primary and secondary immune responses develop, as observed with seroconversion from a primary IgM to a secondary IgG response, and even a switch in IgG from low avidity IgG to a dominance of high-avidity IgG. There is a variable response after vaccination, depending on the type of vaccine preparation used. Some vaccines, such as the live-attenuated, aim to replicate the natural infection in order to induce the primary and secondary responses. However, a single vaccine dose may not be sufficient for lifelong immunity (e.g. diphtheria, tetanus, etc.) and many vaccines require a primary series, or primary series and boosters to maintain the secondary responses.

During a first encounter with an antigen, only a small number of naïve B cells and T cells are able to recognize a given antigen. After a certain time, clones of T and B cells are selected and expand and give rise to a small pool of memory B and T cells, which is often too small and lasts for a too short period to offer protection against a given pathogen. Following subsequent encounters with the given antigen, memory B and T cells proliferate and expand. These cells respond more rapidly and more strongly following a smaller amount of antigen. This explains the principle of vaccines, which allows to

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produce a pool of memory B and T cells able to respond rapidly to a given antigen after infection, and also give rise to long-lived plasma cells that persist in the bone marrow [1]. The long-lived plasma cells and potentially the memory B cells contribute to the persistence of protective antibodies in the blood (Figs. 2.1 and 2.2).

In order to understand the effect of each immunosuppressive drug on the immune response to vaccination, it is important to understand what happens specifically at the cellular level. After a first encounter with the antigen, naïve CD4 T-cells in lymph nodes recognize a peptide antigen presented on the surface of dendritic cells (DCs) in the major histocompatibility complex (MHC) molecule via the binding of their T cell receptor (TCR) and co-stimulatory signals given by the CD80 and CD86 on the surface of DCs and CD28 on T cells. The extent and quality of antigen-presenting cell activations condition the T cell responses. This is often dependent on the inflammatory milieu (innate immune responses) created at

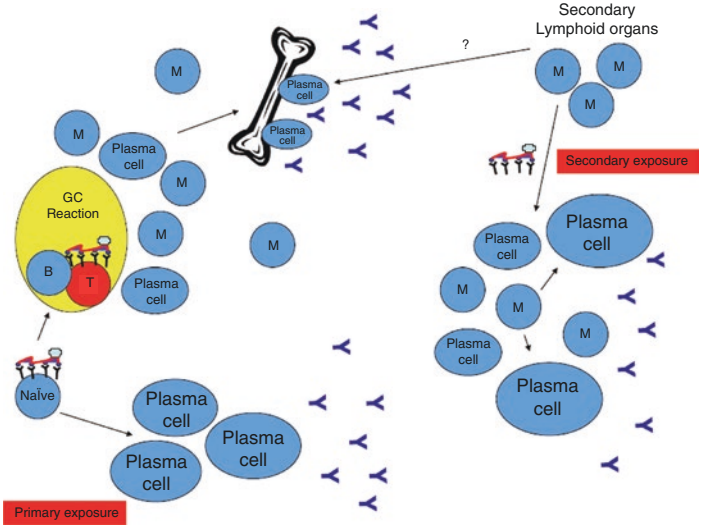

FIGURE 2.1 Activation of the B and T cells in a T-dependent immune response

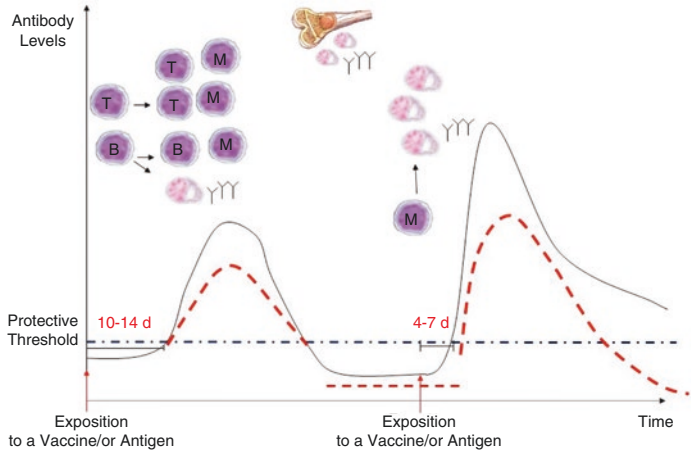

FIGURE 2.2 Kinetics of the antibody response in a primary and secondary immune response. Adapted from [2]

the time of vaccination and this could be impacted by the various immunosuppressive drugs. This activates three signal transduction pathways in T cells: (1) the calcium-calcineurin pathway; (2) the RAS-mitogen-activated protein-(MAP) kinase pathway; and (3) the nuclear factor-κB (NF-κB) pathway (Fig. 2.3). These three pathways activate the transcription of various factors that induce the expression of several molecules and, most importantly, IL-2, which binds to the CD25 receptor on the surface of activated T cells and induces its survival and proliferation. After 4–5 days of division, the activated T cells differentiate into helper and regulatory effector and memory T cells [3, 4].

Naïve B cells that have bound antigen to their surface Ig receptors require co-stimulatory signals from CD4 helper T cells that are specific for the same antigen. This allows them to initiate a germinal centre reaction in secondary lymph nodes, proliferate, and mutate their antibody genes through somatic hypermutation to achieve higher affinity and then differentiate into antibody-producing plasma cells and memory B cells. Note that the encapsulated bacteria, which are

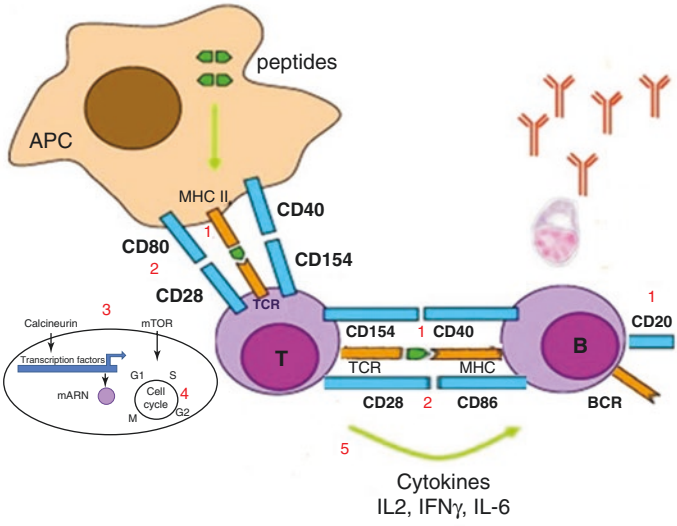

FIGURE 2.3 Steps of the activation and proliferation of T and B cells and possible targets of immunosuppressive drugs. Adapted from [2]

surrounded by a polysaccharide capsule, can induce mature B cells to proliferate without the help of T cells (T cell independent antigens), but without the production of memory B cells. This is also how polysaccharide-based vaccines work.

Cellular interactions leading to the activation of T and B cells during a primary and secondary exposure with a vaccine, with an extra-follicular reaction producing short-lived plasma cells and a germinal centre reaction with the production of memory B cells (M) and long-lived plasma cells that migrate in the bone marrow.

Following a first exposure with an antigen, there is an interval of 1 week before the production of low-affinity IgM, while IgG only appears after 10–14 days. By contrast, following a secondary exposure with the antigen, memory B and T cells are rapidly reactivated, with a more rapid and higher IgG increase that last longer [5, 6].

During an immune response, naïve T cells recognize a peptide antigen presented on the surface of antigen-presenting

cells (APCs) in the MHC molecule via the binding of their TCR and co-stimulatory signals given by the CD80 and CD86 on the surface of DCs and CD28 on T cells. This activates various signal transduction pathways in T cells, which activate the transcription of various factors that induce the expression of several molecules, such as IL-2. Naïve B cells that have bound antigen to their surface Ig receptors require co-stimulatory signals from T cells that are specific for the same antigen. This allows to initiate a germinal centre reaction with the proliferation and mutation of the antibody genes and then differentiate into antibody-producing plasma cells and memory B cells. Each of the steps of the immune response can be the target of an immunosuppressive drug: (1) depletion of the specific or cognate T and/or B cells (e.g. anti-CD20); (2) interference with the co-stimulatory signals (e.g. cytotoxic T-lymphocyte associated protein (CTLA4)-analog); (3) blockade of the intracellular signal (e.g. calcineurin inhibitor or mTOR inhibitor); (4) inhibition of DNA synthesis and cell proliferation (e.g. purine analog or alkylating agents); and (5) modulation of the effector T or B cell responses (various anti-cytokine monoclonal antibodies), including blocking inflammation-reducing antigen presentation (anti-IL6, TNF, JAK, etc.).

2.2 Vaccines

In 1796, Edward Jenner successfully used cowpox material as a vaccine to induce protection against smallpox and also demonstrated the effectiveness of herd immunity, followed by the development of rabies vaccine in 1885 by Louis Pasteur. Many more vaccines were then developed including against diphtheria, tetanus, anthrax, cholera, plague, typhoid, tuberculosis, and others over the twentieth century, thus helping to reduce the burden of disease worldwide (Table 2.1). According to Plotkin et al. the fruit of this work has been so extraordinary that “no other intervention […] has had such a major effect on mortality” [32]. The first con-

TABLE 2.1 Characteristics of selected diseases and their vaccines by date of discovery and estimates of vaccine efficacy

Vaccine	Vaccine type (year available)	Mortality among unvaccinated individuals	Vaccine efficacy	References
Smallpox	Live attenuated (1798)	30%	95%	[7, 8]
Rabies	Live attenuated (1882), killed (1980)	100%	100% (with post-exposure prophylaxis)	[8]
Cholera	Killed whole cell (1884), recombinant toxin B (1993), oral (2016)	50–60% (historic) 3.3% (modern)	53–86% (Cochrane injected vaccine: 48%) (Cochrane oral vaccine: 50–60%)	[8–10]
Typhoid	Killed whole cell (1896), live oral (1989), polysaccharide (1994), conjugate (2008)	10–20% (historic) <1% (modern)	51–88% (killed whole cell) 62–96% (live oral; Cochrane: 50%) 55–72% (polysaccharide; Cochrane: 55–69%) 100% (conjugate; Cochrane: 50–96%)	[8, 11]
Plague	Killed whole cell (1897)	100% (untreated pneumonic form) 20–40% (sepsis) 6.7% (recent estimate)	60–100% (animal studies)	[8]
Diphtheria toxoid	Protein (1923)	6%	70–99%	[8]
Pertussis	Killed whole cell (1926), acellular (1996)	1% (infants)	64–90% (whole cell) 83–95% (infants pertussis) 90–95% (maternal immunization)	[12, 13]

Table 2.1 (continued)

Vaccine	Vaccine type (year available)	Mortality among unvaccinated individuals	Vaccine efficacy	References
Tetanus toxoid	Protein (1926)	25–100% (generalized tetanus) 10–20% (modern critical care unit)	70–100%	[8]
Tuberculosis	Live attenuated (1927)	23%	20% (infection) 0–80% (pulmonary) 86% (meningitis and miliary disease)	[8, 14]
Yellow fever	Live attenuated (1935)	47% (severe cases)	100%[a]	[15]
Influenza	Killed whole organism (1936), live attenuated (2003)	Up to 60% (pandemic)	8–91% (Cochrane: 59%)	[16, 17]
Tick-borne encephalitis	Killed whole organism (1937, 1981)	Up to 35% (far eastern type)	99%	[8]
Polio	Inactivated (1955), live attenuated oral (1963)	0–57%	80–96% (inactivated, paralytic polio) 90% (oral)	[8]
Measles	Live attenuated (1963)	2–15% (low-, middle-income countries)	90–98%	[18–20]
Mumps	Live-attenuated (1967)	<0.1%	85%	[21]
Meningococcus	Polysaccharide (1974), conjugate (1999, group C; 2006, group ACWY), recombinant (2014, group B)	70–85% (historic) 10–15% (antibiotic era) 40% (severe cases)	61–97% (group C) 61–85% (group ACWY) 82.9% (group B)	[8]

(continued)

Table 2.1 (continued)

Vaccine	Vaccine type (year available)	Mortality among unvaccinated individuals	Vaccine efficacy	References
Pneumococcus	Polysaccharide (1977), conjugate (2000)	11–30% (invasive diseases)	77–100% (invasive diseases)	[22–24]
H. influenza type b	Polysaccharide (1985), conjugate (1990)	40–90% (historic)	55–92% (polysaccharide) 80–100% (conjugate)	[8, 25]
Chickenpox	Live attenuated (1995)	<0.1%	77–100%	[8]
Shingles	Live attenuated (2006), recombinant (2017)	<0.1%	51–61% (live-attenuated) 89–97% (recombinant)	[8, 26, 27]
Human papillomavirus	Recombinant (2006)	3–66% (cervical cancer)	43–100% (cancer or precursor lesions)	[8, 28, 29]
Dengue	Recombinant (2016)	0.1–5%	30–60%	[8]
Ebola	Recombinant (2017)	36–90%	100%[a] (rVSV-ZEBOV)	[8, 30]

Adapted from [31]
rVSV-ZEBOV recombinant vesicular stomatitis virus–Zaire Ebola virus
[a]Limited data available

jugate vaccine against Hib was introduced in 1990. It was composed of purified capsular polysaccharide or oligosaccharide antigens covalently linked to a carrier protein, changing the polysaccharide to a T-dependent antigen and increasing its immunogenicity. It is postulated that polysaccharide-specific B cells internalize the polysaccharide-carrier and that proteolysis of the carrier protein generates peptides that are presented in association with MHCII

molecules. This leads therefore to an activation of T cells and a germinal centre reaction with the ability to generate polysaccharide-specific plasma cells and memory B cells. New techniques now drive vaccine discovery, with recombinant DNA technology and new delivery systems.

Classical vaccines can be subdivided into two groups, including the live vaccines and the inactivated-subunit-killed vaccines (commonly named "non-live" vaccines). These groups differ in the way they stimulate the immune system. Inactivated vaccines are used against bacteria and viruses that cannot be attenuated. Their advantage is that the product is chemically defined, stable, safe and contains only B and T cell-specific epitopes. They can be administered without any risk in any patient, including those who are immunosuppressed. However, they require frequent booster immunizations.

Live viral vaccines can be created with less virulent (attenuated) mutants of the wild-type virus or with viruses from other species that share antigenic determinants. Virus can be attenuated via a passage through a foreign host, such as embryonated eggs or tissue culture, where they acquire mutations to infect the new host. The new virus population will be significantly different from the initial population and will not grow well in the original host. The disadvantages of these vaccines are that they require to be maintained in refrigeration, in addition to the fact that they cannot usually be administered to immunocompromised patients because of the risk of disease caused by the vaccine strains.

There is also the possibility to create vaccines with viruses that lack virulence properties using genetic engineering. Molecular techniques are now being used to develop new vaccines. By genetic engineering, new live vaccines can be generated by the induction of mutations to delete or inactivate genes encoding virulence factors. These new techniques appear to be more reliable than random attenuation of the virus via a passage through tissue culture. Hybrid virus vaccines can be formed when genes from infec-

tious agents that cannot be easily attenuated can be inserted into safe viruses. A defective, infectious, single-cycle (DISC) virus vaccine is formed by a virus with a deletion of an essential gene that is grown in a tissue culture cell that expresses the defective gene. In DNA vaccines, the genes coding for a protein that express an important B and T cell-specific viral or bacterial epitopes are inserted into a plasmid vector, thus permitting the protein to be expressed in eukaryotic cells. Plasmid DNA is injected into muscle or skin and then taken up by DCs where the cDNA is transcribed and the immunogenic protein expressed, thus permitting the induction of a cell-mediated and humoral immune response. Attenuated viruses or bacteria, such as *Escherichia coli*, may be used as vectors containing the plasmid. Reverse vaccinology, which utilises genomic sequence data, is a new approach for the development of vaccines. These new technologies are exploding in the context of the current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic and it is anticipated that they will also influence the development of new vaccines for different populations such as the "too young, too old, or too dysimmune". Hopefully, these new vaccines and also the development of new adjuvant will help to develop vaccines that are more adapted for immunosuppressed patients.

2.3 General Principles of the Effect of Underlying States or Immunosuppressive Drugs on the Immune Response to Vaccination

Innate humoral and cellular immune dysregulation can influence the effectiveness of immunization as is the case in patients suffering from primary or secondary immunodeficiency. For example, in HIV-infected children, a reduced seroresponse to vaccination may result from poor

primary responses, impaired ability to generate memory responses and/or loss of memory cells [33, 34]. Other examples are infants in whom the immune system is still 'immature', thus resulting in poorer vaccine responses and a higher risk of infection [35]. This population displays limited B cell responses, with a poor ability to be activated by T-independent polysaccharide antigens, such as polysaccharide vaccines. In addition, they also have lower and less persistent antibody responses to T-dependent protein antigens [36].

Each of the steps of the immune response discussed above can be the target of an immunosuppressive drug (Fig. 2.3) [3].

Overall, the result is that the various immunosuppressors block the clonal expansion of specific T and B cells. In general, the primary immune response to a novel antigen is more severely affected than a secondary immune response as the threshold for activation of memory B and T cells is lower. However, some drugs may impact directly on T/B cell activation/trafficking. In addition, the clonal expansion of the memory cells will still be reduced and the antibodies produced in a lower amount and of reduced quality, thus resulting in a shorter duration of protection.

Therefore, revaccination with non-live vaccine is expected to induce a reduced immune response in immunosuppressed compared to healthy children. By contrast, during a primary vaccination with a novel antigen, additional doses may be necessary to reach the protective antibody threshold. For this reason, when possible, it is very important to verify the antibody titre post-vaccination to decide on whether additional doses must be given. Following immunization with live vaccines, there is also the risk that the inhibition of the clonal expansion of T and B cells may lead to the inability to clear the replicating attenuated vaccine-strain virus, leading to the possibility of severe vaccine-associated disease and adverse events. For this reason, live vaccines are usually contraindicated during immunosuppressive treatment.

2.4 Mode of Action of Various Immunosuppressive Drugs, Effects on Vaccine Responses and Recommendations

2.4.1 Introduction

Since the introduction of csDMARDs in the 1980s, especially MTX, and bDMARDs in 1995, many more patients have managed to achieve disease remission. Table 2.2 lists the immunosuppressive treatments considered here. Of note, although there is a continuous introduction of new monoclonal antibodies, only those currently used in children are discussed. There will be a need to revise and adapt vaccination guidelines regularly due to constant advances in this field. The type and doses of immunosuppressive treatments can have various effects on the immune response to vaccination. Thus, it is very important to understand on which compartment of the immune system the various immunosuppressive agents exactly act. As mentioned last line of previous page, live vaccines are usually contraindicated during immunosuppressive treatment. The interval after which a live vaccine can safely be given after interruption of the immunosuppressive drug is dependent on the pharmacokinetics and pharmacodynamics of the molecule. In principle, it is considered that five times the specific half-life of a drug correspond to the time needed to clear the drug from the body, but the immunosuppressive effect can last longer. For anti-cytokine drugs, the immunosuppressive effects are expected to be of shorter duration than for drugs inhibiting cell division or cell function. Therefore, some guidelines recommend "5 × T1/2 elimination + immunosuppressive effect" (which is 2 weeks for anti-cytokines and 4 weeks for other drugs [37].

In this chapter, the modes of actions of the various immunosuppressive treatments on the immune system are described and the measured or expected effects on vaccines are summarized, including the recommendations (Table 2.2).

Table 2.2 List of immunosuppressive agents and current recommendations concerning vaccination

Cellular target	Medication	Administration route	Half-life	Low/high dose	Non-live vaccines	Live vaccines
GC-Receptors	Glucocorticoids	Diverse	2–4 h (prednisolone)	*Low:* <14 days or <0.2–0.5 mg/kg/day or <10 mg/day or substitutive treatment or non-systemic [37–40] *High:* ≥14 days or ≥ 2 mg/kg/day [41] or ≥10 mg/kg/day or ≥0.2–0.5 mg/kg/day [37–40] [40] or intravenous pulse methylprednisolone	Anytime, but best between 2 and 4 weeks before treatment	– Best 4 weeks before treatment – Under treatment: only if low dose – If high dose: wait 1–2 months after end of treatment

(continued)

TABLE 2.2 (continued)

Cellular target	Medication	Administration route	Half-life	Low/high dose	Non-live vaccines	Live vaccines
csDMARDS						
Inhibitors of DNA/RNA synthesis through the inhibition of the synthesis of one of the nitrogen bases						
Pyrimidine synthesis	Methotrexate	Sub-cutanous or oral	3–15 h	*Low:* <15 mg/m²/week *High*: ≥15 mg/m²/week	Anytime, but best between 2 and 4 weeks before treatment	– Best 4 weeks before treatment – Under treatment: only if low dose; can consider booster dose of MMR, VZV – If high dose: wait 4 weeks before treatment or 2–3 months after treatment [37–39]
	Leflunomide (Arava®)	Intravenous	14 days	*Low:* ≤0.5 mg/kg/day *High*: >0.25–0.5 mg/kg/day [41]	Anytime, but best between 2 and 4 weeks before treatment – Under treatment, best in the middle of the interval	– Best 4 weeks before treatment – Under treatment: can consider booster of live vaccines only if low dose (off-label [39]) – If high dose: wait 4 weeks before treatment or 2 years after treatment (long-half-life, if necessary, wash-out option with colestyramin or activated carbon [40])

Purine synthesis	Azathioprine (Imurek®)	Oral	2 h	*Low:* ≤3 mg/kg/day [39] *High*: >1–3 mg/kg/day [41]	Anytime, but best between 2 and 4 weeks before treatment	– *High*: Contraindicated Minimum 4 weeks before treatment or 3 months after [39, 40] – *Low*: Can be considered for booster immunization with MMR, VZV [39]
	6-mercaptopurine (6-MP)		2 h	*Low:* ≤1.5 mg/kg/day [40] *High*: >1.5 mg/kg/day [41]	Anytime, but best between 2 and 4 weeks before treatment	– *High*: Contraindicated Minimum 4 weeks before treatment or 3 months after [39, 40] – *Low*: Can be considered for booster immunization with MMR, VZV [40]
	Mycophenolate-mofetil (CellCept®)	Oral	17 h	*Low*: ≤1200 mg/m^2 *High:* >1200 mg/m^2 [39]	Anytime, but best between 2 and 4 weeks before treatment	– *High:* Contraindicated Minimum 4 weeks before treatment or 1–3 months after [37–40] – *Low:* Can be considered for booster immunization with MMR, VZV [40, 42]
Alkylating agents (DNA synthesis)	Cyclophosphamide (Endoxan®)	Oral Intravenous	3–12 h	0.5–2 mg/kg/day in a single oral dose or as an intravenous pulse every 2–4 weeks	Anytime, but best between 2 and 4 weeks before treatment During treatment, best in the middle of the interval	Contraindicated During treatment Minimum 4 weeks before treatment or 1–3 months after [37–40]

(continued)

TABLE 2.2 (continued)

Cellular target	Medication	Administration route	Half-life	Low/high dose	Non-live vaccines	Live vaccines
Inhibitors of intracellular signal transduction from the antigen-recognizing TCR through the inhibition of calcineurin pathways						
Calcineurin inhibitors	Cyclosporine (Sandimmun®)	Oral	7–19 h	*Low*: ≤2.5 mg/kg/day *High*: >2.5 mg/kg/day	Anytime, but best between 2 and 4 weeks before treatment	– *High:* Contraindicated Minimum 4 weeks before treatment or 1–3 months after [37–40] – *Low:* Can be considered for booster immunization with MMR, VZV [40, 42]
	Tacrolimus	Oral	23–46 h	High interpatient and intrapatient variability, monitoring of levels necessary	Anytime, but best between 2 and 4 weeks before treatment	– *High:* Contraindicated Minimum 1–4 weeks before treatment or 1–3 months after [37–40] – *Low:* According to studies in liver transplant recipients, if dosage of <0.3 mg/kg/day tacrolimus (blood level <8 ng/mL) live vaccines can be considered [42–44]
Inhibitors of mammalian target of rapamycin (mTOR)	Sirolimus Everolimus	Oral	62 h 30 h	High interpatient and intrapatient variability, monitoring of levels necessary	Anytime, but best between 2 and 4 weeks before treatment	– *High:* Contraindicated Minimum 4 weeks before treatment or 1–3 months after and verify CD4 and CD19 before [38, 45]

Other molecules considered as csDMARDs with little or no immunosuppressive effect

PGLs synthesis (analogue of 5-ASA)	Sulfasalazine (Azufidine®)	Oral	6–8 h [5]	*Low*: ≤40 mg/kg/day *High*: >4 mg/kg/day or 2 g/day [39]	Anytime, but best between 2 and 4 weeks before treatment	OK, no pause of treatment required; however, oral typhus vaccine should be administered at least 24 h after administration of sulfasalazine [39]
	Mesalazine (Pentasa®, Asacol®, Claversal®, Salofalk®)	Oral	5 h	Standard dose	Anytime, but best between 2 and 4 weeks before treatment	No restriction, no interruption
Antimalarials	Hydroxychloroqine	Oral	40 days	6.5 mg/kg/day (max 400 mg/day)	Anytime, but best 2–4 weeks before treatment	No restriction, no interruption
Others	Colchicine	Oral	13 h	0.5–2 mg/day	Anytime, but best 2–4 weeks before treatment	No restriction, no interruption
	Thalidomide	Oral	7 h	2.5–4 mg/kg/day	Anytime, but best 2–4 weeks before treatment	No restriction, no interruption

bDMARDs

(continued)

TABLE 2.2 (continued)

Cellular target	Medication	Administration route	Half-life	Low/high dose	Non-live vaccines	Live vaccines
Anti-TNFα	Adalimumab (Humira®) mAb to TNFα	Sub-cutaneous	10–20 days	15–30 kg: 20 mg every 2 weeks >30 kg: 40 mg every second week	Anytime, but best 2–4 weeks before treatment, or in the middle of the treatment interval	– Best 4 weeks before starting treatment or 3 months after last dose – For newborns exposed during pregnancy, wait a minimum of 5 months after last dose during pregnancy [39] – Breastfeeding: OK [39]
	Infliximab (Remicade®) mAb to TNFα	Intravenous	12 days	6–10 mg/kg intravenous at weeks 0, 2 and 6, then every 4–8 weeks	Anytime, but best 2–4 weeks before treatment, or in the middle of the treatment interval	– Best 4 weeks before starting treatment or 3 months after last dose – For newborns exposed during pregnancy, wait a minimum of 6 months after last dose during pregnancy [39]
	Golimubab (Simponi®) mAb to TNFα	Sub-cutaneous	14 days	50 mg 1× per month	Anytime, but best 2–4 weeks before treatment, or in the middle of the treatment interval	– Best 4 weeks before starting treatment or 3 months after last dose – For newborns exposed during pregnancy, wait a minimum of 6 months after last dose during pregnancy [39]
	Certolizumab pegol (Cimzia®) Pegylated mAb to TNFα	Sub-cutaneous	14 days	200–400 mg every 2 weeks	Anytime, but best between 2 and 4 weeks before treatment During ongoing treatment, administration in the middle of the treatment interval	– Best 4 weeks before starting treatment or 3 months after last dose – For newborns exposed during pregnancy, wait a minimum of 5 months after last dose during pregnancy [39] – Breastfeeding: OK [39]
	Etanercept (Enbrel®, Erelzi®) TNFRII/FcIgG1	Sub-cutaneous	70 h	0.4 mg/kg 2×/weekly Or 0.8 mg/kg/week Subcutaneous: maximum 50 mg/week	Anytime, but best 2–4 weeks before treatment	– Best 4 weeks before starting treatment or 1–2 months after last dose [39, 45] – For newborns exposed during pregnancy, wait a minimum of 4 months after last dose during pregnancy [39] – Breastfeeding: OK [39]

Anti-IL-1	Anakinra (Kineret®) IL1-Rec1	Sub-cutaneous	4–6 h	1 mg/kg subcutaneous daily (max 100 mg)	Anytime, but best between 2 and 4 weeks before treatment	– Best 4 weeks before starting treatment or 2–4 weeks after last dose [39, 45]
	Rilonacept (Arcalyst®) IL1R/IL1AcP/IgG1	Sub-cutaneous	1 week	2.2 mg/kg 1× per week (initiate with double dose)	Anytime, but best between 2 and 4 weeks before treatment	– Best 4 weeks before starting treatment or probably 1 month after last dose
	Canakinumab (Ilaris®) mAb to IL1β-Rec	Sub-cutaneous	30 days	*Low*: 2 mg/kg	Anytime, but best between 2 and 4 weeks before treatment During treatment: in the middle of the treatment interval l	– Best 4 weeks before starting treatment or 7 months after last dose [45] – During treatment: minimum of 3 months after the last and before the next injection [39] – Newborns exposed in utero should wait 16 weeks after delivery for live-attenuated vaccine [39]
Anti-IL-6R	Tocilizumab (RoActemra®) mAb to IL6R	Intravenous	6–23 days	Poly JIA >2 year, <30 kg, 10 mg/kg, every 4 weeks >2 year, >30 kg, 8 mg/kg every 4 weeks Systemic JIA >2 year, <30 kg 12 mg/kg every 2 weeks >2 year, >30 kg, 8 mg/kg every 2 weeks	Anytime, but best 2–4 weeks before treatment, or in the middle of the treatment interval	– Best 4 weeks before starting treatment or 2–3 months after stopping treatment [39, 45]
CD80/CD86-Receptor	Abatacept (Orencia®) CTLA4-Ig	Iv	13 days	Standard dose: 10 mg/kg at weeks 0, 2 and 4, then every 4 weeks	Anytime, but best 2–4 weeks before treatment, or in the middle of the treatment interval	– Best 4 weeks before starting treatment or 3 months after stopping treatment [39, 45] – For newborns exposed during pregnancy: wait 14 weeks before live vaccine [39]

(continued)

TABLE 2.2 (continued)

Cellular target	Medication	Administration route	Half-life	Low/high dose	Non-live vaccines	Live vaccines
B cell inhibitor	Rituximab (MabThera®) mAb to CD20	Intravenous	20.8 days	375–500 mg/m² intravenous every 2 weeks × 2 doses	– 4 weeks (2 weeks) before treatment start – 6 months after last dose [39]	– Minimum of 6 weeks before starting treatment – 12 months after last dose and after checking restoration of B cells [39] – For newborns exposed during pregnancy: wait for normalization of B cells [39]
	Ocrelizumab (Ocrevus®) mAb to CD20	Intravenous	28 days	300 mg intravenous every 2 weeks × 2 doses, then 600 mg every 6 months	– 6 weeks (2 weeks) before treatment start – 6 months after last dose [39]	– Minimum of 6 weeks before starting treatment [39] – 18 months after last dose and after checking restoration of B cells [39] – For newborns exposed during pregnancy: wait for normalization of B cells [39]
	Belimumab (Benlysta®) mAb to B-cell activating factor (BLys)	Intravenous	12.5–19.4 days	10 mg/kg every 2 weeks × 3 then every 4 weeks	Anytime, but best 2–4 weeks before treatment or in the middle of the treatment interval	– Best 4 weeks before starting treatment – 3 months after stopping treatment [39]
Anti-CD52	Alemtuzumab (Lemtrada®/Campath®)	Intravenous	6 days	Various doses, depending on indications	Anytime, but best 6 weeks (2 weeks) before treatment [45]	– Best 6 weeks before starting treatment – 12 months after stopping treatment, and checking reconstitution of B/T cells [39]
Anti-C5	Eculizumab (Soliris®)	Intravenous	12 days	Various doses, depending on indications	Vaccination against *N. meningitidis* at least 2 weeks before starting treatment [45]	– Best 4 weeks before starting treatment – 32 months after stopping treatment [45]

Integrin $\alpha_4\beta_7$ (LPAM-1)	Vedolizumab (Entyvio®)	Intravenous	25 days	Between 100 and 300 mg intravenous at weeks 0, 2 and 6, then every 8 weeks	Anytime, but best 2–4 weeks before treatment [39]	Anytime, except for live vaccines; should be given at least 3 months after stopping treatment [39, 45]
Anti-IL-17A	Ixekizumab (Taltz®)	Sub-cutaneous	13 days	>50 kg: 160 mg subcutaneous at week 0, 80 mg every 4 weeks <50 kg: 80 mg week 0, 40 mg every 4 weeks	Anytime, but best 2–4 weeks before treatment, or in the middle of the treatment interval	– Best 6 weeks before starting treatment – 12 months after stopping treatment, verify B/T cell reconstitution
	Secukinumab (Cosentyx®)	Sub-cutaneous	27 days	Variable dosage 1× per week	Anytime, but best 2–4 weeks before treatment [45]	– Best 4 weeks before starting treatment – 3 months after stopping treatment [45]
Anti-ILl-2-IL-23	Usterkinumab (Stelara®)	Sub-cutaneous	15–46 days	45 mg subcutaneous week 0 and week 4, then every 12 weeks	Anytime, but best 2–4 weeks before treatment, or in the middle of the treatment interval	– Best 2 weeks before starting treatment – 15 weeks after stopping treatment

Adapted from [39, 46]

6-MP 6-mercaptopurine, *Ab* antibody, *AZA* azathioprine, *Blys* B-cell activating factor, *CD* cluster of differentiation 80/86, *CsA* cyclosporine, *CTLA-4* cytotoxic T-lymphocyte-associated protein 4, *CYC* cyclophosphamide, *DMARD* disease-modifying antirheumatic drug, *GC* glucocorticoid, *HCQ* hydroxychloroquine, *IFN* interferon, *IL* interleukin, *mAb* monoclonal antibody, *JAK* Janus kinase inhibitor, *MMF* mycophenolate mofetil, *MMR* measles-mumps-rubella vaccine, *MTX* methotrexate, *L PAM-1* lymphocyte Peyer patch adhesion molecule 1, *PGLs* prostaglandins, *Tac* tacrolimus, *TNF* tumor necrosis factor, *VZV* varicella vaccine

2.4.2 Glucocorticoids (GCs)

2.4.2.1 Mode of Action

GCs are among the most potent anti-inflammatory drugs used since the 1950s in children with dysimmune disorders and have both anti-inflammatory and immunosuppressive effects. They inhibit chemokines and cytokines, such as prostaglandins, lipocortins, platelet-activating factor, TNF, and IL-1. GCs also limit the trafficking of leucocytes to the inflammation sites. In macrophages, the GC-receptor complex interferes with the transcriptional activation of the RAS-MAP kinase activator protein 1 and the nuclear factor-kappa B (NF-κkB), suppressing pro-inflammatory signals (Fig. 2.2) [47]. GCs also inhibit the activation of various transcription factors in T cells such as AP-1, NF-κB and the nuclear factor of activated T-cells (NFAT) family, rendering them less responsive to activation and more prone to aptoptosis [48]. Therefore, the adaptive immune system can also be partially inhibited through the effect of GCs on T lymphocytes, especially when they are used systemically for a prolonged period at high dosage.

2.4.2.2 Safety and Immunogenicity Data

A few studies have assessed the immune response in children treated with GCs. Most studies have been performed in children on low-dose GCs (<20 mg/day) and have shown lower seroconversion rates or antibody concentrations compared to healthy controls. However, in most cases, protective antibody titres could still be reached, even among those treated with high-dose GCs or GCs combined with other treatments. No T-cell data were available [49–56].

2.4.2.3 Recommendations

First, there is controversy over the definition of high- and low-dose GCs. High doses are defined in the European League Against Rheumatism (EULAR) recommendations

as equivalent to prednisone ≥2 mg/kg/day or ≥20 mg/day or for more than 2 weeks [41]. However, according to other guidelines, high-dose GCs are defined in children as >1 mg/kg/day [37] or ≥0.5 mg/kg/day [38, 39]. By contrast, low-dose GCs are defined by EULAR as <2 mg/kg/day or <20 mg/day or for less than 2 weeks [41]. According to Belgian guidelines, <1 mg/kg/day is taken as a cut-off [37], while German and Austrian guidelines recommend to consider <0.3–0.5 mg/kg/day as low dose GCs [38, 39]. In the USA, it is recommended to delay live vaccines for at least 1 month after discontinuation of high-dose GCs, and also to verify the numbers of CD4 and CD8 in peripheral blood to exclude lymphopenia induced by long-lasting T cell apoptosis before administering live vaccines [3]. Again, according to the 2011 EULAR recommendations, live vaccines can be administered on low-dose GCs, although the definition of low-dose GCs remains uncertain as the dosage of patients treated for a chronic condition with 20 mg/day GCs, dosage <2 mg/kg/day are also considered to be high dosages [41]. However, it is generally expected that a daily dose <10 mg/day or <0.2–0.5 mg/kg/day of prednisone will not result in a significant immunosuppressive effect and live vaccines are permitted under this regimen [37–40].

2.4.3 csDMARDs

2.4.3.1 Drugs That Destroy Dividing Cells Through the Inhibition of DNA Synthesis of Nitrogen Base: Pyrimidine (MTX, Leflunomide) or Purine (AZT, 6-MP, MMF) or by Alkylation of DNA (Cyclophosphamide)

2.4.3.1.1 MTX

Mode of Action

MTX administered weekly is widely used for various dysimmune disorders in children. It is a folic acid analogue that competes against dihydrofolate reductase, which reduces

dihydrofolate into tetrahydrofolate [39], an essential co-factor of synthesis of thymidine, and decreases the synthesis of DNA and cellular proliferation. It also has an anti-inflammatory effect through an increased liberation of adenosine by cells which, in turn, decreases the expression of inflammatory cytokines such as TNFα, IFNϒ, IL-1, IL-6 and IL-8 and, as such, acts as an inhibitor of cell-mediated immunity [41, 57]. MTX also induces the apoptosis of activated naïve and memory T cells and the clonal deletion of activated naïve T cells due to the altered DNA synthesis [58].

Safety and Immunogenicity Data

During treatment with low-dose MTX (defined as <15 mg/m^2/week [41]), it appears that there is no decrease in the immune response to vaccination as demonstrated in a prospective, controlled, observational cohort study comparing the immune response to HPV in children suffering from JIA compared to healthy females [59]. Another prospective controlled study assessing the immune response to two schedules of HBV (0, 1 and 3 months vs 0, 1 and 6 months) in children with JIA with or without immunosuppressive treatment (MTX and prednisolone) compared to healthy children reported a protective antibody response with both schedules, but overall lower antibody levels compared to healthy controls [52].

Concerning live vaccines, several retrospective and prospective studies have shown that booster vaccination with MMR was safe and immunogenic in children with either low-dose MTX alone or combined with an anti-TNFα (etanercept) [50, 60, 61].

Recommendations

Live vaccines can be considered on doses ≤15 mg/m^2/week [39, 41]. At a higher dose, a delay of 1–3 months is recommended between the interruption of MTX and the administration of live vaccines [39, 45].

2.4.3.1.2 Leflunomid (Arava®)

Mode of Action

Leflunomide diminishes the synthesis of pyrimidine by inhibiting the enzyme dihydrooroate dehydrogenase, thus decreasing the synthesis of DNA and RNA and impairing the reproduction of rapidly dividing cells, mostly lymphocytes. It also inhibits the production of prostaglandins, matrix metalloproteinase-1 (MMP-1) and IL-6, as well as various tyrosine kinases and growth factor receptors [58].

Safety and Immunogenicity Data

There are few data on the immune response post-vaccination in patients treated with leflunomide. At low doses (<0.5 mg/kg/day), it appears that there is no impact on the immune response to vaccination [41, 62]. However, in a prospective cohort study in adults, there was a decrease in the antibody response to the adjuvanted split influenza (H1N1) vaccine in patients treated with leflunomide at a standard dose (no clear information on the dosage) compared to healthy controls [63].

Recommendations

The immune response is expected to be reduced, especially following primary vaccination.

Live vaccines are strictly contraindicated under high-dose leflunomide, defined as >0.5 mg/kg/day [39, 41]. The half-life of the drug is 14 days [5]. Concerning the delay between termination of treatment and vaccination with live vaccines, there are contradictory recommendations. A delay of 6 months is recommended by some sources [39], but much longer (2 years) by others [37, 40], with a specific wash-out option with inactivated carbon or colestyramin, similar to that recommended for pregnancy [39, 40]. This can be followed before administration of a live vaccine, i.e. "after cessation of leflunomide therapy, 'wash out' with 8 g colestyramin three times daily over 11 days or 50 g activated carbon four times

daily over 11 days. Independent of the wash-out method, determination of the plasma level of leflunomide is necessary in two tests at least 14 days apart. After the first test with a plasma level <0.02 mg/L, it is necessary to wait for another 1.5 months before fertilization is possible" [39]. It is probably helpful to assess the plasma level of leflunomide before considering any live vaccines, even if a delay shorter than 2 years could be considered. A low-dose regimen is defined as ≤0.5 mg/kg/day and, according to German recommendations, live vaccines can be considered under this dosage off-label in adults [39].

2.4.3.1.3 AZT and 6-MP

Mode of Action

AZT inhibits purine synthesis and therefore impairs the reproduction of rapidly dividing cells, such as all the lymphocytes. It is converted within tissues to 6-MP. Severe leucopenia occurs sometimes in patients treated with AZT.

Safety and Immunogenicity Data

One prospective controlled study assessed the immune response to HBV in 20 non-immune patients with juvenile SLE treated with GCs, AZT and hydroxychloroquine (HCQ) compared to 24 healthy patients and reported a seroconversion rate of 80% after three doses compared to 100% in healthy controls [64]. In addition, adult studies have shown that thee appears to be no decrease in the immune response post-immunization with low-dose AZT [65].

Recommendations

According to EULAR paediatric recommendations, a dose of AZT 1–3 mg/kg is defined as high-dose immunosuppression and this dosage contraindicates live vaccines [41]. A delay of 3 months between termination of this treatment and vaccination with live vaccines is recommended [38, 39].

A low-dose regimen is defined as ≤3 mg/kg/day for AZT or ≤1.5 mg/kg/day 6-MP according to German and Swiss recommendations [39, 40]. According to adult guidelines, live vaccines can be considered under AZT ≤3 mg/kg/day [39, 66].

2.4.3.1.4 MMF

Mode of Action

MMF is a powerful selective inhibitor, non-competitive and reversible from inosine monophosphate dehydrogenase. It inhibits the synthesis of guanine nucleotides. As the proliferation of B and T lymphocytes mostly depends on the de novo synthesis of purines and that other cell types can use alternate metabolic pathways, this molecule specifically inhibits lymphocytes. It inhibits the proliferation of B and T cells and decreases the production of Ig by B cells. It also diminishes the recruitment of lymphocytes into inflammatory sites and the activation of T cells by DCs [67].

Safety and Immunogenicity Data

In a prospective case-control study, the immune response was slightly diminished following HPV vaccine in SLE patients aged 18–35 years and treated with low-dose prednisolone and MMF (mean dose 1.11 ± 0.33 g/day) compared to healthy controls [68]. In a prospective cohort adult study, Gabay et al. also reported a decreased immune response following the adjuvanted split influenza (H1N1) vaccine in adult patients with auto-inflammatory rheumatic diseases treated with various csDMARDs at standard dose, including MMF, compared to healthy controls [63].

Recommendations

Due to its effect on proliferating B and T cells, MMF severely reduces the immune response during primary and secondary vaccination. According to German and Swiss recommendations, a dose of MMF >1200 mg/m^2 is defined as high-dose

immunosuppression and this dosage is contraindicated for live vaccines [39, 40]. A delay of 1–3 months (depending on the guidelines) between termination of this treatment and vaccination with live vaccines is recommended [37, 39, 40]. A low-dose regimen is defined as ≤1200 mg/m^2 and, according to German recommendations, live vaccines can be considered off-label under this dosage in both children and adults [39]. Only very few solid organ recipients have received a live vaccine while under MMF (see Chap. 3). A consensus of worldwide experts in paediatric transplantation have defined the MMF regimen as a "higher-level" of immunosuppression compared with tacrolimus (Tac) or cyclosporine A (CsA) and recommend extra precautions and further immunological evaluation before considering off-label administration of live attenuated vaccine in this population [42].

2.4.3.1.5 Cyclophosphamide (Endoxan®)

Mode of Action

Alkylating agents attach an alkyl group to the guanine base of DNA. They act on all phases of the cell cycle, irrespective of whether or not the cells are replicating. Cyclophosphamide is a nitrogen-mustard derivative, which covalently binds to guanine in the DNA, breaking the purine ring and preventing cell division. It acts on all cells, particularly T cells [69, 70].

Safety and Immunogenicity Data

There are few data in the literature. However, we vaccinated a 14-year old boy newly diagnosed with a cerebral vasculitis at our centre who had received a 4-day methylprednisolone push and started intravenous cyclophosphamide 2 days after vaccination with DTPa-IPV-Hib-HBV and PCV13. An increase in antigen-specific antibodies against tetanus, diphtheria and pneumococci was observed 1 month after vaccination (data not shown).

Recommendations

A dosage of cyclophosphamide 0.5–2 mg/kg/day is defined as a high DMARDs dosage [41]. Cyclophosphamide strictly contraindicates immunization with live vaccines [39, 40]. A delay of 1–3 months (depending on the guidelines) between termination of treatment and vaccination with live vaccines is recommended [37, 39, 40].

2.4.3.1.6 Drugs That Inhibit the Intracellular Signal Transduction from the Antigen-Recognizing TCR Through the Inhibition of Calcineurine Pathways (Cyclosporine, Tac) or the mTOR Pathway (Sirolimus, Everolimus)

Cyclosporine and Tac

Mode of Action

Cyclosporine is a lipophilic cyclic peptide of 11 amino acids, while Tac is a macrolide antibiotic. Both drugs have been isolated from fungi and possess similar suppressive effects on cell-mediated and humoral immune responses.

Both cyclosporine and Tac bind with high affinity to a family of cytoplasmic proteins present in most cells: cyclophilins for cyclosporine and FK-506 for Tac. The complex of drug-receptor inhibits calcineurin, a calcium- and calmodulin-dependent phosphatase. Therefore, they inhibit the translocation of a family of transcription factors and reduce the activation of various genes such as IL-2, TNFα, IL-3, IL-4, CD40L, and IFNϒ, and also block the clonal expansion of activated T and B cells.

Safety and Immunogenicity Data

The effect of cyclosporine and analogues on the immune response to vaccination has mostly been studied in transplant patients. Verolet et al. administered two doses of the live attenuated VZV vaccine to non-seroprotected children treated mostly with <0.3 mg/kg/day Tac (blood level <8 ng/mL) or cyclosporine 1 year after liver transplant. They reported a seroconversion rate of 100% and a good mainte-

nance of VZV antibodies 5 years post-vaccination with 96% of patients maintaining protective antibody concentrations [43]. Similar data have previously been reported from the same cohort of children [44]. Pittet et al. assessed the immune response to MMR booster doses in children of approximately 3 years of age after liver transplantation on low-dose immunosuppression with either Tac, everolimus or cyclosporine, while 24% had a combination of two anti-rejection treatments (calcineurin inhibitor + MMF or systemic steroids). Inclusion criteria for vaccination was low immunosuppression (prednisone <2 mg/kg/day; Tac <8 ng/mL) and a lymphocyte count ≥0.75 G/L. They observed a good immune response in most children with 98% of patients reaching seroprotection following booster vaccination. In addition, they reported that one dose was sufficient in 89% of children, while 38% lost protection within 1 year, thus emphasizing the importance of verifying the immune response in the short term, but also in the longer-term through annual assessment of specific antibody titre. Longer-term seroprotection rates reached 62%, 86% and 89% at 1-, 2- and 3-year follow-up, respectively [71].

Recommendations

According to German and Swiss recommendations, a dose of cyclosporine >2.5 mg/kg/day is defined as high DMARDs, while a dosage ≤2.5 mg/kg/day is considered low [39]. By contrast, a blood level <8 ng/mL for Tac is considered low. According to German recommendations, live vaccines can be considered under cyclosporine low dosage [39]. However, high-dosage cyclosporine and Tac are contraindicated for live vaccines [39, 40]. A delay of 1–3 months (depending on guidelines) between termination of treatment with cyclosporine and Tac and vaccination with live vaccines is recommended [37–40].

In transplant recipients, a consensus of international expert have judged that measles and varicella vaccine could be considered in kidney or liver transplant recipients who are receiving Tac (with levels <8 ng/mL for two consecutive read-

ings) or cyclosporine (with levels <100 ng/mL for two consecutive readings). Other criteria include a prednisone dose equivalent to <20 mg/day (or <2 mg/kg/day for those <10 kg), having undergone liver or kidney transplantation more than 1 year, and more than 2 months after an acute rejection episode, clinically well, and meeting other specific criteria of 'low-level' immunosuppression. 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 [42].

Sirolimus and Everolimus

Mode of Action

Sirolimus (also known as rapamycin) and its derivative everolimus binds to the FK binding protein 12, forming a complex that inhibits a key regulatory protein: the mammalian target of rapamycin (mTOR), suppressing cytokine-driven T-cell proliferation. In CD4 T-helper cells, the inhibition of mTOR prevents the signal of the IL-2-receptor from activating cell proliferation and promotes instead apoptosis. Furthermore, the clonal expansion of B cells is also impaired by inhibiting the signal given from the IL-4 receptor to activate B cell proliferation [3].

Safety and Immunogenicity Data

There are no reports of paediatric studies on the immune response post-vaccination under treatment with sirolimus, or vaccination studies with live vaccines under sirolimus or everolimus. Anecdotally, one patient under treatment with everolimus received one dose of MMR 5 year after transplantation in the context of a prospective study, without any safety concern; the patient remained seroprotected against measles 2 years after vaccination [71]. In another prospective study, 33 adult hepatic and renal transplant recipients were randomized to receive either a calcineurine inhibitor-based or sirolimus-based immunosuppression and were vaccinated against influenza and pneumococci. Both groups developed a

similar rise in antibody titre, although sirolimus-treated patients developed a protective titre to more influenza antigens. The pneumococcal polysaccharide vaccine was equally effective in both patient groups [72].

Recommendations

Treatment with sirolimus and everolimus contraindicate the use of live vaccines [40]. A delay of 1–3 months (depending on recommendations) between termination of this treatment and vaccination with live vaccines is recommended; a dosage of CD4 and CD19 is also recommended before the injection of live vaccines [37, 38, 45].

2.4.3.1.7 Other Molecules Considered as csDMARDs, with Little or No Immunosuppressive Effect

Inhibitors of PGL Synthesis: Derivatives of 5-ASA: Sulfasalazine (Salazopyrin®), Mesalazine (Pentasa®, Asacol®, Salofalk®)

Mode of Action

Sulfasalazine inhibits prostaglandin synthesis and has therefore a local anti-inflammatory effect. It is disaggregated by the gut bacteria into sulfapyridine and 5-ASA or mesalazine. The metabolites have an anti-inflammatory, antibacterial and immunosuppressive effect. It induces a reduction of MMP3, IL-1, IL-2, TNFα, IL-6 and IFNϒ and mostly acts on innate immunity. Mesalazine, also known as 5-ASA, is taken orally or rectally and has the same effect on the digestive mucosa as sulfasalazine.

Safety and Immunogenicity Data

At standard dose, there is no effect of treatment with 5-ASA derivatives on the immune responses post-vaccination [46, 62, 73]. However, in a prospective, randomized, controlled, double-blind study in 25 healthy young adults randomized to receive either placebo or sulfasalazine to assess the cellular and humoral immune responses post-subcutaneous immuni-

zation with tetanus toxoid vaccine and peroral immunization with inactivated influenza vaccine, a small decrease in total IgG and tetanus-specific antibody levels were observed in patients treated with sulfasalazine (1 g twice daily started 14 days before immunization) compared to volunteers treated with placebo [74].

Recommendations

These drugs are not expected to affect the immune response to vaccination and therefore there are no contraindications to vaccination with live vaccines [37–39, 46].

Antimalarials: HCQ

Mode of Action

HCQ acts in various ways on the immune system: (1) it interacts with the nucleic acid, inhibiting DNA and RNA synthesis; (2) it raises the pH in lysosomes of antigen-presenting cells, inhibiting ligand-receptor interaction and antigen processing; (3) it blocks TLRs on plasmacytoid DCs, decreasing the activation of DCs; and (4) it inhibits T cell activation [75]. Therefore, it acts on innate and adaptive immunity.

Safety and Immunogenicity Data

It has mainly been shown in adults that treatment with HCQ did not decrease the immune responses to vaccination. For example, in a prospective observational study in adults suffering from SLE following influenza vaccination [76] and in a prospective, observational, cohort study in adults suffering from rheumatoid arthritis or SLE and immunized with the plain polysaccharide pneumococcal vaccine (Pneumovax®) [77].

Recommendations

Overall, the immunosuppressive power of this molecule is weak and there is no contraindication for live vaccines [37, 38, 46].

Colchicine

Mode of Action

Colchicine is mostly utilized for treatment of auto-inflammatory diseases, such as familial Mediterranean fever (FMF) and recurrent aphthous stomatitis, such as Behcet's disease and Behcet-like syndrome. It binds to cellular microtubules, inhibiting the motility of intracellular granules and decreasing the excretion of various components by the cells, as well as decreasing the expression of adhesion molecules on neutrophils. It mostly acts on neutrophils and therefore decreases the innate immunity [58].

Recommendations

There are no data on the immune response post-immunization in patients treated with colchicine, but it is not expected to affect the immune response to vaccination.

Thalidomide

Mode of Action

Thalidomide is a synthetic derivative of glutamic acid that inhibits the production of pro-inflammatory cytokines TNFα, IL-1, IL-6, IL-12 and IL-10 and also decreases neutrophil chemotaxis, thus diminishing monocyte phagocytosis. Additionally, it helps with co-stimulation of T cells [58].

Recommendations

There are no data on the immune response post-immunization in patients treated with thalidomide and we do not know whether this drug diminishes the immune response to vaccination.

2.4.4 bDMARDs

bDMARDs are a group of proteins, either monoclonal antibodies or cytokine receptors, that block specific pathways of

the immune response. The first bDMARD developed in the early 2000s was etanercept, a soluble TNF receptor, followed by monoclonal anti-TNFα-antibodies infliximab and adalimumab. In the following years, many more molecules targeting specific components of immunity were developed. Abatacept was licensed in 2010, followed by anakinra, canakinumab and tocilizumab, etc.

As in all immunosuppressive therapies, bDMARDs inhibit cells or cytokines of the physiological immune response. As discussed in [78], previous studies have shown that patients treated with bDMARDs demonstrated a lower antibody response than those not using biologics. Additionally, the antibody declined more rapidly, leading to the lowest antibody protection in these children in the long term [79, 80]. Therefore, a regular monitoring of long-term antibody persistence is especially important in children on bDMARDs in order to give booster doses of vaccination when necessary. In general, fully humanized monoclonal IgG antibodies have the longest half-life, resembling that of human IgG (25 days). In the last 20 years, many immunosuppressive monoclonal antibodies or cytokine receptors have been approved for the treatment of children with dysimmune disorders and many more are presently under development or already approved for adults. In this chapter, only those bDMARDs currently available in the marketplace are discussed.

2.4.4.1 Anti-TNFα

2.4.4.1.1 Adalimumab, Golimumab, Certolizumab, Infliximab, Etanercept

Mode of Action

TNFα is an important pro-inflammatory molecule involved in various dysimmune disorders, such as various sub-types of JIA, IBD and uveitis. Various molecules can bind to TNFα in the circulation and therefore prevent the activation of its cellular receptor, inhibiting activation of the cells and the inflammatory cascade linked to TNFα-activation. As TNFα is

also very important for T-cell activation in the context of infection, anti-TNFα treatment is associated with an increased risk of viral and bacterial infections.

Adalimumab and golimumab are fully human monoclonal antibodies. Infliximab is a chimeric monoclonal antibody, with a murine variable region. Etanercept is a fusion protein of two TNFR2 receptor extracellular domains and the Fc region of human IgG1. Certolizumab is a PEGylated humanized Fab fragment [81].

There are two classes of TNF antagonists: soluble TNF receptors and TNF monoclonal antibodies. The soluble TNF receptor, etanercept, consists of two extracellular domains of human TNF receptor-2 fused to the Fc fragment of human IgG1. It binds to only one TNF molecule per molecule of etanercept and has a lower affinity for membrane-bound-TNF (mTNF) than for soluble TNF (sTNF). It has a short half-life (4 days). By contrast, the other TNF monoclonal antibodies have longer half-lives (9.5 days for infliximab, between 14.7 and 19.3 days for adalimumab, 11 days for golimumab) and may bind several molecules of both TNF and mTNF at a higher level (Fig. 2.4).

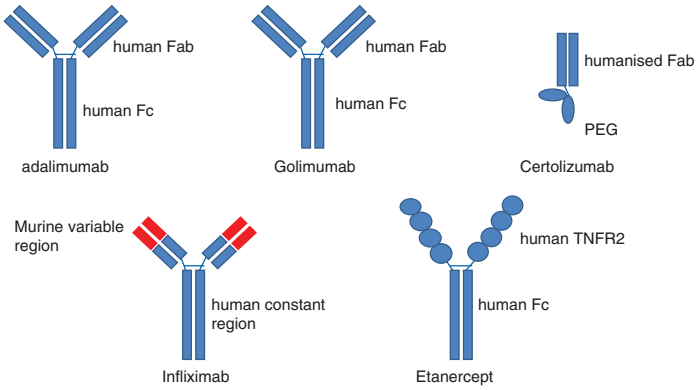

FIGURE 2.4 Schematic diagram of the structures of the five anti-TNF agents

Safety and Immunogenicity Data

Several prospective controlled studies compared the safety profiles of children with JIA and IBD following various vaccines (pneumococcal, meningococcal, HAV and HBV vaccines) in patients treated with various csDMARDs with or without TNFα-inhibitors and reported no increase in serious adverse events or disease flares. However, there was a small decrease in the antibody response in the groups treated with anti-TNFα [73, 82–85]. In conclusion, during treatment with anti-TNFα, the secondary immune response to non-live and live vaccines is preserved, although the antibody titres may be lower than in healthy controls. There are no data on the persistence or effect of anti-TNFα on T cell responses.

Recommendations

Immunization with live vaccines are contraindicated or should be given 3–4 weeks before starting treatment with anti-TNFα. The half-life is shorter for etanercept (4.2 days) and around 7–20 days for the other anti-TNFα. A delay of 3 months between termination of this treatment and vaccination with live vaccines is recommended for most anti-TNFα (adalimumab, certolizumab, golimumab and infliximab) [45] and 1–2 months for etanercept [39, 45].

2.4.4.2 Anti-IL-1

2.4.4.2.1 Anakinra, Canakinumab, Rilonacept

Mode of Action

IL-1 is an important pro-inflammatory cytokine. It exerts its effect by binding to the IL-1-receptor, inducing the activation of various cell signalling through MyD88, IL-1 receptor-associated kinase 4 (IRAK4), and NFκB, which induces the transcription of pro-inflammatory cytokines, chemokines and prostaglandins. The IL-1 receptor antagonist (IL1Ra) or anakinra is a natural physiological regulator of IL1-induced activity (Fig. 2.5). An imbalance between IL-1 and IL1Ra is

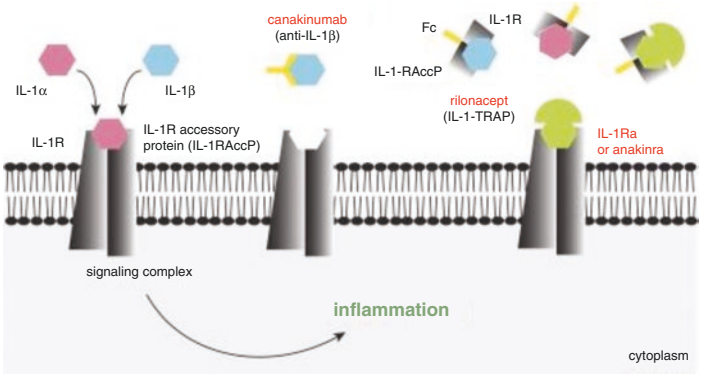

FIGURE 2.5 Current mechanisms of IL-1-targeted therapy

responsible for uncontrolled inflammation. Anakinra is a human recombinant form of IL1Ra. Rilonacept (IL-1 Trap) is a fully human dimeric fusion protein made from the extracellular domain of the IL-1 receptor and the Fc portion of IgG1. It links the IL-1 by impairing its linkage to its cell surface receptor. Canakinumab is a fully human anti-IL1β antibody that selectively blocks IL-1β [86].

Anakinra, a recombinant form of IL-1Ra, targets IL-1R, and rilonacept and canakinumab target IL-1 [86].

Safety and Immunogenicity Data

In a retrospective multicentre survey, the safety of immunization with live-attenuated vaccines was assessed in 17 children treated with anti-IL-1 and anti-IL-6. Two serious adverse effects were reported: (1) a varicella disease (probably a vaccine strain, although no virus could be isolated) 16 days after a VZV booster in a child on anakinra, low GC and several csDMARDs; (2) a flare of systemic JIA with pneumonia 1 week after an MMR booster in a child on canakinumab, low GCs and MTX (although it was not proven whether it was related to vaccination through virus/vaccine-induced transient immune suppression, which could have led to susceptibility to the pneumonia) [87]. In addition, it has been

observed in two prospective randomized studies in adults treated with anti-IL-1 that the immune response to various non-live vaccines was preserved [88, 89]. More studies are needed to assess more specifically the effect of anti-IL-1 treatment on the safety and immunogenicity of live vaccines in children.

Recommendations

Immunization with live vaccines are contraindicated in children treated with anti-IL-1 and should be ideally administered 3–4 weeks before starting treatment. A delay of 1–3 months (depending on recommendations) after the last dose of anakinra [39, 45] and 5–7 months (depending on recommendations) after the last dose of canakinumab [45] and vaccination with live vaccines are recommended [37–39].

2.4.4.3 Anti-IL6

2.4.4.3.1 Tocilizumab

Mode of Action

IL-6 has an important role in various autoimmune and autoinflammatory diseases, such as systemic onset JIA. A disequilibrium between IL-6 and its soluble receptor can induce an increase in the IL-6 binding on the cell surface receptor, with increase in the signalling cascade of inflammation [58]. IL-6 is also important for B-cell differentiation. Tocilizumab is a genetically engineered, humanized monoclonal antibody that inhibits ligand binding to the IL6 receptor, which competes with the soluble and membranous IL-6 receptor.

Safety and Immunogenicity Data

A randomized clinical trial reported a similar antibody response 1 month after immunization with tetanus toxoid and 23-valent polysaccharide pneumococcal vaccines (PPV23) in adult patients with rheumatoid arthritis treated with MTX alone or combined with anti-IL-6 [90]. The question remains

as to whether a vaccine that may depend on antigen-presenting cell activation/T-cell help will work with anti-IL-6.

Recommendations

During treatment with anti-IL-6, live vaccines are contraindicated. A delay of 2–3 months after the last dose of tocilizumab and vaccination with live vaccines is recommended [37–39, 45].

2.4.4.4 CTLA-4 Analogue

2.4.4.4.1 Abatacept

Mode of Action

Abatacept is a fusion protein containing the CTLA4 extracellular domain and the IgG1 Fc. It works by blocking CD28 co-stimulation of T-cell activation and therefore limits the activation of T cells [58]. It remains to be elucidated whether other co-stimulatory molecules could compensation for this defect.

Safety and Immunogenicity Data

There are no data on the effect of abatacept treatment on the immune response to vaccination in children. One prospective, parallel group, controlled study reported a decreased immune response following vaccination with the influenza A/H1N1 vaccine in adult patients receiving abatacept with other traditional DMARDs compared to those treated with MTX and healthy controls [91, 92]. Additionally, in a prospective observational study in adult patients with rheumatoid arthritis treated with abatacept and various csDMARDs, there was an appropriate antibody response to the PPV23 vaccine (defined as a ≥2-fold increase in post-vaccination titres to ≥3 of 5 pneumococcal serotypes and a protective antibody level of ≥1.6 μg/mL to ≥3 of 5 pneumococcal serotypes) and the trivalent seasonal influenza vaccine (defined

as a ≥4-fold increase in post-vaccination titres to ≥2 of 3 influenza strains and a protective antibody level of ≥1:40 to ≥2 of 3 influenza strains) [91, 92]. In a nested study within a randomized, double-blind, placebo-controlled study, Migita et al. evaluated the efficacy of the PPV23 in 111 rheumatoid arthritis patients divided into three treatment groups (various csDMARDs, MTX alone or abatacept). They observed a good immune response to the PPV23 vaccine in all groups, but the antibody responses were significantly lower for serotypes 6B and 23F in the abatacept group compared to the two other groups, although the functionality of the antibodies measured by opsonophagocytic assay was preserved in all three groups [93].

Recommendations

Live vaccines are strictly contraindicated under abatacept and should be administered 4 weeks before starting this treatment. A delay of 3–4 months (depending on recommendations) after the last dose of abatacept and vaccination with live vaccines is recommended [37–39].

2.4.4.5 B-Cell Targeting Drugs

2.4.4.5.1 Rituximab (MabThera®), Ocrelizumab (Ocrevus®), Belimumab (Benlysta®)

All these treatments are expected to severely impact on the antibody response to vaccines in general.

Mode of Action

Rituximab is a chimeric monoclonal mouse human antibody specific for the CD20 B-cell receptor present on pre-B cells and mature B cells, but not on stem and plasma cells. It acts by removing 95% of CD20+ B cells from the circulation by antibody- and complement-dependent cellular cytotoxicity, thus inducing apoptosis of B cells.

Ocrelizumab is a second-generation anti-CD20 monoclonal antibody very similar to rituximab, but derived mostly from human antibodies. Similar data to Rituximab are expected concerning vaccination under this treatment.

Belimumab is a human neutralizing monoclonal antibody against B lymphocyte stimulating factor (BLys), also known as B-cell activating factor (BAFF), which is a member of the TNF ligand superfamily. BLys exists in a soluble and membranous form. It is expressed on monocytes, macrophages and DCs and is upregulated following IFNϒ and IL10 secretion, increasing B cell activation and antibody secretion. Belimumab binds to BLys and inhibits the activation of B cells.

Safety and Immunogenicity Data

There are no data on the immune response post-vaccination in children treated with anti-CD20. In a prospective controlled study, Oren et al. assessed the humoral immune response to the seasonal influenza vaccine in three groups, i.e. 29 adults with rheumatoid arthritis, 14 rheumatoid arthritis adults treated with rituximab in the previous 18 months, and 21 healthy adults. They observed that patients treated with rituximab responded less well compared to the two other groups, but still developed a partial immune response to the seasonal influenza vaccine [94].

Nagel et al. showed in a prospective controlled study that belimumab given in addition to csDMARDs did not decrease the antibody response to PCV13 in SLE patients [95]. In a phase 4, open-label study among patients randomized to receive the PPV23 either 4 weeks prior to belimumab or 24 weeks after starting 4-weekly belimumab treatment, Chatham et al. observed that both groups responded similarly to the PPV23 [96]. Other groups have shown that there is very little antibody induced, but T cells may be preserved (*unpublished data*).

Recommendations

During 6–9 months following treatment with anti-CD20 monoclonal antibodies or anti-BLys, immune responses to vaccination are severely impaired as many antibody-producing plasma cells are short-lived and require replacement from CD20+ precursors. In addition, the number of memory B cells in the bone marrow is also reduced [97] and B cells returning from the bone marrow to the peripheral blood have an immature phenotype (CD27-IgD-) or naïve (CD27-IgD+), rather than memory B cells. The development of new memory B cells appears to be delayed for many years. However, it appears that long-lived plasma cells may not be affected by rituximab. Therefore, it is recommended to administer primary immunization before anti-CD20-depleting antibodies. Secondary immunization can be administered 6 months after these treatments for non-live vaccines, but only after 12 months for live vaccines [3, 37, 38]. Prolonged hypogammaglobulinemia and B cell depletion has been reported following rituximab. Since there are recommendations to document prior to therapy and then monitor Ig and B cell levels during therapy, it may be reasonable to ensure that these levels have normalized prior to any immunizations.

Although the immune response is expected to be diminished in individuals under B cell-depleting drugs, the seasonal influenza vaccine is still recommended [40].

2.4.4.6 Anti-CD52 Receptor

2.4.4.6.1 Alemtuzumab (Lemtrada®/Campath®)

Mode of Action

Alemtuzumab is a monoclonal antibody directed against the CD52 receptor, which is present on the surface of mature lymphocytes (most T and B lymphocytes), but not stem cells. It is used to treat chronic lymphocytic leukaemia and multi-

ple sclerosis. Alemtuzumab leads to an important depletion of the lymphocyte population, following which complete recovery of B and T cells can take many years.

Safety and Immunogenicity Data

In a pilot case-control study in 24 adult multiple sclerosis patients treated with alemtuzumab, McCarthy et al. observed no decrease in the immune response to various inactivated vaccines given less than 6 months after the last dose of alemtuzumab [98].

Recommendations

The immune response post-vaccination is expected to be strongly affected by treatment with anti-CD52. Therefore, vaccinations are not recommended because of the weak efficacity under this treatment. In the case of vaccination with non-live vaccines, it is recommended to verify the antibody response 1 month later. It is preferable to administer non-live vaccines before starting treatment or 6 months after the last dose of treatment. Vaccination with live vaccines is recommended 6 weeks before treatment starts or 12 months after the end of treatment and after verifying the reconstitution of B/T cells [39].

2.4.4.7 Anti-C5

2.4.4.7.1 Eculizumab

Mode of Action

Eculizumab is a humanized monoclonal antibody targeted against complement component C5. It inhibits the cleavage of C5 into C5a and C5b and hence inhibits the terminal complement pathway, including the formation of membrane attack complex, which binds and permeabilizes bacterial walls (e.g. *Neisseria*), thereby killing the microorganism. It is used for treating paroxysmal nocturnal haemoglobinuria

(caused by a genetic defect in one of the natural complement inhibitors, CD59) and atypical haemolytic uremic syndrome caused by chronic uncontrolled activation of the complement due to mutations in the complement regulatory proteins (factor H and I) or acquired auto-antibody inhibiting these components of the complement (e.g. anti-factor H antibodies) [58]. Patients treated with eculizumab are therefore particularly at risk of infection by *N. meningitides* and should be vaccinated against these bacteria. Special recommendations for the different serotypes differ among countries.

Recommendations

It is recommended to give live vaccines 1 month before starting treatment or 3 months after the last dose of treatment [45]. However, it is recommended to vaccinate children against meningococcal infections at least 2 weeks before starting eculizumab [45].

2.4.4.8 Anti-integrin α4β7

2.4.4.8.1 Vedolizumab (Entyvio®)

Vedolizumab is a monoclonal antibody specific for intergrin $\alpha_4\beta_7$ (LPAM-1, lymphocyte Peyer patch adhesion molecule 1) and it has a specific anti-inflammatory activity on the digestive tube.

Recommendations

Vedolizumab might have only a small impact on vaccines administered intramuscularly or subcutaneous, but it may have an impact on vaccines given orally. Oral live vaccines are contraindicated and can only be administered after a delay of 3 months before the last dose of treatment. However, it is unknown whether T cell migration in mucosa may be needed for some vaccines, such as HPV. Other live vaccines administered parenterally are allowed [39].

2.4.4.9 Anti-IL-17A

2.4.4.9.1 Ixekizumab (Cosentyx®), Secukinumab

Mode of Action

Ixekizumab is a humanized monoclonal antibody specific to IL-17A and produced by Th17 cells. IL-17A is upregulated in individuals suffering from various auto-inflammatory disorders, such as psoriasis and ankylosing spondylitis. It increases the inflammatory responses when it binds to the IL-17 receptor. Secukinumab is another anti-IL-17 inhibitor under development. It is unclear whether there is an influence on vaccine responses.

Recommendations

Live vaccines are recommended a minimum of 4 weeks before starting treatment and earliest 3 months after the last dose of these treatments [37, 38, 45].

2.4.4.10 Anti-IL-12 and IL-23

2.4.4.10.1 Usterkinumab (Stelara®)

Mode of Action

Usterkinumab is a monoclonal antibody directed against IL-12 and IL-23 and is very important for the activation of Th1 and Th17 cells, which are implicated in the dysregulated inflammatory response in psoriasis.

Safety and Immunogenicity Data

In a prospective case control study, Brodmerkel et al. observed no decrease in the immune response to the PPV23 and tetanus toxoid vaccines in psoriasis patients treated with usterkinumab compared to psoriasis patients not treated with systemic therapy [99].

Recommendations

Live vaccines are recommended a minimum 1 month before starting treatment with usterkinumab and earliest 3–4 months after the last dose of treatment [37, 45].

2.4.5 tsDMARDs

New molecules, such as JAK and phosphodiesterase inhibitors, have been studied in adults and trials in children are warranted or already ongoing.

2.4.5.1 Janus Kinase (JAK) Inhibitors

2.4.5.1.1 Mode of Action

The JAK-STAT system involves a receptor (JAK) and a signal transducer and activator of transcription (STAT). The JAK inhibitors available are selective, but not specific for a single JAK. Given the overlap between JAKs in their interaction with STATs and the association with multiple cytokines, each molecule will affect various immunological pathways (Fig. 2.6). Thus, it is likely to affect the innate and adaptive immunity. Indeed, the JAK receptor can be activated through autophosphorylation by various cytokines, growth factors and other

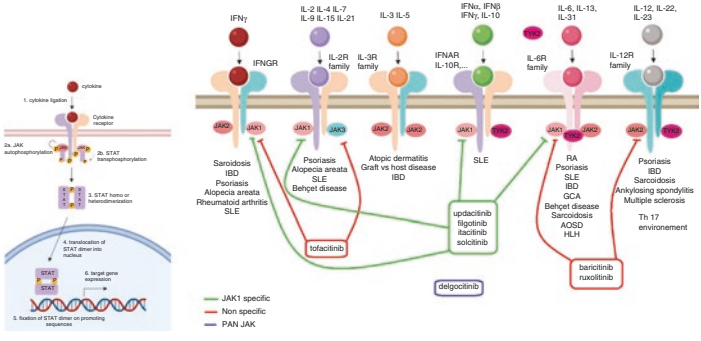

FIGURE 2.6 JAK-STAT signalling pathway

messengers. It induces the binding of STAT protein, which is then phosphorylated by JAK, inducing its dimerization with another STAT molecule and translocation into the cell nucleus where it activates the transcription of various genes. JAK1 induces the transcription of IL-6, IL-11, IFN-α/β, IFN-γ, and IL-10. JAK2 induces the transcription of IL-3, granulocyte-macrophage colony stimulating factor (GM-CSF), erythropoietin (EPO), and IFN-γ. JAK3 induces the transcription of IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 [100].

Each receptor is linked to a specific combination of JAKs/STATs that activates different pathways in cells. The inhibition of a specific JAK may block more than one pathway, which clarifies the potential adverse effects of JAK inhibitors [100].

Tofacitinib (Xeljanz®): blocks JAK3, JAK1 and, to a lesser extent, JAK2. It inhibits the differentiation of Th1 cells that produce IFN-γ and Th17 cells. Winthrop et al. assessed the immune response to PPV23 and influenza in adults with rheumatoid arthritis treated with MTX and a starting dose of tofacitinib and observed a small decrease in the humoral immune response to pneumococci, but not to influenza [101]. Other JAK inhibitors include baricitinib (Olumiant®) and ruxolitinib, which inhibit JAK1/JAK2.

2.4.5.1.2 Recommendations

Non-live vaccines can be given at any time. Live vaccines are recommended to be given a minimum 1 month before starting treatment with baricitinib or 1 month after the last dose of treatment [39], while live vaccines can be given 1 month before starting treatment with tofacitinib or 2 months after the last dose [37–39].

2.4.5.2 Phosphodiesterase Inhibitors

2.4.5.2.1 Apremilast

Mode of Action

Apremilast specifically inhibits phosphodiesterase 4 (PDE4), resulting in increased cyclic adenosine monophosphate

(cAMP), an intracellular second messenger that activates many pro- and anti-inflammatory mediators in various cells, including DCs and T cells. By inhibiting PDE4, apremilast decreases the expression of inflammatory cytokines and increases the expression of anti-inflammatory mediators. There are no data on the effect of PDE4 inhibitors on the immune response to vaccination.

Recommendations

Live vaccines are recommended 1 month before starting treatment with apremilast or 2 weeks after the last dose of treatment [45], while non-live vaccines can be given at any time.

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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

(continued)

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

(continued)

Table 3.1 (continued)

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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Table 3.1 (continued)

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

(continued)

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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Table 3.1 (continued)

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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Table 3.1 (continued)

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

(continued)

Table 3.1 (continued)

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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Table 3.1 (continued)

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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Table 3.1 (continued)

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

(continued)

Table 3.1 (continued)

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].

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Chapter 4
Vaccination with Non-live Vaccines

4.1 Introduction

Data on children are reviewed when available and the adult literature is discussed when they are lacking. Several studies have shown that non-live vaccines in children with dysimmune disorders treated with different immunosuppressive drugs do not worsen the disease or cause serious adverse events compared with healthy subjects (reviewed in detail in [1, 2]).

For children with rheumatic diseases, EULAR recommends adhering to national vaccination guidelines for diphtheria, Hib, HAV, HBV, pertussis, pneumococci, poliomyelitis, meningococci, rabies, tetanus and tick-borne encephalitis. Vaccination schedules differ among countries [3–6]. Table 4.1 summarizes the general recommendations for the various non-live vaccines.

When a disease that can potentially require an immunosuppressive treatment is diagnosed, the vaccine status of the child should be verified. All non-live vaccines can be given without restriction, but they should be given 2 weeks before treatment starts in order to increase immunogenicity. When possible, the vaccine-specific antibody responses should be verified, especially following primary immunization and for children treated with high-dose immunosuppression and

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Table 4.1 Recommendations for non-live vaccines [3–9]

Vaccine	Patient population	Dose and timing	Control of serology – short-term – long-term	Comments
Influenza	All	– One dose 1× per year during the influenza season – First year, two doses are recommended in patients <9 years	No (no correlate of protection)	Should also be administered to family members and close contacts
HBV	Seronegative for anti-HBs (<10 UI/L)	See national vaccination schedule, usually: three doses at 0, 1 and 6 months, and two doses at 0 and 6 months for children 11–15 years	– Yes, 1 month after primary immunization and then regularly if remaining under immunosuppression	Should be continuously >10 IU/L

HAV	– Seronegative for anti-HAV – Frequent travellers	See national vaccination schedule; usually, two doses at 0 and 6 months	– Yes, 1 month after primary immunization
HPV	9–26 years	See national vaccination schedule; usually, three doses at 0, 1 and 6 months and two doses at 0 and 6 months for children 11–15 years	No (no correlate of protection)
PPV23	Only recommended in some countries (North America)	One dose at least 8 weeks after PCV13	

(continued)

Table 4.1 (continued)

Vaccine	Patient population	Dose and timing	Control of serology – short-term – long-term	Comments
PCV13	All, especially patients with low complement or functional asplenia [1]	See national vaccination schedule; usually, one dose after general immunization in infancy	– Yes, if possible 1 month after vaccination – Verify maintenance of antibodies regularly in children remaining on immunosuppression if possible	Give booster doses when below protective threshold (see Table 3.5 in Chap. 3)
Hib	All, especially patients with low complement or functional asplenia [1]	One dose	– Yes, if possible 1 month after vaccination	
MenACWY	All, especially patients with low complement or functional asplenia and those who will start eculizumab [1, 6, 10]	See national immunization guideline; usually, one dose <5 years or between 11 and 15 years	No (no correlate of protection)	Doses to be repeated every 5 years if hyposplenism

Serogroup B meningococcal vaccine	All, especially patients with low complement or functional asplenia and those who will start eculizumab [1]	See national immunization guideline; usually, two or three doses, depending on the vaccine	No (no correlate of protection)	Not licensed in all countries
Diphtheria tetanus	Seronegative for tetanus	See national immunization guideline	– Yes, 1 month after primary immunization and then regularly if remaining under immunosuppression	– Regardless of the age, a paediatric formulation is recommended because of higher antigen concentration [11] – Tetanus antibody titre should be checked after vaccination if poor response is suspected [11] – Depending on the age, use combined DTPa-IPV+-Hib/HBV

(continued)

Table 4.1 (continued)

Vaccine	Patient population	Dose and timing	Control of serology – short-term – long-term	Comments
Inactivated polio virus	All, but particularly those who may travel to endemic countries	See national immunization guideline	No (no correlate of protection)	
Pertussis	Concerning pertussis: those in contact with small children	Schedule according to national plan	No (no correlate of protection)	
Tick-borne Encephalitis	Children living in or travelling to endemic regions (many countries in Western, Northern Europe; see World Health Organization map)	Three doses at 0, 2–4 weeks, and 6–12 months, then booster every 10 years	– Yes, if possible 1 month after primary immunization	

Typhoid fever	In case of travel to endemic regions	Schedule according to national plan	Only this non-live vaccine is allowed in immunosuppressed children
Rabies	In case of travel to endemic regions	Schedule according to national plan	

DTBa-IPV diphtheria-tetanus-acellular pertussis-inactivated poliovirus combination vaccine, *HAV* hepatitis A vaccine, *HBV* hepatitis B vaccine, *Hib* Hemophilus influenza type b, *HPV* human papilloma virus, *MenACWY* quadrivalent polysaccharide conjugate meningococcal vaccine, *PCV13* 13-valent pneumococcal conjugate vaccine, *PPSV23* 23-valent pneumococcal plain polysaccharide vaccine

bDMARDs (see Table 3.3 in Chap. 3) [1, 2, 12]. Table 3.5 in Chap. 3 shows whether a meaningful serological test is available.

4.2 Influenza

Safety and Immunogenicity Data

The response to influenza vaccine in children with rheumatic disease on immunosuppression treatment has been widely studied, especially during the influenza A H1N1/2009 pandemic. In a case-controlled study in 95 patients with JIA compared to 91 healthy controls, it was observed that the immune response was generally good, but sometimes associated with a reduced immune response in children with polyarticular JIA [13]. In addition, another case-control study assessed the antibody response in 118 SLE patients and 102 healthy controls and reported that high disease activity was associated with a decrease in the antibody response to influenza A H1N1/2009 [14]. Two other case-control studies in children with various rheumatic diseases (JIA, SLE, JDM) compared to healthy children reported a decreased immune response in those treated with high-dose GCs [15, 16] or combination treatment with GCs, MTX and cyclosporin [16].

Therefore, the recommendation to vaccinate all children under the age of 9 years receiving the seasonal influenza vaccine for the first time with two doses at 1 month apart should perhaps be extended also to older immunosuppressed children. In a prospective case-control study, Aikawa et al. assessed the efficacy of two doses of the non-adjuvanted influenza A H1N1/2009 vaccine in children younger than 9 years with rheumatic disease compared to healthy controls and reported it to be safe and immunogenic in this patient population [17].

Recommendations

Seasonal influenza vaccination is recommended annually to all children with dysimmune disorders treated or not with immunosuppressive drugs as influenza can be very severe

and increase the risk of secondary bacterial infections [1]. The first year, two doses are recommended in patients <9 years who have never been vaccinated against influenza or for whom the vaccination history is unknown [3–6]. The vaccination status of the household and other close contacts should be verified and they should be encouraged to receive the current seasonal influenza vaccine.

4.3 Hepatitis A

Safety and Immunogenicity Data
Previous studies have reported a good immunogenicity of the hepatitis A vaccine (HAV) in children on immunosuppressive treatment, except in some conditions. Indeed, a case-control study assessing the antibody response to HAV in JIA and healthy controls reported a decrease of the antibody response in children with active systemic JIA on anti-TNFα [18]. However, other case-control studies have reported high seroconversion rates following HAV vaccine in patients with IBD on infliximab (an anti-TNFα) [19], 6-MP or AZA [20] compared to healthy controls.

Recommendations
HAV should be offered to seronegative children with dysimmune disorders who travel frequently to endemic countries. The schedule should be followed according to national guidelines [3–6]. A control of the response to HAV is recommended in immunosuppressed children by serology [7]. If short-term protection is necessary, a serology can be performed 1 month after the first dose and, if necessary, a second dose can be administered at a short interval. For long-term protection, a serology should be performed 1 month after the last dose (6 months after the first dose) and, if necessary, further vaccine doses should be administered [7].

4.4 Hepatitis B

Safety and Immunogenicity Data

Several case-control studies in children suffering from various dysimmune disorders (auto-immune hepatitis, IBD and JIA) have observed a reduced immune response following HBV vaccine in children with dysimmune disorders compared to healthy children and also a decreased long-term antibody persistence, particularly int those treated with GCs, AZA and anti-TNFα [21–24]. In another case-control study, 14 children with IBD non-responders to three doses of hepatitis B vaccine (20 μg) received a booster dose of hepatitis B vaccine. After this additional dose, 7/14 (50%) seroconverted. Overall, seroprotection was 85% after a full vaccination scheme plus a booster dose [25], even if an adjuvant was used (Aluminium), suggesting that this may not be sufficient.

Recommendations

Hepatitis B vaccination is recommended in children with dysimmune disorders, because of potential severe disease during immunosuppression. All children should be screened by serology soon after the diagnosis. Hepatitis B should be administered to children seronegative (no anti-HBs antibodies) according to national guidelines [3–6], which is three doses at 0, 1 and 6 months for most countries (and in some countries two doses at 0 and 6 months for children 11–15 years). If protection is needed more rapidly, the accelerated scheme (1, 7, 21 days, 6–12 months) is indicated, e.g. patients who rapidly need to start immunosuppression. In cases where the family travels extensively and no natural immunity against hepatitis A has been acquired yet, the combined hepatitis A and B vaccine (Twinrix®) should be chosen, as it is known to be more immunogenic than the monovalent HBV. It is recommended to verify the antibody titre 1 month after the third vaccination (scheme 0, 1 and 6 months) and after the fourth dose if the scheme is 0, 7, 21 days and 6–12 months. Levels of anti-HBs >100 mIU/mL should be achieved. If necessary, booster doses should be administered. There are

no data on the maximal number of doses to give in the case of an absence of response, but usually up to six doses are given. In addition, Twinrix® can be given in immunosuppressed children in the case of an absence of response (usually three doses at 0, 1 and 2 months), according to a recent study [26].

Maintenance of HBs antibody should be monitored on a regular basis in immunosuppressed children. A booster dose of hepatitis B vaccine should be given if anti-HBs fall below 10 IU/L [7, 11].

4.5 HPV

Safety and Immunogenicity Data

Heijstek et al. assessed the immunogenicity and safety of the bivalent HPV in young females with JIA, SLE and JDM in a case-control study and reported lower antibody and memory B cells concentrations in patients compared to healthy controls, although the difference was not statistically significant. There was no significant effect of the various immunosuppressive treatments (MTX and anti-TNFα) on the immune response to HPV-vaccine. However, it has been reported in two case-control studies in patients with JIA or juvenile dermatomyositis (JDM) that the antibody concentrations tended to be lower in patients than in healthy controls. This was even observed in adolescent girls who were not receiving any immunosuppression due to an unclear mechanism that remains to be elucidated [27, 28], despite the fact that the vaccine was adjuvanted with aluminium. Similarly, an adult case-control study reported a reduced immunogenicity of the quadrivalent HPV vaccine in adult patients with SLE compared to healthy controls [29].

Recommendations

HPV vaccination is recommended in young adults aged 11–26 years with dysimmune disorders, according to the national vaccine schedule [3–6]. For immunosuppressed patients, the three-dose schedule is recommended rather than

the two-dose schedule, regardless of age. The immunogenicity results of previous studies suggest that assessing the vaccine response and antibody persistence following HPV vaccination in this population may be useful, although there is still no recognized seroprotection cut-off for this age group.

4.6 Pneumococcoccal Vaccines

Safety and Immunogenicity Data

In a case-control study of JIA children and healthy controls, Farmaki et al. observed that following the pneumococcal protein 7-valent conjugate vaccine (PCV7), JIA-children had a normal antibody response when treated with MTX or cyclosporine, either with or without GCs, but a lower antibody response if treated with anti-TNFα [30].

Recommendations

Both the PCV13 and PPV23 pneumococcal vaccines are still recommended in many countries, such as the USA, Canada, Cyprus, Greece, France and Spain [3–6]. For example, the US Advisory Committee on Immunization Practices recommends the following vaccination plan for children with chronic diseases: four doses of Prevnar13® at 2, 4, 6 and 12–15 months of age, followed by two additional doses of PPV23 at 5 years' interval between the ages of 2 and 18 years [4]. The rationale being that the PPV23 adds protection against a larger number of serotypes than the PCV13. However, because of its T-independent characteristic, it only induces short-term immunity and weaker immune responses than PCV13, which is a T-dependent antigen [8]. For this reason, only PCV13 is recommended in Switzerland. In general, conjugate pneumococcal vaccine should be preferred over polysaccharide vaccine as conjugate vaccines produce higher affinity antibody responses, longer lasting immune responses, as well as the production of memory B cells. Booster vaccinations after conjugate vaccines permit an amplification of the pool of memory B and T cells. In contrast, booster vaccination with plain polysaccharide vaccines may deplete the pool of memory B cells

due to a lack of induction of memory cells [31]. The fact that some countries still include the polysaccharide vaccine in their recommendations depends on the pneumococcal serotype distribution circulating in the country.

Vaccination against pneumococcal disease is recommended for all children with dysimmune disorders according to national immunization guidelines [3–6]. Ideally, the vaccination should be administered prior to the start of immunosuppressive therapy. If immunosuppressive therapy has already been started, the vaccination should be administered at a time point when the level of immunosuppression is lowest. Whether and when booster vaccination may be needed following PCV13 priming remains to be defined. Immunogenicity may be reduced under some immunosuppressive treatments and, if possible, verification of the immune response should be performed 1 month after vaccination and regularly in children remaining under immunosuppression [7].

4.7 Meningococcal Vaccines

Safety and Immunogenicity Data

Stoof et al. conducted a retrospective cohort study on the kinetics of specific antibody responses following the meningococcal serogroup C-conjugate vaccine in children with JIA. They observed a similar antibody response and waning of meningococcus-specific IgG titres over time in patients and healthy controls. However, the loss of antibodies was more rapid in patients on bDMARDs than on csDMARDs [32].

Recommendations

Monovalent (capsular groups A and C) or quadrivalent polysaccharide conjugate meningococcal vaccine (MenACWY), as well as the vaccine against serogroup B (MenB), are recommended in several European countries and in the USA and Canada, depending on the endemicity of the various meningococcal serogroups in the different locations [3–6]. Patients with acquired complement deficiency, such as

patients receiving the monoclonal antibody eculizumab, and other children receiving an immunosuppressive treatment are also at risk of hyposplenism and should be up to date with their meningococcal immunization [10].

4.8 Tetanus-Diphtheria-Acellular Pertussis-Polio Vaccines

Safety and Immunogenicity Data
In general, the antibody response to tetanus-diphtheria vaccination is similar in patients with dysimmune disorders and healthy controls. However case-control studies assessing tetanus antibodies in children with SLE observed that the antibody titres tended to decrease more rapidly in patients treated with immunosuppressive drugs [33, 34]. Another retrospective, cross-sectional study in children with various rheumatic diseases and healthy controls also reported a decrease in antibody in children with rheumatic disease [33, 34].

Recommendations
Tetanus, diphtheria, acellular pertussis and poliomyelitis vaccinations are recommended for all children with dysimmune disorders, according to the national immunization guidelines specific to the country [3–6]. The timing and number of doses depend on the number of previous doses received and the interval since their last dose of vaccination. In young adults, after primary vaccination, booster doses of diphtheria/tetanus vaccine should probably be given more frequently than in healthy persons, i.e. every 10 years [7].

4.9 Hib

Recommendations
Hib vaccination should be administered according to national immunization guideline [3–6]. Based on the current epidemiology, Hib immunization is not recommended after the age of

5 years, even in immunosuppressed patients, except in the Czech Republic, Greece, the USA and Canada [3–6].

4.10 Other Vaccines: Rabies, Japanese Encephalitis, Parenteral Typhoid Vaccines, Tick-Borne Encephalitis

Safety and Immunogenicity Data

In the literature, no data were found on the safety and immunogenicity of the inactivated vaccinations against rabies, Japanese encephalitis, typhoid fever, or tick-borne encephalitis in children with dysimmune disorders.

Recommendations

Vaccinations against rabies, Japanese encephalitis, or typhoid fever are indicated for specific risk situations according to national immunization guidelines before travelling to endemic areas [3–6]. The indications should be discussed individually with specialists before planning international travel.

A vaccination against tick-borne encephalitis is recommended for children with an increased risk of exposure according to the national immunization guidelines for each country [4, 6]. The usual course of vaccination should be followed (three dose-scheme, with a booster dose every 10 years). In immunosuppressed patients, a serology should be performed 1 month after the last dose.

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Chapter 5
Vaccination Schedules in Immunocompromised Children

5.1 Introduction

Vaccination schedules in immunocompromised children are the same as for healthy individuals. Their particularity consists in that they may include supplementary vaccinations (e.g. usually not given beyond a certain age), an accelerated schedule, extra doses for primary vaccination, extra boosters, as well as specific conditions for the administration of live-attenuated vaccine. These are detailed in Tables 5.1 and 5.2, and in the following sections below.

Vaccine recommendations are slightly different between immunocompromising conditions and are determined by the individual risk of infection and the data available. Among the various guidelines available, the Infectious Diseases Society of America (IDSA) provides a good overview of the current evidence available and covers most medical conditions (Table 5.1) [1]. The different national immunization schedules can also be found online [2].

5.2 Supplementary Non-live Vaccines

Protection against pneumococcus, influenza, meningococcus, and human papilloma virus (HPV) are particularly needed in

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Table 5.1 Summary of the Infectious Diseases Society of America guidelines on vaccination of immunocompromised patients

	HIV	CTX	After CTX	Before HSCT	After HSCT	Before SOT	After SOT	Inflammatory diseases	Asplenia or SCD	Cochlear implants or CSF leak
HIB	C	U	U	U	H	U	U	U	R	U
HAV	U	U	U	U	R	R	R	U	U	U
HBV	H	U	R	U	R	H	R	U	U	U
DTP	U	U	U	U	H	U	U	U	U	U
HPV	H	U	U	U	H	U	H	U	U	U
IIV	R	R	U	R	R	R	R	R	U	U
LAIV	C	NO	U	NO	NO	NO	NO	NO	NO	U
MMR	C	NO	U	C	C	C	NO/C	C	U	U
MMRV	NO	NO	U	C	NO	C	NO	C	U	U
MEN	H	U	U	U	H	U	U	U	H	U
PCV	R	R	U	R	H	R	R	R	R	R

PPSV	R	R	U	R	R	R	R	R	R	R
IPV	U	U	U	U	H	U	U	U	U	U
ROT	U	NO	U	NO	NO	C	NO	C	U	U
VZV	C	NO	U	C	C	C	NO/C	C	U	U
ZV	NO	NO	U	C	NO	C	NO	C	U	U

HIV: human immunodeficiency virus-infected patients. Vaccine recommendations differ according to lymphocyte count (CD4 counts of ≥ or <200 cells/mm^3 in adults and ≥ or <15% CD4 T-lymphocyte percentage). **CTX**: during chemotherapy. **After CTX**: 3 months after chemotherapy or 6 months after anti-B-cell antibodies; patients should be vaccinated according to the routine vaccination schedule. Vaccines administered during cancer chemotherapy should not be considered valid doses unless there is documentation of a protective antibody level. **Before HSCT**: candidates should be updated with their vaccination according to the routine schedule. Live-attenuated vaccine should be given at least 4 weeks and inactivated vaccines at least 2 weeks before starting the conditioning regimen. **After HSCT**: patients should be fully re-immunized with more vaccine doses than for immunocompetent individuals. **Before SOT**: candidates should be updated with their vaccination according to the routine schedule. Live-attenuated vaccine should be given at least 4 weeks before transplantation. **After SOT:** recipients should be updated with inactivated vaccine according to the routine schedule. Live-attenuated vaccines could be used with caution after assessment of the risks and benefits if the patient is seronegative and clinically stable on low immunosuppression, together with close follow-up and appropriate education of the patient and primary care physician. **Inflammatory diseases**: vaccine recommendations depend on the level of immunosuppression, whether it is planned, and if low- or high-level. Low-level immunosuppression includes treatment with prednisone <2 mg/kg with a maximum of ≤20 mg/day; methotrexate

(continued)

TABLE 5.1 (continued)

	HIV	CTX	After CTX	Before HSCT	After HSCT	Before SOT	After SOT	Inflammatory diseases	Asplenia or SCD	Cochlear implants or CSF leak

≤0.4 mg/kg/week; azathioprine ≤3 mg/kg/day; or 6-mercaptopurine ≤1.5 mg/kg/day. High-level immunosuppression regimens include treatment with doses higher than those listed for low-dose immunosuppression and biologic agents such as tumor necrosis factor antagonists or rituximab. **Asplenia or SCD**: patients should be continuously vaccinated against encapsulated bacteria. Influenza vaccination is essential given the high risk of pneumococcal infection following influenza. **Cochlear implants or CSF leak**: patients with profound hearing loss who have or are scheduled to receive a cochlear implant, and an inner ear-CSF communication or other sort of CSF leak should be vaccinated against pneumococcus

C recommended under certain conditions (see Rubin et al. [1] for details, and Suresh et al. for the latest recommendation on MMR and VZV after SOT [31]), *CSF* cerebrospinal fluid, *CTX* chemotherapy, *DTP* diphtheria-tetanus-pertussis vaccine, *H* highly recommended, some patients will require more doses and/or higher dosage than immunocompetent persons, *HAV* hepatitis A vaccine, *HBV* hepatitis B vaccine, *Hib Haemophilus influenzae* type b vaccine, *HIV* human immunodeficiency virus, *HPV* human papillomavirus vaccine, *HSCT* hematopoietic stem cell transplantation, *IIV* inactivated influenza vaccine, *IPV* inactivated poliovirus vaccine, *LAIV* live-attenuated influenza vaccine, *MEN* meningococcal conjugate vaccine, *MMR* measles-mumps-rubella vaccine, *MMRV* measles-mumps-rubella-varicella vaccine, *NO* not recommended, *PCV* pneumococcal conjugate vaccine, *PPSV* pneumococcal polysaccharide vaccine, *R* highly recommended (patient is at increased risk), *ROT* rotavirus vaccine, *SCD* sickle cell disease, *SOT* solid organ transplantation, *U* recommended as usually (in routine vaccination of immunocompetent persons), *VZV* varicella vaccine, *ZV* zoster vaccine

Table 5.2 Practical summary for clinician in charge of the vaccination of immunocompromised patients

Medical condition	Non-live vaccines recommendation	Live-attenuated vaccines recommendation	Additional vaccine(s) recommendation	Serological monitoring	Guidelines, references
Primary immunodeficiency					
Primary immunodeficiency disorders	Routine, but effectiveness doubtful, depends on the underlying disease and whether IVIG are given regularly.	Permitted in certain situations only	IIV PCV (± PPSV23) MCV4 MenB if complement deficiency	'Regularly', but no guidance on how often	ACIP [3] Reviews [10–14]
Acquired immunodeficiency					
Underlying state					
Prematurity	Accelerated schedule, based on chronological age	Accelerated schedule, based on chronological age	IIV PCV MCV RSV (see country)	No indication	Review [15] AAP (RSV) [9]
Malnutrition Anorexia nervosa	Routine	Permitted	IIV? *Insufficient data to date*	No indication	Review [16]

(continued)

Table 5.2 (continued)

Medical condition	Non-live vaccines recommendation	Live-attenuated vaccines recommendation	Additional vaccine(s) recommendation	Serological monitoring	Guidelines, references
Obesity	Routine	Permitted	IIV	No indication, few studies reported lower vaccine responses	Reviews [17–19]
Underlying infection					
HIV infection	Delay vaccination until viral load <50 copies/mL and CD4 >15% for 6 months. Use high-dose HBV vaccine (40 µg) in adolescents. Give Hib vaccine regardless of age if not immune. DT booster at least 1× per 10 year.	Permitted only if CD4 >200 cells/µL (or >15–24% in infants and children) for >6 months	IIV PCV (± PPSV23) MCV4 two doses 2 months apart, then every 5 years	Anti-HBs Ig periodically (if ongoing exposure) Anti-tetanus, anti-diphtheria 1× per 5 year Anti-measles, anti-rubella 1× per 3–5 year	PENTA [20] CHIVA IDSA [1] ACIP [3]

Underlying disease					
Diabetes mellitus	Routine, HBV vaccination highly recommended	Permitted	IIV PCV (± PPSV23)	Documentation of protection against HBV No other indication, antibody response to vaccinations seems to be normal overall	ACIP [3] Review [21] CDA (adults) [22]
Asplenia/hyposplenia Sickle cell disease	Routine, catch-up Hib vaccination regardless of age, HBV vaccination highly recommended if frequent transfusion. Anticipate 2 weeks between vaccination and elective splenectomy	Permitted, as of a few days after splenectomy	IIV PCV (± PPSV23) MCV4 two doses 2 months apart, then every 5 years MenB	Frequent monitoring of serotype-specific pneumococcal IgG to guide booster doses	IDSA [1] ACIP [3]

(continued)

Table 5.2 (continued)

Medical condition	Non-live vaccines recommendation	Live-attenuated vaccines recommendation	Additional vaccine(s) recommendation	Serological monitoring	Guidelines, references
Haemophilia	Routine, HAV and HBV vaccination highly recommended	Permitted		No indication, adequate response to HBV vaccine could be documented	WFH [23]
Coeliac disease	Routine, HBV vaccination highly recommended	Permitted	IIV PCV (± PPSV23) ± MCV if hyposplenism confirmed	HBV serology (data suggest poor response to HBV vaccine administered prior to gluten-free diet)	Review [24, 25]

Renal failure, chronic kidney disease (including dialysis)	Accelerate schedule before dialysis, but continue during and after, HBV vaccination highly recommended	Permitted	IIV PCV (± PPSV23)	No indication, but monitoring could guide booster doses and inform on protection (vaccine responses likely to be impaired)	ACIP [3] Review [26]
Chronic liver disease	Routine, HAV and HBV vaccination highly recommended	Permitted	IIV PCV (± PPSV23)	No indication, but monitoring could guide booster doses and inform on protection	ACIP [3]
Chronic heart disease or malformation	Routine	Permitted	IIV PCV (± PPSV23) RSV (cf country and underlying disease)	No indication	ACIP [3] AAP (RSV) [9]

(continued)

Table 5.2 (continued)

Medical condition	Non-live vaccines recommendation	Live-attenuated vaccines recommendation	Additional vaccine(s) recommendation	Serological monitoring	Guidelines, references
Chronic lung disease Asthma Cystic fibrosis Bronchopulmonary dysplasia	Routine	Permitted	IIV PCV (± PPSV23) RSV (cf country and underlying disease severity)	No indication	ACIP [3] AAP (RSV) [9]
Chronic neurological disease and neurodevelopmental disorder	Routine	Permitted, VZV vaccination highly recommended (higher risk of neurological complications)	IIV PCV	No indication	Recent article [27]
CNS anatomic barrier defect (e.g. CSF leak, inner ear dysplasia, or cochlear implant)	Routine	Permitted	PCV (± PPSV23)	No indication	IDSA [1] ACIP [3]

Inborn errors of metabolism	Routine	Permitted	IIV? PCV? *Insufficient data to date*	Unpredictable vaccine responses, depending on underlying immune defect	Review [28]
Transplant recipients					
HSCT	Revaccination starting 3–6 months after HSCT (including Hib, regardless of age)	Revaccination permitted under certain condition as of 1.5–2 years after HSCT	IIV PCV, three doses (± PPSV23) MCV, two doses	No indication Could be useful to monitor seroprotection against measles and varicella	CCLG [29] EBMT [30] IDSA [1] ACIP [3]
SOT	Accelerated schedule before SOT. Continue after SOT (2–6 months post-SOT)	Accelerated schedule if >4 weeks before SOT. Permitted in certain situation after SOT, as of 1 year post-SOT [31]	IIV PCV (± PPSV23)	Frequent monitoring to guide vaccination; it can also inform on protection against measles and varicella	AST, IPTA [31] IDSA [1] ACIP [3]

(continued)

Table 5.2 (continued)

Medical condition	Non-live vaccines recommendation	Live-attenuated vaccines recommendation	Additional vaccine(s) recommendation	Serological monitoring	Guidelines, references
Dysimmune disorders					
IBD	Accelerate schedule before immunosuppression, but continue during and after	Permitted if low immunosuppression	IIV PCV (± PPSV23)	No indication, but monitoring could guide booster doses and inform on protection, in particular against measles and varicella	IDSA [1] Reviews [32, 33]
Non-systemic JIA	Accelerate schedule before immunosuppression, but continue during and after	Permitted if low immunosuppression	IIV PCV (± PPSV23)	No indication, but monitoring could guide booster doses and inform on protection, in particular against measles and varicella	IDSA [1] Review [32]

Systemic JIA	Accelerate schedule before immunosuppression, but continue during and after	Permitted if low immunosuppression	IIV PCV (± PPSV23)	No indication, but monitoring could guide booster doses and inform on protection, in particular against measles and varicella	IDSA [1] Review [32]
Vasculitis	Accelerate schedule before immunosuppression, but continue during and after	Permitted if low immunosuppression	IIV PCV (± PPSV23)	No indication, but monitoring could guide booster doses and inform on protection, in particular against measles and varicella	IDSA [1] Review [32]

(continued)

Table 5.2 (continued)

Medical condition	Non-live vaccines recommendation	Live-attenuated vaccines recommendation	Additional vaccine(s) recommendation	Serological monitoring	Guidelines, references
Kawasaki disease	Accelerate schedule before immunosuppression, but continue during and after	Permitted if low immunosuppression	IIV PCV (± PPSV23)	No indication, but monitoring could guide booster doses and inform on protection, in particular against measles and varicella	IDSA [1] Review [32]
Juvenile dermatomyositis	Accelerate schedule before immunosuppression, but continue during and after	Permitted if low immunosuppression	IIV PCV (± PPSV23)	No indication, but monitoring could guide booster doses and inform on protection, in particular against measles and varicella	IDSA [1] Review [32]

SLE and other connective tissue diseases	Accelerate schedule before immunosuppression, but continue during and after	Permitted if low immunosuppression	IIV PCV (± PPSV23)	No indication, but monitoring could guide booster doses and inform on protection, in particular against measles and varicella	IDSA [1] Review [32]
Nephrotic syndrome	Accelerate schedule before immunosuppression, but continue during and after	Permitted if low immunosuppression, VZV vaccine highly recommended	IIV PCV (± PPSV23)	Monitoring of serotype-specific pneumococcal antibody useful to guide booster. Monitoring of seroprotection against measles and varicella could be useful as well.	ACIP [3] Review [26]

(continued)

Table 5.2 (continued)

Medical condition	Non-live vaccines recommendation	Live-attenuated vaccines recommendation	Additional vaccine(s) recommendation	Serological monitoring	Guidelines, references
Hemolytic uremic syndrome	Routine	Permitted	IIV PCV MCV4 MenB	No indication	Review [34]
Auto-inflammatory syndrome (TNF receptor-associated periodic syndrome, FMF)	Accelerate schedule before immunosuppression, but continue during and after	Permitted if low immunosuppression	IIV PCV (± PPSV23)	No indication, but monitoring could guide booster doses and inform on protection, in particular against measles and varicella	IDSA [1] Review [32]

Interferonopathy	Accelerate schedule before immunosuppression, but continue during and after	Permitted if low immunosuppression	IIV PCV (± PPSV23)	No indication, but monitoring could guide booster doses and inform on protection, in particular against measles and varicella	IDSA [1] Review [32]
Multiple sclerosis and other autoimmune diseases of the brain (neurosarcoidosis, cerebral vasculitis)	Accelerate schedule before immunosuppression, but continue during and after	Permitted if low immunosuppression	IIV PCV (± PPSV23)	No indication, but monitoring could guide booster doses and inform on protection, in particular against measles and varicella	IDSA [1] Review [32]

(continued)

Table 5.2 (continued)

Medical condition	Non-live vaccines recommendation	Live-attenuated vaccines recommendation	Additional vaccine(s) recommendation	Serological monitoring	Guidelines, references
Dermatological diseases (psoriasis, severe atopic dermatitis, cutaneous erythematosus lupus, alopecia areata)	Routine	Permitted if low immunosuppression, VZV vaccination highly recommended		No indication	Review [35]
Undesirable side—effects of treatment					
Oncological diseases	Routine during chemotherapy Re-start vaccination 3–6 months after completion of chemotherapy (including Hib, regardless of age)	Permitted as of 3–6 months after completion of chemotherapy	IIV (even during chemotherapy) PCV (± PPSV23) MCV	No indication Could be useful to monitor seroprotection against measles and varicella	CCLG [29] IDSA [1] ACIP [3] AIEOP [36]
Non-chemotherapy idiosyncratic drug-induced neutropenia	Routine	Routine		No indication	

Contacts of immunocompromised individuals

Parents, close contact of immunocompromised individuals	Routine	Highly recommended IIV or LAIV if not immune, OPV and smallpox vaccine are the only LAV contraindicated in close contact	Documentation of immunity against measles and varicella if disease/ vaccination history uncertain (or immunize regardless)	IDSA [1] Review [13]

Adapted from [40]

AAP American Academy of Paediatrics, *ACIP* Advisory Committee on Immunization Practices, *AIEOP* Italian Association Paediatric Haematology Oncology, *CDA* Canadian Diabetes Association, *CHIVA* Children's HIV Association, *CSF* cerebrospinal fluid, *DTaP* diphtheria-tetanus-pertussis vaccine, *EBMT* European Society for Blood and Marrow Transplantation, *HAV* hepatitis A virus, *HBV* hepatitis B virus, *Hib Haemophilus influenzae* type b, *HSCT* hematopoietic stem cell transplantation, *IDSA* Infectious Disease Society of America, *Ig* immunoglobulin, *IIV* inactivated influenza vaccine, *IPTA* International Paediatric Transplant Association, *IPV* inactivated poliovirus vaccine, *IVIG* intravenous immunoglobulins, *LAIV* live-attenuated influenza vaccine, *LAV* live-attenuated vaccine, *MCV* meningococcal conjugated vaccine, *MenB* meningococcus type B vaccine, *MMR* measles-mumps-rubella vaccine, *NLV* non-live vaccine, *OPV* oral polio vaccine, *PCV* pneumococcal conjugate vaccine, *PPSV23* 23-valent pneumococcal polysaccharide vaccine, *PENTA* Paediatric European Network for Treatment of AIDS, *RSV* respiratory syncytial virus, *SOT* solid organ transplantation, *VPD* vaccine-preventable disease, *VZV* varicella vaccine, *WFH* World Federation of Hemophilia

immunocompromised children. Vaccinations against these diseases are included in many national guidelines for healthy children, so they may not necessarily be considered as 'supplementary vaccines' in this context.

To prevent invasive pneumococcal diseases, pneumococcal conjugate vaccine (PCV) is usually recommended in healthy children before the age of 5 years, but also in all medical conditions with immunosuppression, regardless of age. Although some guidelines also recommend to subsequently administer the 23-valent polysaccharide vaccine (PPSV23) to those at high risk [3], many experts disagree as non-conjugate polysaccharide vaccine elicits a non-follicular B-cell response without inducing immune memory, and hyporesponsiveness is observed after repeated administrations [4].

Given the high burden of influenza disease, the vaccine is recommended in virtually all immunocompromised condition from 6 months of age. Moreover, preventing influenza also helps preventing secondary pneumococcal infection. Immunocompromised children should always receive the inactivated vaccine and not the live-attenuated influenza vaccine (in Europe, the latter is only available in the United Kingdom).

Meningococcal vaccines are recommended to asplenic patients, HIV-infected individuals, those with complement deficiencies, or receiving a treatment affecting the complement (such as eculizumab) [5]. Most guidelines recommend a two-dose schedule of the 4-valent conjugate vaccine (MCV4) and, when available, vaccination against serogroup B as well (Table 5.1).

As the risk of malignancy related to HPV is greatly increased in immunocompromised individuals [6], a three-dose schedule is strongly recommended for all. The two-dose schedule used routinely in immunocompetent 11- to 15-year-old individuals may not be sufficiently immunogenic and for this reason the three-dose schedule should be preferred [7].

Recommendations for passive immunization (e.g. administration of immunoglobulins against respiratory syncytial virus [RSV]) are beyond the scope of this book, but details can be

found in a recent review by Luna et al. [8], the American Academy of Paediatrics' 2014 recommendations [9], and Table 5.2.

5.3 Supplementary Dose

As vaccination may be less immunogenic in immunocompromised children and immunity may wane faster, it is sometimes useful to administer vaccines with a higher antigenic content, additional primary vaccine doses, or more frequent booster doses to ensure an adequate response (via serological monitoring) and subsequent protection against vaccine-preventable diseases.

High-dose vaccine As an example, the use of high-dose vaccine for vaccination against HBV is recommended by some experts in HIV-infected adolescents (and adults) and adult haemodialysis patients. Studies involving adults suggest it could be beneficial for oncological patients or those with dysimmune disorders [1]. Another example is high-dose influenza vaccine, which is being currently evaluated in immunocompromised individuals, including oncological patients, SOT recipients, and haemodialysis patients [37–39]. However, data in paediatric patients are scarce.

More vaccine doses Regarding vaccination schedules, a three-dose (rather than a two-dose) schedule is recommended for HPV in all immunocompromised conditions, and a two-dose (rather than a single dose) schedule is recommended for MCV4 [1].

More boosters Regular MCV and PCV boosters are recommended in many immunocompromised conditions, whereas they are not recommended in healthy children. Diphtheria-tetanus booster doses are also recommended more often, as guided by serological monitoring.

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Chapter 6
Practical Approach to the Vaccination of Children with Dysimmune Disorders Before the Introduction of Immunosuppression or Already Under Immunosuppressive Treatment

In a child newly-diagnosed with a dysimmune disorder

- Check the immune status of the child through natural infection and vaccine history and serology.
- Administer missing vaccines according to the age and condition if possible and prior to initiation of immunosuppressive treatment.
- For non-live vaccine, 2 weeks are generally required for the development of the immune response following primary immunization and around 1 week following booster immunization.

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- Verify when possible the vaccine response 1 month later and if vaccine antibodies remain below the protective threshold defined in Table 3.5 in Chap. 3; administer additional doses of vaccine.
- For live vaccine, if time is sufficient (at least 4 weeks), administer one or two doses of the live vaccine at 4 weeks' interval. Verify the response after the first or second dose.

In children already under immunosuppression

- Define the effect of the underlying disease and/or immunosuppressive treatment on the immune response to vaccination.
- Using Table 2.1 in Chap. 2, determine how the immunosuppressive treatment will affect the cellular and humoral immune response to vaccines and whether any precautions are required before administering non-live or live vaccines.
- For non-live vaccine, all vaccines are allowed. However, the immune response may be diminished with high-dose immunosuppression (see Table 3.3 in Chap. 3). Therefore, it is recommended to check the antibody response 1 month after vaccination when possible.

If a live vaccine is required despite immunosuppression

- Live vaccines are usually contraindicated during immunosuppressive treatment. They can be considered in some circumstances (see Table 3.4 in Chap. 3) if the personal risk of exposure to a given disease is high.
- If the child has already received in the past the vaccine antigen for which he has no longer protective antibody levels, revaccination can be considered under certain conditions (low-dose immunosuppression as defined in Table 3.2 in Chap. 3).
- If primary immunization with a live vaccine is needed, depending on the planned duration of the treatment and risk of exposure to the pathogen, it may be possible to interrupt temporarily the immunosuppressive treatment. In this case, follow Table 3.4 in Chap. 3 showing the mini-

mal time interval between interruption of a certain immunosuppressive treatment and the administration of live vaccines. However, the risk of exacerbation of the dysimmune disorders should also be considered.

When the vaccine antibodies should be verified

- Under immunosuppression, the antibody response to primary immunization should be verified at 1 month post-vaccination when possible as the immune response may be decreased depending on the treatment and additional doses may be necessary.
- Secondary immunization is expected to give rise to protective antibody levels, although at lower levels and for a shorter duration than in healthy children. Therefore, it is useful to regularly assess vaccine antibody in order to decide when revaccination may be required, in particular for those pathogens that present a significant risk for community acquisition because of poor vaccine uptake (measles, varicella) and/or pathogens that present a significant lifelong risk and for which regular boosters are recommended (tetanus, pneumococci, hepatitis B).

Patients treated with IVIG

- These treatments are not considered as immunosuppressive. However, they affect the immune responses to vaccinations.
- Vaccine serology is not reliable.
- The responses to live vaccines are altered as the Igs will inhibit the replication of the live virus. Therefore, a delay of 3–11 months is recommended between the end of the IVIG and the administration of live vaccine, depending on the IVIG dose. It is also recommended to verify that vaccine antibodies (passively transferred through the IVIG) have disappeared before administering live vaccines.
- There is no delay necessary between non-live vaccines and IVIG perfusion.

Chapter 7
Discussion

Overall, there are many studies assessing the vaccination of children with dysimmune disorders or after transplantation [1–12]. All published studies are very reassuring from a safety point of view and most vaccines appear to be safe in children on immunosuppressive treatment. They do not frequently cause serious adverse events and do not increase disease activity or induce rejection. However, there are only a few studies that have assessed vaccination with live vaccines in this patient population [7–43].

It appears to be safe to vaccinate children treated with low dose csDMARDs and GCs or after transplantation, including primary vaccination and booster doses of MMR and VZV, as there has been no report of severe adverse reactions, no cases of vaccine-derived viral infections, or no worsening of the disease activity or transplant rejection. In the setting of solid organ transplantation, a consensus of experts have dictated strict conditions enabling vaccination with MMR or VZV [12]. However, larger studies are necessary to define the exact conditions under which live vaccines can be given in children on high-dose DMARDs, bDMARDs and tsDMARDs, such as JAK inhibitors. In all cases, live vaccines should be considered on a case-by-case basis for children with higher immunosuppression. For these patients, it is important to have a

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systematic approach to assess vaccine status and to plan the vaccinations at a specific time of the disease.

Concerning immunogenicity, most immunosuppressive treatments at low dose induce a normal antibody response in the short term. However, immunogenicity of some vaccines under higher immunosuppression is less clear. Although all non-live vaccines can be given even under high immunosuppression, it is not always very clear how the child will respond to the vaccination. Therefore, when possible, it is important to assess the antibody response 1 month after vaccination as it might be necessary to give a supplementary dose of vaccine for some children [8].

Most studies have analysed the short-term responses post-vaccination in immunocompromised children. However, long-term protection depends on persisting antibody levels above the threshold of protection until we know if the immunological memory can act rapidly enough to induce protective antibody levels in case of infection. Of note, this threshold of protection has been only established in healthy children and may be different in immunocompromised children. Therefore, a correlate of protection needs to be defined for this specific population to ensure that long-term protection is maintained. Hence, it is very important to verify that children treated continuously with immunosuppressive treatment or suffering from various immunosuppressive conditions that can affect their response to vaccination maintain protective antibody in the long term. Indeed, it has been observed that specific antibodies wane more rapidly post-vaccination than in healthy children. The speed of decline of the specific antibodies post-immunization in immunocompromised children may depend on various parameters, such as the type and dose of immunosuppressive treatment, previous vaccinations, time since last vaccines, age, and the activity of the disease, but more studies are needed to define the exact factors that affect the rapidity of this decline. It is important to recommend how frequent the vaccine serology should be assessed in this population and how often vaccine booster doses should be given. For the moment, antibody persistence should be

assessed more systematically in all children on immunosuppressive treatments, especially those on bDMARDs, and against diseases for which the risk of exposure is continuous, such as pneumococci, influenza, tetanus, hepatitis B, VZV and measles. There is also a need to develop laboratory tests, which are more widely available to help monitoring long-term immunity to all vaccine-preventable diseases in high-risk children.

Assessment of immunity is largely restricted to antibody responses because of the difficulty measuring B and T- cell-specific responses outside of specialized laboratories. However, long-term protection is more complex than just measuring the level of neutralizing antibodies. The quality of antibody and B cells (function, repertoire) is also important. There are only few data on recall responses in immunocompromised children and no data on B cell memory functions. It is well-known that antibody levels can be under the protective threshold, although the individual may still be protected by the memory immunity, which can be re-activated very rapidly for some antigens, at least in healthy individuals. Studying the antibody and cellular immune responses in the short- and longer-term post-vaccination in this vulnerable population is crucial for the improved development of vaccine strategies (such as the use of new adjuvants or the use of DNA vaccines) to increase vaccine protection among these children.

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Chapter 8
Conclusions and Future Perspectives

Vaccination of immunocompromised children is safe and immunogenic and should be a priority and a concern of every physician in charge of these patients. As soon as a dysimmune disorder is suspected, vaccine status should be verified and all missing vaccines administered if time is sufficient. During immunosuppression, immune responses may be decreased, especially in children treated with high-dose csDMARDs or bDMARDs. In addition, antibody titres decrease more rapidly in the long term in this population than in healthy children. Therefore, the vaccine response should be assessed not only at 1 month post-immunization when possible, but also on a regular basis in order to administer booster doses when necessary. Of note, it is important to determine who has the responsibility for these assessments among the health care providers of these children. Specialists are often the primary care providers of these complex patients and they should be more pro-active in verifying the vaccine status of their patients and making recommendations as to when to administer particular vaccines. In summary, even if larger studies are needed, live vaccines appear to be safe under low-dose immunosuppression or after temporarily interrupting immunosuppressive treatment. Thus, clear guidelines are needed to define in which situations live vaccines can be used.

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There is a need to develop tools enabling the assessment of the "net immunosuppression state", to better define for an individual patient his immunological capacity. These would guide clinicians for the individualisation of vaccination schedule in the various immunosuppressive conditions, in particular when administrating live vaccines. This score could be based on clinical factors, as well as laboratory assessments. In-depth immunological evaluation could help to predict the safety and immunogenicity of a given vaccine, in a given individual.

Further, it would be important to decrease the burden of blood sampling in children by decreasing the blood volume required for immunity assessment and vaccine responses, and optimising the current technic. In addition, standardization of cellular vaccine response assessment in clinical setting would help to predict infection susceptibility in immunocompromised patients.

New vaccine technologies are exploding in the context of the *severe acute* respiratory syndrome *coronavirus* 2 (SARS-CoV-2) pandemic, based mostly on gene analysis to indicate targets and then combining this information with new ways to target and 'trick' the immune system into responding appropriately. Similarly, a better understanding of the pathology of dysimmune disorders has led to the development of more targeted approaches. It is to be hoped that the current pandemic will also trigger the development of an array of vaccines to be used in different populations for the same pathogen, with special vaccines for immunocompromised and dysimmune children.

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