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-

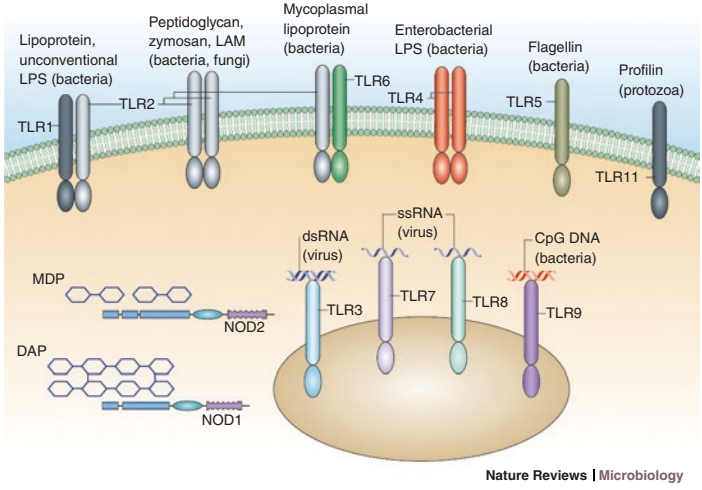

FIGURE 1.1 Pattern-recognition receptors: Toll-like receptors and nucleotide-binding oligomerization domain. Reproduced from [4]

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

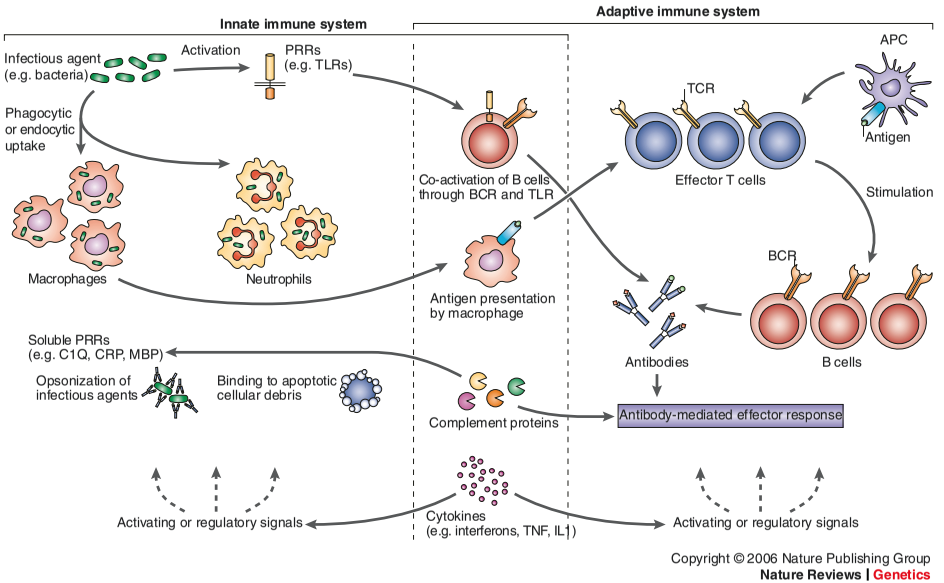

FIGURE 1.2 Presentation of the innate and adaptive immune systems. Reproduced from [7]. *APC* antigen-presenting cell, *BCR* B-cell receptor, *C1Q* complement protein 1Q, *CRP* C-reactive protein, *IL1* interleukin 1, *MBP* mannose-binding protein, *PAMP* pathogen-associated molecular patterns, *PRR* 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

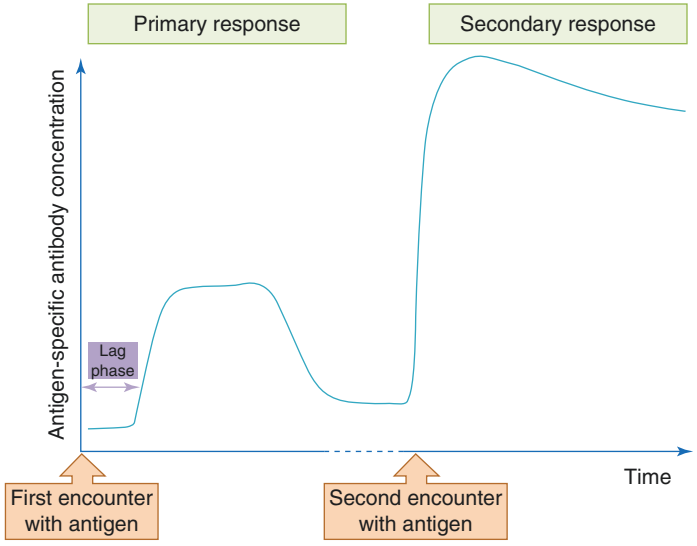

FIGURE 1.3 Primary and secondary immune responses to a given antigen. Adapted from [1]

"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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