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Vaccination in immunocompromised host: Recommendations of Italian Primary Immunodeficiency Network Centers (IPINET)

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ABSTRACT

Infectious complications are a major cause of morbidity and mortality in patients with primary or secondary immunodeficiency. Prevention of infectious diseases by vaccines is among the most effective healthcare measures mainly for these subjects. However immunocompromised people vary in their degree of immunosuppression and susceptibility to infection and, therefore, represent a heterogeneous population with regard to immunization. To date there is no well- established evidence for use of vaccines in immunodeficient patients, and indications are not clearly defined even in high-quality reviews and in most of the guidelines prepared to provide recommendations for the active vaccination of immunocompromised hosts. The aim of this document is to issue recommendations based on published literature and the collective experience of the Italian primary immunodeficiency centers, about how and when vaccines can be used in immunocompromised patients, in order to

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facilitate physician decisions and to ensure the best immune protection with the lowest risk to the health of the patient.

1. Introduction

Vaccinations are the most important tool to prevent infectious diseases. Immunocompromised patients have an increased susceptibility to infections that often affects the clinical outcome, thus vaccination represents a critical issue in this population. The safety and effectiveness of vaccines depends on the nature and degree of immunosuppression. The response to vaccination is generally reduced or completely absent in these patients, depending on the type of immune disorders [1]. However vaccination studies demonstrate, in many cases, an overall protective effect resulting in reduced health-care costs and lower morbidity and mortality rates. Currently, there are more than 300 primary immunological disorders with different degrees of immune impairment and susceptibility to infection, which makes it difficult to draw universal recommendations regarding immunization [2]. Therefore, vaccination schedule in people with immune deficiency requires a precise assessment of risk-benefits to ensure the greatest protection, and to prevent risks of adverse events in patients who are not deemed eligible for vaccination. In the present review we report vaccine schedule recommendations in patients with primary or secondary immune disorders, based on the currently available evidence and on the standardized experience and practice in the context of the Italian Primary Immunodeficiency Network (IPINET) centers. Of course their application must take into account the evolution of knowledge in this field. Primary immunodeficiency were classified in 4 principal types, namely: B- cell defects and minor antibody deficiencies, T-lymphocyte deficiencies, immune disorders characterized by selective susceptibility to infections and innate immunity defects. A distinct section on "syndromic immunodeficiency" has been included. Patients with secondary immune deficiency (SID) represent a heterogeneous and continuously increasing group of patients. SIDs are acquired and occurs in people with HIV infection/AIDS, malignant neoplasms, stem cell or solid organ transplantation, asplenia (functional, congenital anatomic, or surgical asplenia); people receiving immunosuppressive or antimetabolite drugs, and people with protein loss, chronic diseases and inflammatory conditions (such as diabetes, kidney, heart, liver or lung disease). In these patients short- and long-term anti infectious prophylaxis mainly relies on vaccine and antimicrobial treatments.

2. Vaccination in antibody deficiencies (Table 1)

Primary antibody defects (PAD) represent more than 50% of all primary immunodeficiencies and, according to the last classification of the Union of Immunological Societies (IUIs) Expert Committee on Primary Immunodeficiency [2], can be divided into the following groups, depending on their immunological features:

(a) severe reduction of all serum immunoglobulin isotypes with profoundly decreased or absent B cells;
(b) severe reduction of at least two serum immunoglobulin isotypes with normal or low B cells count;
(c) severe reduction of serum IgG and IgA with normal/elevated IgM and normal B cells count;
(d) isotype or light chain deficiencies with generally normal B cell counts;
(e) specific antibody deficiency with normal Ig concentrations and normal B cell counts;
(f) Transient Hypogammaglobulinemia of Infancy with normal B cell counts.

PAD feature an increased susceptibility to bacterial infections, which mainly occur within the first years of age or after the third decade of life. Most infections are caused by encapsulated bacteria, such as *Streptoccoccus pneumoniae* and *Haemophilus influenzae* [3]. However, both CNS infections by enteroviruses and gastrointestinal infections by *Giardia lamblia* and *Cryptosporidium* may be observed [4]. Furthermore, patients with PAD may develop autoimmune diseases and/or neoplasia. Their natural history is affected by the severity of hypogammaglobulinemia and the extent of circulating B cell counts reduction. Therefore, some conditions such as Selective IgA Deficiency (SIGAD) and Transient Hypogammaglobulinemia of Infancy (THI) are usually asymptomatic, whereas others, such as X Linked Agammaglobulinemia and Common Variable Immunodeficiency (CVID) are characterized by severe and recurrent infections.

The management of antibody defects is tightly bound to its clinical course, thus the prevention and monitoring of infectious episodes represent a key issue [5]. Immunoglobulin replacement therapy, either administered intravenously or subcutaneously and antibiotic therapy of acute infectious episodes, represent the mainstays of treatment. Although antibiotic prophylaxis is used in several clinical settings for an increased control of infectious episodes despite the high risk to induce antibiotic resistance.

Vaccination is a also used as diagnostic tool to assess specific antibody response to protein and/or polysaccharide antigens. Currently growing evidence is available on the potential benefits of this practice. However, caution is mandatory in some conditions according to either severity or presence of associated diseases. When contraindications to selected vaccines are not reported, timing and doses should follow national immunization recommendations [6,7]. Active immune response can be extremely heterogeneous because vaccines can evoke either an adequate response, as in healthy subjects, or an impaired/absent immune response [5,8–10]. Additionally, the lapse of time between immunoglobulins and vaccine administration is another important factor that need to be considered [11]. Nowadays vaccines belong to the two following categories:

– Inactivated vaccines;
– Live attenuated vaccines.

2.1. Inactivated vaccines

Inactivated vaccines consist of purified/synthesized antigens as in vaccines against Tetanus, Diphtheria, Pertussis, Haemophilus influenzae, Pneumococcus, Meningococcus (serotypes A, B, C, W135, Y), Salmonella typhi, Hepatitis B virus, Papillomavirus or inactivated microorganisms (Influenza virus). Generally, they are considered safe and well tolerated as no relevant adverse events have been reported in PID patients as compared to healthy subjects [12].

As advised by the Advisory Committee on Immunization Practices (ACIP), in light of the accumulating data of the 23-valent

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Table 1
Vaccination in primary immunodeficiency disorders.

	TDP	IPV	Hib	HBV	HPV	Influenza	Pneumococcus	Meningococcus	MMR Varicella	Rotavirus	BCG S. typhi
Major antibody deficiencies (XLA, CVID)	*Yes	*Yes	*Yes	*Yes	*Yes	*Yes	*Yes	*Yes	No	No	No
Minor antibody deficiencies (selective IgA deficiency, isolated IgG subclass deficiency, specific antibody deficiency)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
SCID	°No	°No	#Yes	°No	°No	°No	#Yes	#Yes	No	No	No
CID	#Yes	#Yes	Yes	#Yes	#Yes	Yes	Yes	Yes	§No	§No	No
MSMD	#Yes	#Yes	#Yes	#Yes	#Yes	#Yes	#Yes	#Yes	No	No	No
Invasive bacterial infections	#Yes	#Yes	Yes	#Yes	#Yes	#Yes	Yes	Yes	No	No	No
CMCD	#Yes	#Yes	#Yes	#Yes	#Yes	#Yes	#Yes	#Yes	No	No	No
TLR deficiency	#Yes	#Yes	#Yes	#Yes	#Yes	#Yes	#Yes	#Yes	No	No	No
IL12/IFN-gamma pathway deficiency	#Yes	#Yes	#Yes	#Yes	#Yes	#Yes	#Yes	#Yes	No	No	No
Complement deficiency	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No data available
Congenital defects of phagocytes (CGD,LAD, MPO Neutropenia)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	‡Yes	‡Yes	No

* May be administered when indicated: immune response may be impaired and is uncertain if depends only on humoral response.
° Not recommended: these vaccines are safe but probably ineffective.
May be administered, the response to these vaccines is likely to be poor.
§ Generally contraindicated but they could be considered according to patient immune system function.
‡ Not recommended in LAD.

pneumococcal polysaccharide vaccine (PPSV23) related immune hyporesponsiveness, the 13-valent pneumococcal conjugate vaccine (PCV13) is recommended for protection of high-risk individuals of all ages. However a PCV13/PPSV23 combined schedule might be used to extend antibody responses to additional serotypes [13,14].

To simplify the recommended timing in the age group 2–18 years, ACIP recently harmonized it as it follows: ≥8-week interval for PCV13-PPSV23 sequence; ≥8-week interval for PPSV23-PCV13 sequence [14]. In CVID patients the antibody response to polysaccharide antigens (meningococcal C and pneumococcal) may be appropriated yet related to memory B cell count [10].

Papillomavirus vaccine is recommended in patients with primary immunodeficiency who have not been previously vaccinated or have not completed the dose series, as reported by the Morbidity and Mortality Weekly Report of 2015 [15]. Furthermore, the Vi capsular polysaccharide Salmonella Typhi vaccine seems to be safe in patients with PAD [16].

Inactivated vaccines consisting of purified antigens can be administered to CVID and XLA patients even if it could not generate a protective response. Conversely, patients with selective IgA deficiency and IgG subclasses deficiency should receive vaccines according to the immunization schedule for healthy subjects. Inactivated poliovirus is the only polio vaccine recommended in patients with antibody deficiency and their household contacts. Of note, as reported in the ACIP Recommendations, some patients may already be immune to poliovirus because they have been vaccinated before the diagnosis, but a protective immune response may not be guaranteed in these subjects [17]. As reported by the Infectious Diseases Society of America (IDSA) the inactivated influenza vaccine (IIV) is recommended in patients with PAD aged >6 months [6]. Patients with hypogammaglobulinemia can mount a CD4-mediated antibody response against influenza vaccine [18]. IIV vaccine, similarly to Pneumococcus vaccine, is also recommended in patients receiving gammaglobulin replacement therapy, as antibodies against influenza virus are not usually included in immunoglobulin products, because of the viral antigen variability. Furthermore, it could also stimulate an adequate protective response provided a residual immune function [5,6]. The inactivated hepatitis A vaccine may be administered to patients with antibody defects even if it could not generate a protective response and additional doses may be required [19].

2.2. Live attenuated vaccines

As reported by Bonilla et al. [20] and Shearer et al. [21], live attenuated virus vaccines are not recommended in XLA and CVID patients because of their potential side effects. Actually, few data are available on measles, chickenpox and rotavirus vaccines in patients affected by PAD [21]. According to CDC, live attenuated vaccines may be considered in these patients according to their risk of exposure and immune status [11]. Rotavirus vaccine has been added to the vaccination schedule. Two live attenuated vaccines are currently available but new vaccines are being investigated. No data are available on the side effects of rotavirus vaccine in patients with PAD.

Therefore, this vaccine should not be given to patients with a family history of primary immunodeficiency unless an immunological evaluation has ruled out a PAD [22].

In contrast, all available vaccines can be administered to patients with IgA deficiency or IgG subclass deficiencies [21]. Yellow fever is still contraindicated in patients with PAD since no data are available on the effects of this vaccine in this group of patients. Indeed, patients with antibody deficiency may be at increased risk of adverse events, such as visceral disease [23]. Live attenuated poliovirus administration is per se not recommended in patients with PAD and their relatives. Several studies have reported the occurrence of CNS infection after poliovirus vaccine in XLA patients [21] and, although less frequently, in CVID patients [24]. In particular, this vaccine could cause CNS invasive infection in patients with undiagnosed PID or in those patients who have not started gammaglobulin replacement [25]. Patients with PAD who are travelling should be warned that immunoglobulin products contain anti-poliovirus antibodies at various concentrations, suggesting the exposure risk is still present in those areas where OPV vaccine is used. Several studies have reported that in approximately 10% of patients with PAD poliovirus excretion is still observed even several months after vaccination [26]. Furthermore, this vaccine cannot be used in selective IgA deficiency patients because some of them can develop more severe primary immunodeficiency such as CVID [5]. Live attenuated influenza vaccine (LAIV) is contraindicated in XLA and CVID patients [27] as no data are available about the infection or the virus spread from CVID patients vaccinated with LAIV [28]. Furthermore, this vaccine is not recommended to the household contacts for potential virus transmission. However,

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in patients with minor antibody deficiencies, such as selective IgA deficiency or IgG subclasses deficiencies, LAIV vaccine seems to be safe, even if the immune response is impaired [21]. Live attenuated bacteria vaccines include Bacillus Calmette-Guerin (BCG) and Salmonella Typhi vaccines. Few studies are available about the effects of these vaccines in patients with PAD, therefore they remain contraindicated as reported in the Red Book [27]. A recent study on 50 XLA patients vaccinated with BCG demonstrates the absence of systemic reactions and suggests its use in these patients [21].

Salmonella attenuated Ty21a vaccine should not be used in patients with PAD as reported in the CDC Morbility and Mortality Weekly Report [16]. Although the Ty21a strain can be found in the stools of vaccinated people, the transmission has not been observed and blood cultures remain negative after vaccination [16]. Moreover, in the mouse model the occurrence of a moderate immune defect does not increase the susceptibility to Salmonella Typhi infection after vaccination. Despite this evidence, the vaccine is currently contraindicated [5].

2.3. Vaccines and replacement therapy

Before a vaccine is administered, information on whether and when gammaglobulin replacement therapy has been last performed is required. Available products contain antibodies with a wide range of immunological and anti-microbial effects such as neutralization of bacterial toxins, opsonization for complement-mediated lysis, opsonization for killing by phagocytes and cell-mediated killing of pathogens induced by NK cells or phagocytes [29]. Inactivated antigens, which include recombinant vaccines, are generally not affected by circulating antibody, so they can be administered before, after, or at the same time as the antibody. Immunoglobulin therapy may interfere with immune responses to measles, rubella and varicella live vaccines. The effect on mumps vaccine is not known. Therefore, it is recommended to avoid these vaccines for a period between 3 and 12 months after receiving immunoglobulin, depending on the dose given [27]. Simultaneous administration of antibody (in the form of immune globulin) and vaccine is recommended for postexposure prophylaxis of certain diseases, such as hepatitis B, rabies, and tetanus [19].

3. Vaccination in major T-cell deficiencies and defects in intrinsic immunity with susceptibility to specific organisms (Table 1)

SCID is a congenital disorder characterized by the impaired generation of a diverse repertoire of mature T lymphocytes, which leads to a severe T lymphopenia with a lack of a T- and B-dependent specific-antibody response. All patients have few autologous T cells, while half the patients show a decreased number of B and NK cells. Even if B cell counts may be normal or increased in some patients with SCID, their maturation in SCID infants is incomplete and fail to produce specific antibodies. Thus, IgA and IgM concentrations are extremely low, while IgG concentrations are related to the mother's IgG levels at birth and decrease after 3 months. Other laboratory features of SCID patients include undetectable T-cell receptor excision circles (TRECs), very poor mitogen response and absence of the thymus. Patients with SCID display profound immunodeficiency, which leads to severe susceptibility to infections. Therefore, SCID diagnosis should be made early in life to prevent patients exposure to infectious agents and perform hematopoietic stem cell transplantation. No live viral or bacterial vaccines should be given to SCID patients [21] who should otherwise receive passive immunization with immunoglobulins. In fact, disseminated vaccine- acquired varicella and vaccine acquired-rubella have been reported in a 13 month-old female with an atypical SCID due to IL7R mutation [30]. Killed or inactivated vaccines are safe because they cannot replicate. Nevertheless, their effectiveness is very limited. Bacterial conjugate polysaccharide vaccines, including pneumococcal, meningococcal and *Haemophilus influenzae* type b vaccines, are recommended even in patients with complete T cells defect, but immune response to those vaccines is likely to be poor. Oral Polio vaccine (OPV) should not be administered to immunocompromised patients or to their household contacts. In most countries, inactivated Poliovirus vaccine (IPV) has replaced OPV vaccine. Recently in the United States a case of vaccine- associated paralytic poliomyelitis has been described in a child with SCID and a history of OPV vaccination in India [31]. Live-attenuated *M. bovis* bacille Calmette-Guérin (BCG) is routinely administered in most countries within the first month of life. However, only a small number of SCID patients receive diagnosis before the age of 1 month, as the median age at diagnosis is 138.5 days [32]. Marciano et al. reported BCG complications in 51% of SCID patients vaccinated before SCID diagnosis, two-thirds disseminated and one-third localized, especially in those vaccinated within the first month of life [33]. Thus, the absolute contraindication of BCG vaccine in SCID patients is not sufficient to prevent vaccine complications. This suggests that BCG vaccination should not be performed in children with familial history of PID. Moreover, in countries where newborn screening for SCID is available, BCG vaccination should be shortly postponed.

Oral rotavirus vaccine is also a live vaccine that is recommended at two months of life in the United States and in several European countries. Nine patients who received rotavirus vaccination before SCID diagnosis have been reported. They presented with a severe gastroenteritis associated with protracted viral shedding, which led to the diagnosis of SCID. Thus, as for other live vaccines, SCID is a contraindication for rotavirus vaccination [34]. However, a delay in rotavirus vaccination cannot be considered because rotavirus vaccination must be administered early in life to prevent the first yet most severe infection in children. The only strategy to avoid rotavirus vaccination in SCID patients is early diagnosis through newborn screening, if available.

Combined immunodeficiency (CID) is characterized by impaired, but not completely absent, T- and B-cell immunity and by less profound immunological abnormalities than SCID, such as reduced in vitro T-cell function and thymus output. The diagnosis of CID is often delayed because the clinical course is usually less severe than SCID and newborn screening programs fail to identify CID with normal TRECs levels at birth [35]. In patients with impairment of T-cell functions, live viral vaccines are contraindicated, but live measles, mumps, rubella and varicella vaccines could be considered in patients according to the immune system function. Moreover, inactivated viral and bacterial vaccines are safe and vaccines against *Streptococcus pneumoniae, Haemophilus influenzae* type b and *Neisseria meningitides* are recommended. However, the response could be poor and a misdiagnosed immunodeficiency could reveal itself as a vaccine response failure [36,37].

PIDs associated with alteration of Toll-like-receptor signaling (TLR) are caused by distinct genetic defects that result in impairment of cytokines production, cellular activation and, in some cases, adaptive immune responses. Genetic alterations of *UNC93B1, TBK1, TRIF, TICAM1, TLR3, TRAF3* genes confer a peculiar and selective susceptibility to *Herpes* simplex encephalitis type 1 [27]. Mendelian susceptibility to mycobacterial diseases (MSMD) is characterized not only by inherited predisposition to infections mainly caused by poorly virulent mycobacteria, but also by *Mycobacterium tuberculosis*. Affected individuals are also predisposed to infections caused by *Salmonella* and other intracellular bacteria (*Listeria*, *Nocardia* and *Klebsiella*), fungi (*Candida*, *Histoplasma*, *Paracocidomyces*), parasites (*Leishmania*, *Toxoplasma*) and viruses (*Cytomegalovirus*, *Human Herpes Virus 8* and *Varicella Zoster*

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Virus) [38]. The genes causing MSMD (IFNGR1, IFNGR2, STAT1, IRF8, GATA2, CYBB, IL12B, IL12RB1, ISG15 and NEMO) are involved in the IL-12/IFN-γ axis which are triggered by BCG [39,40]. After BCG vaccine, patients with MSMD can develop localized (such as lymphadenitis or osteomyelitis) or disseminated (fever, weight loss, anemia and hepatosplenomegaly) complications. In 1996, a case of fatal disseminated BCG infection led to the identification of the IFN-γ receptor deficiency [41]. In 1998, inherited IL-12 deficiency was identified in a patient with a history of BCG lymphadenitis and *Salmonella enteritidis* disseminated infection [42]. Disseminated osteomyelitis mimicking metastatic neuroblastoma was found in a patient with heterozygous mutation in STAT1 [43].

As previously discussed, the absolute contraindication of BCG vaccine in immunocompromised patients is not enough to prevent complications. Thus, while it is necessary to develop a safer vaccine, it is important to identify high-risk patients, such as patients with a family history of consanguinity, immunodeficiency or vaccine complications.

Predisposition to invasive bacterial infections, mostly caused by *S. pneumoniae*, *S. aureus*, and *P. aeruginosa* is associated with inherited mutations in IRAK4, NEMO and MYD88 [44]. Recommendations to manage predisposition to invasive bacterial infections include antibiotic prophylaxis, IVIG replacement therapy and vaccination with both 13-valent pneumococcal conjugate vaccine (PCV-13) and 23-valent pneumococcal polysaccharide vaccine (PPSV23), Haemophilus type b conjugate vaccine and Neisseria meningitides conjugate (Men A,C,W,Y) or subcapsular protein (MenB) vaccine. Patients require repeated vaccination and recurrent determination of the antibody response. However, a fatal pneumococcal meningitis despite PCV-13 vaccination 6 weeks before and a satisfactory IgG response to vaccine antigens in a 7 year-old girl with IRAK-4 deficiency [45]. Thus, the vaccine strategy is not sufficient to prevent IPD in high-risk patients because the antibody response against vaccine antigens could not ensure the protection against natural exposure to *S. pneumoniae*. Chronic mucocutaneous candidiasis disease (CMCD) is characterized by impaired IL-17 immunity, which leads to an increased susceptibility to recurrent and persistent infections of skin, nails and mucosae caused by *Candida species* [46]. The majority of CMCD cases are due to heterozygous STAT1 gain-of-function mutations (GOF). However, other genes associated with CMCD have been identified, namely: STAT3, CARD9, AIRE, IL-17RA, IL17RC, IL17F, CLEC7A and TRAF3IP2. CMCD is not only associated with localized fungal infections, but also with bacterial and viral infections, invasive fungal infection, autoimmunity and cancer. In a cohort of 274 patients with STAT1 GOF mutations, Toubiana et. all reported localized and disseminated disease caused by BCG vaccine and severe disease due to live viral vaccine (smallpox and measles) [47,48]. Inactivated vaccines can generally be administered, while live attenuated pathogens are contraindicated.

4. Vaccination in innate immunity deficiency (Table 1)

4.1. Phagocytic defects

Patients affected by inherited disorders of phagocytes show an increased susceptibility to bacterial infections, especially to *Staphilococcus aureus, Serratia marcescens*, *Nocardia spp*, *Burkholderia cepacia* and fungi as *Candida and Aspergillus*. The prototype of these disorders is the Chronic Granulomatous Disease (CGD) [49]. Although preventive strategies for most infections that occur in this disorder are not available, active immunization policy is highly recommended. Even in the absence of controlled trials, vaccines with inactivated germs are considered useful, safe and well tolerated [6]. Conversely, as for the administration of vaccines with live viruses, previous evaluation by an Immunologist should be sought. In particular, while patients affected by CGD or congenital neutropenia are capable to respond properly to antigenic stimulation of live viruses vaccines, in a few cases affected by Leukocyte Adhesion Deficiency (LAD) or Chediak-Higashi syndrome (CHs), which is characterized by a failure in releasing the cytolytic granules, severe side effects have been reported as a consequence of the impairment of cell mediated and cytolytic activity [50,51]. Furthermore, it has been reported that CGD patients display significantly lower antibody titers against measles and not fully characterized abnormalities of the B-cell compartment, hence a suspect defect in long-term maintenance of the memory response [52]. An increased risk of bacterial complication of viral infections (such as staphylococcus infections on varicella lesions) should be considered in patients with neutropenia, so that, with the exception of LAD or CHs, viral vaccines are recommended in those patients.

As for attenuated live bacterial vaccines, an increased risk to develop a disseminated form of Mycobacteriosis following BCG vaccination has been reported even a long time after the vaccination [53,54]. Multiple BCG reactivations can also occur [55]. Several studies show that 62–75% of the CGD patients with mycobacterial complications had BCG-related disease [56]. Conversely, the risk of disease caused by environmental mycobacteria seems very low. Therefore, BCG vaccination is contraindicated in patients with a diagnosis of CGD and needs to be delayed in their newborn siblings. Despite the lack of data in the literature, live *Salmonella typhi* vaccines should be avoided, due to the high occurrence of such infections in CGD patients [57]. While inactivated *Salmonella thyphi* vaccines can be used. *Aspergillus fumigatus* is a common cause of infection in CGD patients, but unfortunately no specific vaccine is currently available for this pathogen. However, in a mouse model of CGD a long-lasting antifungal protection leading to the disease control was successfully achieved through the vaccination with purified fungal antigens that can activate CD4+ T cells, suggesting a new potential preventive approach for this condition [58].

4.2. Complement deficiency

Complement deficiency (CD) is a group of rare primary immunodeficiencies characterized by a high susceptibility to invasive bacterial infections, mainly caused by encapsulated pathogens as *Streptococcus pneumoniae, Neisseria meningitidis* and *Haemophilus influenza*; immune dysregulation and autoimmunity [6,59]. Different degrees of severity and type of infections have been reported within the three major activation pathways, namely the classical pathway (CP), the alternative pathway (AP) and the lectin pathway (LP). Since CP components are essential for the response against encapsulated bacteria, the spectrum of infections observed in these patients is similar to that observed in patients affected with other primary B-cell disorders. Deficiency in the LP, also known as Mannan-Binding Lectin (MBL) pathway, is usually asymptomatic or responsible for airways or skin recurrent bacterial infections. Chronic cryptosporidial diarrhea, meningococcal meningitis, recurrent herpes simplex infections have also been reported. Patients diagnosed with the extremely rare deficiency of ficolins suffer from multiple and precocious lower respiratory tract infections and recurrent warts. Deficiencies in either factors involved in the AP (i.e. properdin, factor B and D) or proteins involved in the terminal sequence (i.e. C5, C6, C7, C8 and C9) are mainly associated with a significant risk to develop meningococcal disease (7000- to 10,000-fold higher risk). In particular, it has been estimated that nearly 50% of subjects lacking a terminal complement component had an invasive meningococcal disease in their life with a high risk of relapse within one month after the first infection, suggesting that the infection itself does not provide full protection. Thus far, no significant adverse events related to vaccines have been

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reported in CD patients. The occurrence of post-vaccine immunocomplex-mediated glomerulonephritis has been described in a patients with C2 deficiency who had received the first dose of the combined vaccine with purified antigens [60]; but, the presence of specific antigens was not detected in glomerular immunocomplexes [60]. Moreover, the occurrence of glomerulonephritis has been described in C2 deficient patients as well, without correlation with previous vaccination.

Concerning the effectiveness of vaccination, few studies are available in patients with CD. The serum bactericidal and opsono-phagocytosis activity of patients with CD, who had received an anti-meningococcal tetravalent polysaccharid vaccine (MPSV), were similar or only slightly lower than those of healthy subjects. However, a significantly increased risk of meningococcal disease persisted in the years following the vaccine administration, especially in the cohort of children who had developed a lower antibody titer [61,62]. A subsequent study, performed on 22 C2-deficient patients, who had received a tetravalent polysaccharide vaccine [63] reported a normal antibody response against the serogroups C, Y and W, but lower against the serogroup A. Based on these observations, all vaccines, including viral vaccines, can be considered safe and sufficiently immunogenic. In particular, conjugate vaccines (pneumococcal, anti-haemophilus influentiae and anti-meningococcus) are strongly recommended in patients suffering from both early component and late component deficiency. Additional immunization against these pathogens is indicated: a booster dose of tetravalent conjugate meningococcal vaccine every 3 years for 2 month- to 6 year- old patients, or every 5 years for patients older than 6 years of age [6]. Furthermore pneumococcal conjugate vaccine (PCV13) should be followed by pneumococcal polysaccharide 23 vaccine (PPV23) 8 weeks later, to retain protection levels of antibodies [1,64,65].

5. Vaccination in syndromic immnodeficiencies (Table 2)

5.1. Hyper IgE-syndrome

Hyper-IgE syndrome (HIES) is characterized by eczema, mainly at birth or within the first years of life, severe cutaneous infections and skin abscesses, pyogenic pneumonias with tendency to pneumatocele and mucocutaneous candidiasis. Lymphadenitis, sinusitis, otitis, arthritis, osteomyelitis and sepsis are common as well. Most cases are sporadic, but autosomal dominant and recessive forms are mainly due to mutations of STAT3 gene (AD-HIES) and of dedicator of cytokinesis 8 gene (DOCK8) or PGM3 (AR-HIES) respectively. Few autosomal recessive cases caused by Tyk2 mutations have been identified as well [66–68]. STAT3 signaling is required for the differentiation of naive T cells into Th17 lymphocytes that defend the host against extracellular pathogens and fungi which explains the high susceptibility of HIES STAT3 patients to these pathogens. Conversely, DOCK8 protein is involved at multiple stages in T cell development. Viral infections, mainly due to Herpes simplex are frequently observed in these patients. Common pathogens are *Staphylococcus aureus, Haemophilus influenzae, Streptococcus pyogenes* group A, *Pseudomonas aeruginosa, Escherichia coli.* Chronic candidiasis of mouth and nails is frequent, together with invasive infections caused by *Candida, Aspergillus, Criptococcus.* Some cases of *Pneumocystis jiroveci* pneumonia and nocardiosis have also been described. In HIES patients all killed, inactivated and recombinant vaccines are recommended. Many authors demonstrate a variable capacity to produce protective antibody response in these patients [69,70]. In particular, the administration of two doses of conjugate vaccines (13-valent pneumococcal and tetravalent anti- meningococcal Men A-C-W-Y vaccines) at 12-month interval may be useful. Live attenuated viral vaccines can be used without risks in AD-HIES patients. Conversely, live vaccines should not be administered in HIES patients with DOCK8 or PGM3 mutations with signs of T immune defects, as evaluated by CD4+ T cell counts $\geq$500 cells/μl, CD8+ T cells $\geq$200 cells/μl and normal T cells response to mitogen. Conversely, live attenuated bacterial vaccines (BCG and Salmonella typhi vaccines) are contraindicated because of the common association with a functional defect of anti- bacterial response.

5.2. Wiskott-Aldrich syndrome

Wiskott-Aldrich syndrome (WAS) is a X-linked recessive disorder, characterized by thrombocytopenia with small platelets, eczema, recurrent infections, increased risk of autoimmunity and malignancy. It is caused by mutations in the WAS protein (WASP) gene. Patients with WAS show a progressive immune impairment over time, characterized by lymphopenia, hypogammaglobulinemia and reduction of antibody response in particular against polysaccharidic antigens. Increased risk of encapsulated bacterial but also viral and fungal infections has been described. Among viruses, Herpes simplex type 1 and 2 are frequent and associated with recurrent yet disseminated infections. Poxvirus and warts, usually non responsive to common treatments, are described. Candida and *Pneumocystis jiroveci* infections are frequent, too.

Killed, inactivated and recombinant vaccines are all recommended, using both the unconjugated and conjugated forms as

Table 2
Vaccination in syndromic immunodeficiency.

TDP	IPV	Hib	HBV	HPV	Influenza	Pneumococcus	Meningococcus	MMR	Rotavirus	BCG Varicella	S. typhi
Complete Di George	°No	°No	*Yes	°No	°No	*Yes	*Yes	*Yes	No	No	No syndrome
Partial Di George syndrome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	&Yes	&Yes	No
Ataxia-Telangiectasia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	&Yes	No data	No available
Wiskott-Aldrich syndrome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
Hyper IgE syndrome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	&Yes	&Yes	No
IPEX syndrome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No data available	No data available	No data available
APECED syndrome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No data available	No data available	No data available

1000 CD4+ cells/microliter between 1 and 6 years, at least 1500 cells/microliter under one year of life (*Red Book, 29th Edition 2012, Report of the Committee on Infectious Diseases*).

° Not recommended: these vaccines are safe but probably ineffective.

* May be administered, the response to these vaccines is likely to be poor.

& Can be administer only if T CD4+ lymphocytes> = 500 cells/microliter, T CD8 + lymphocytes > = 200 cells/microliter and T lymphocytes mitogen response is normal. Center for Disease Control and Prevention recommends higher CD4+ levels if children are under 6 years: al least.

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appropriate. In particular patients aged 2–5 years should receive 1 dose of 13-valent pneumococcal conjugate vaccine (PCV13) if they have received 3 doses of PCV (either 7-valent PCV [PCV7] or PCV13) before age 24 months and 2 doses of PCV13 (8 weeks apart) if they have received an incomplete schedule of ≤2 doses of PCV7 (PCV7 or PCV13) before age 24 months [6]. Live attenuated viral and bacterial vaccines should not be administered, as a defective number or function of T lymphocytes is common in these patients [71].

5.3. Ataxia-telangiectasia

Ataxia-telangiectasia is an autosomal recessive disorder caused by mutations of ATM gene located on chromosome 11 that is involved in DNA repair mechanisms. The defect induces a high fragility of DNA, which leads to frequent translocations, inversions and breakages of chromosomes. The first manifestation is the appearance of progressive cerebellar ataxia over the first years of life; mucocutaneous and ocular telangiectasia generally appears afterwards, especially on the face and on the folds of knees and elbows. These patients show increased susceptibility to respiratory infections over time, with high risk of bronchiectasis or chronic obstructive pulmonary disease. The increased susceptibility to infections can also be due to "mechanical" causes (e.g. ab ingestis pneumonia). Encapsulated germs, especially *Haemophilus influenzae, Streptococcus pneumoniae* and *Pseudomonas aeruginosa*, are responsible for recurrent bacterial infections. Gastrointestinal infections/infestations are frequent too. Immunological impairment is the consequence of errors in VDJ recombination of T cell receptor (TCR) and/or B cell receptor (BCR). In the case of a severe reduction of CD4+ T cells, prophylaxis with cotrimoxazole against *Pneumocystis jiroveci* is mandatory. Patients can safely receive killed, inactivated and recombinant vaccines. Despite the reduced specific antibody production against polysaccharides, conjugated vaccines against *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis* are effective and thus recommended. Live attenuated viral vaccines can be administered only when CD4+ T cells are ≥500 cells/μl, CD8+ T cells are ≥200 cells/μl and T cells response to mitogen is normal [72,73].

5.4. Di George syndrome

Di George syndrome, also termed as chromosome 22q11 deletion syndrome or CATCH syndrome (Cardiac anomalies, Abnormal facies, Thymic hypoplasia, Cleft palate, Hypocalcemia) is due to an embryogenetic disorder from the third and fourth branchial pouches. Di George syndrome may be sporadic or have an autosomal dominant inheritance. Most cases display a "partial" DiGeorge syndrome with residual thymus, milder T lymphocyte abnormalities and lymphopenia. Humoral response is generally normal. Only 1% of patients are affected by the "complete" form with absence of thymus. As this sign is typical of Severe Combined Immunodeficiency (SCID) children, these PIDs share the same recommendations. All live attenuated viral and bacterial vaccines are contraindicated because of the potential risk of vaccine-related diseases. Conversely, vaccines against capsulated germs and inactivated influenza vaccine are recommended [19].

As to the "partial" syndrome, the same recommendations observed in partial defects of T lymphocytes are to be followed. Vaccines against *Streptococcus pneumoniae, Haemophilus influenzae* and *Neisseria meningitidis* and influenza are recommended. Live attenuated viral vaccines can be administered if CD4+ T cells are ≥500 cells/μl, CD8+ T cells are ≥200 cells/μl and T cell response to mitogen is normal. If these criteria are not satisfied, delaying the vaccination with immunological monitoring is advised. The Center for Disease Control and Prevention recommends even higher CD4+ levels in children below the age of 6 years, namely: CD4+ ≥1000 cells/μl between 1 and 6 years and ≥1500 cells/μl under one year of life [74].

5.5. IPEX syndrome (Immune dysregulation, polyendocrinopathy, enteropathy X-linked)

IPEX syndrome is a recessive X-linked disorder, characterized by immune dysregulation, polyendocrinopathy, dermatitis and enteropathy since the first months of life. It is caused by mutations of FOXP3 gene that has a key role in the development of regulatory T cells. Patients can be more susceptible to infections (sepsis, meningitis, osteomyelitis, pneumonia) caused by Staphylococcus, Candida and CMV, probably due to modifications in cutaneous and gastrointestinal barriers. In IPEX patients killed, inactivated and recombinant vaccines can be administered [75]. However, additional studies on the immune response to these vaccines are required. No data are available on live attenuated vaccines, suggesting that each patient will require a complete immunologic evaluation before administering these types of vaccines.

5.6. APECED syndrome (autoimmune polyendocrinopathy-candidiasis-ectoderma dystrophy)

APECED syndrome is also known as autoimmune polyglandular syndrome type 1 (APS1). It is due to the mutation of AIRE (autoimmune regulator) gene, which is located on chromosome 21 and is inherited as an autosomal recessive trait. The gene product regulates nuclear transcription responsible for immune self-tolerance. When the gene is mutated, thymic suppression of lymphocyte clones specific for self molecules does not occur, causing high risk of autoimmunity. Patients are prone to viral and bacterial infections. Most patients have normal levels of immunoglobulins and a good response to vaccines. All killed, inactivated and recombinant vaccines are safe [66]. Live attenuated vaccines are at present contraindicated for the lack of studies.

6. Vaccination in secondary immune deficiencies (Table 3)

Secondary immune deficiencies are a wide and heterogeneous group of disease affecting immune system as a consequence of various conditions: infectious diseases (mainly HIV infection), hematological malignancies and cancers, metabolic disorders, treatment with immunosuppressive, anti-inflammatory or biological drugs. The impairment in immune response may be at various stages with different degree of severity. It involves multiple mechanisms of the innate and adaptive immunity, thus accounting for the susceptibility to different types of pathogens depending on the underlying immune defect and on the time and the extent of immunosuppressive therapy. Criteria have been defined to distinguish high- or low-level immune impairment in the different disease entities among SID patients. (The Advisory Committee on Immunization Practices, (ACIP) or IDSA). Numerous small and medium-sized studies, as well as meta-analysis clearly show that vaccination with influenza and inactivated vaccines can be safe and effective and can reduce the healthcare related costs. However, randomized controlled studies of large populations are not available in most instances. Most authors recommend vaccination after evaluating risk/benefit ratio on the basis of the patient's clinical history and laboratory tests.

6.1. Vaccination and chemotherapy

One of the major side effects related to the use of chemotherapy is the patient's immunosuppression that lasts for the entire period of treatment up to 6–12 months after suspension. This results in

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Table 3
Vaccination in secondary immunodeficiency disorders.

	TDP	IPV	Hib	HBV	HPV	Influenza	Pneumococcus	Meningococcus	MMR Varicella	Rotavirus	BCG S. typhi
Pediatric haematology and oncology patients during chemotherapy	¨Yes	¨Yes	¨Yes	¨Yes	No data	¨Yes	¨Yes	¨Yes	No	No	No
Pediatric haematology and oncology patients after chemotherapy	[1]Yes	[1]Yes	[1]Yes	[1]Yes	[1]Yes	[1]Yes	[1]Yes	[1]Yes	Yes^	No data available	No data available
HSCT recipients (autologous or allogenic)	[2]Yes	[2]Yes	[2]Yes	[2]Yes	[2]Yes	[2]Yes	[2]Yes	[2]Yes	Yes§	No	No
Anatomical/Functional Asplenia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No data available
Biological drugs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	[3]Yes	No data available	No data available
HIV	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	[4]No	[4]No	No

Footnotes: Pneumococcal Vaccines
PCV13 (1 dose) followed by PPV23 (1 dose at least 8 weeks after PCV13 and a booster 3–5 years later) in the case of anatomical/functional asplenia and congenital/acquired immunodeficiency
PCV13 (1 dose) followed by PPV23 (1 dose at least 8 weeks after PCV13) in the case of complement deficiency, TLR 4 and properidin deficiency, hematopoietic stem cell transplant, immunosuppression due to organ transplant, chemotherapy, high dose steroids, leukaemia, lymphoma, multiple myeloma and diffuse neoplasia.
¨ Do not administer in the case of lymphocytes count < 1.0×10^9/L.
[1] Administer a booster dose 6 months after the end of chemotherapy.
^ Administer varicella vaccine only in patients in remission for at least 1 year.
[2] Administer 6 months after stopping any immunosuppressive therapy.
§ Do not administer within 24 months after SCT, up to 3 months after immunosuppressive therapy or in the case of GVHD.
[3] Consider al least one month after stopping of therapy according to patient immune system function.
[4] Consider in HIV asymptomatic patients with CD4+ T >200 cells/μl, if older than 5 years, or ≥15% of lymphocytes if children below the age of 5 years.

the disappearance of vaccination immunity in patients who had completed the vaccination schedule before starting chemotherapy [76,77]. The incidence of the lack of protective antibody titers, measured 6–12 months after chemotherapy, varies depending on the type of vaccine: it is greater for HBV (approximately 50% of patients), whereas it is lower for measles, mumps, rubella (between 20% and 40%) and diphtheria-tetanus-polio (between 10% and 30%) [78–80]. In addition, levels of immunoglobulins normalize within weeks after the end of chemotherapy whilst the functional response of T cells against antigens such as Cytomegalovirus, Herpes Simplex Virus 1, Varicella-Zoster, Candida, Tetanus and Diphtheria recovers in a year or more after treatment [80]. The correlation between the disappearance of vaccination immunity and the type of cancer (acute lymphoblastic leukemia vs acute myelogenous leukemia vs solid tumors) is not clear. A recent study has shown that the recovery of new transitional B cell and naïve B and T lymphocyte occurs rapidly, while the recovery of memory B and T cells is slower and may be incomplete up to 5 years after the end of treatment especially in the case of high intensity regimens of chemotherapy. It is obvious that appropriate vaccination strategies can reduce complications arising from vaccine preventable infections, however, some precautions should be taken in relation to the state of immunological impairment of oncology patients. In particular, the risk–benefit ratio should be considered for each vaccine as well as the correct timing, in order to both avoid any vaccine diseases and to allow the patient's immune system to mount an adequate antibody response.

- Vaccination during chemotherapy

The major drawbacks of administering vaccinations during chemotherapy are the potentially suboptimal antibody response, resulting in reduced protective effectiveness on one side and the risk associated with live vaccines on the other. However, in this period patients show an increased susceptibility to vaccine-preventable infections.

Regarding the indication to vaccinations, the quality of evidence in support of the recommendations is fairly low because of the lack of methodologically strong studies.

In general, during chemotherapy, vaccines containing inactivated organisms or purified antigens are not contraindicated [81–88]. In contrast, vaccination with live attenuated viruses are contraindicated to avoid risks of vaccination disease and/or for lack of data of effectiveness [89,90]. Vaccination is recommended when there is both a favorable cost/benefit ratio of the desired protective effect and the patient's immune system has the ability to mount an adequate vaccine response. Currently this ratio is known to be positive for vaccinations against hepatitis B and against influenza with inactivated virus. Conjugate pneumococcal vaccine should be administered at diagnosis and inactivated influenza vaccine should be administered annually [6]. In any case, the immunization of patients, when considered useful, should only be done during the low intensity phase of chemotherapy regimen, as indicated by a lymphocyte count > 1000/mm3, that allows the patient to mount an adequate immune response and/or reduce the risk of side effects. Administration of live attenuated virus vaccines is contraindicated.

- Vaccination after chemotherapy

Regarding the indication to vaccinations after stopping chemotherapy, the quality of evidence is better. The previously acquired immunity does not appear to be completely lost [80,91,92] and most authors agree that the interval of 6–12 months is adequate to achieve a sufficient immune recovery, allowing patients to be protected and to contribute to herd immunity. Revaccination or administration of a booster dose either 6 months after the end of chemotherapy for vaccines based on proteins, extracted cellular components or obtained by recombinant DNA or after 6–12 months for live attenuated vaccines based on viruses has been proved effective in bringing protective antibody high titer values in almost all patients, with no significant side effects [89,93–95]. With regards to varicella zoster virus, vaccination may be considered in patients in remission for at least 12 months [90] As for capsulated bacteria (meningococcus, haemophilus influenza and pneumococcus), vaccination is indicated in patients with surgical or post-chemotherapy functional asplenia (eg. splenic radiation therapy) in order to prevent meningitis and sepsis [87,93,96]. Differently from other vaccinations, inactivated influenza vaccine is already recommended from 3 months after the end of chemotherapy [97]. There is no need to assess antibody titers either before or after the revaccination program.

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6.2. Vaccination and stem cell transplant

The loss of vaccine immunity that occurs after SCT depends on:

- Strength of pretransplant immunity of the patient and the donor's immune status;
- Age of the patient at the time of transplantation,
- Combination of pretransplant chemotherapy regimens and/or radiation therapy;
- Occurrence of GVHD;
- Immunosuppressive therapy following transplantation.

The risk of losing the vaccine immunity is similar after allogeneic and autologous SCT.

Up to now, there are only limited data regarding the effectiveness of vaccines in patients undergoing allogeneic haematopoietic stem cell transplantation. The antibody titer against the vaccine antigens, (eg. tetanus, polio, measles, mumps, rubella) is reduced after HSCT in a period of time comprised between 1 and 10 years. The immune response to the vaccine is usually low in the first 6 months after SCT. The count of B-cells, takes 3–12 months to return to normal values. Furthermore, newly generated B cells often show defective Ag-specific response during the first year after transplantation, due to a limited capacity of naïve B cells to undergo isotype switching and somatic mutations [98]. The majority of circulating T cells in the first year after transplantation are T memory/effector, derived from the graft and able to respond to antigens encountered by the donor before transplantation. The naive T cells capable of responding to new antigens are generated only 6–12 months after transplant and this occurs earlier in young children than in older ones. A better response to vaccination has been demonstrated in the cases in which donors themselves have been immunized against hepatitis B, tetanus, Hib and with pneumococcal conjugate vaccines [99]. Vaccines containing inactivated organisms or purified antigens, have a good safety profile and are not associated with an increased risk of side effects compared to healthy patients. They should be considered in every single case and should be given 6 months after stopping any immunosuppressive therapy. Three doses of DTP-Polio-Hib-HBsAg, separately or in combination according to age (hexavalent can be used up to the 7th year), 2 doses of conjugate pneumococcal vaccine, 2 doses of MenB and 2 doses of conjugate Men A,C,W,Y vaccine should be given. Inactivated influenza vaccine should be given annually [6]. Vaccines containing live organisms may cause significant disease in immunocompromised patients and should not be used within 24 months from SCT or in patients with GVHD or immunosuppressive therapy ongoing [100].

Two doses of MPR and varicella vaccines should be given 24 months after HSCT, provided that the last Ig infusion was given at least 11 months before, no GVHD is present and immunosuppressive therapy has been stopped at least 3 months before [101].

Inactivated influenza vaccine is recommended for all SCT patients at least 4–6 months after SCT [6,11,101]. Stem cell or BM donor who has not received recommended vaccinations should be vaccinated for his/her own health; vaccination of donor aimed to the recipent's benefit is nor recommended. Vaccination of donor with live vaccines (MPR, varicella, zoster) should be avoided within 4 weeks of donation [6].

6.3. Solid organ transplant

Individuals with chronic or end-stage organ diseases and solid organ transplantation candidates, should receive all vaccinations as appropriate for age, and immune status based on the annual immunization schedule for immunocompetent people before entering the waiting list for transplantation. Transplanted patients should receive 2 doses of PCV13 2–6 months after transplantation if not administered before. Inactivated vaccines should be given 2–6 months after the organ transplant, according to the vaccination schedule considering the state of immunosuppression. Live vaccines should be avoided; there are no data on safety and effectiveness except for varicella in non-immune children undergoing liver or kidney transplant and no signs of immunosuppression and rejection [6].

6.4. Vaccination and asplenia

Individuals with anatomic or functional asplenia (sickle cell anemia, irradiated subjects, thalassemia, Gaucher, etc.) have an increased risk of fulminant bacteremia associated with a high mortality rate. *Streptococcus pneumoniae* is the most common pathogen causing septicemia in children with asplenia, followed by *Haemophilus influenzae* type b, *Neisseria meningitidis, Escherichia coli, Staphylococcus aureus,* and gram-negative bacilli such as *Salmonella* species, *Klebsiella* species and *Pseudomonas aeruginosa.* These patients are at increased risk of fatal malaria and severe babesiosis. The risk of invasive bacterial infection is higher in the first years after surgical splenectomy and in younger children than in older ones. All vaccines are safe and probably effective and none is contraindicated except live attenuated influenza vaccine in patients with sickle cell disease [6]. Pneumococcal conjugate and polysaccharide vaccines (Hib vaccine and meningococcal conjugate) are essential for all children with asplenia and must follow the schedule of healthy subjects. In general, when planning an elective splenectomy all these vaccines should be administered (if not already practiced) at least 2 weeks prior to surgery [27]. PPSV23 should be administered to asplenic patients aged $\geq$2 years at least 8 weeks after PCV13 and a second dose of PPSV23 should be administered 5 years later. Quadrivalent meningococcal vaccine MCV4 should be administered to patients aged $\geq$2 months with a revaccination every 5 years[6].

6.5. Vaccination and steroid therapy

Children receiving either a dose of prednisone (or equivalent of other steroids) equal to or more than 2 mg/kg/day or a total dose of 20 mg/day if they weigh mote than 10 kg, must not be vaccinated with live viruses before 2 weeks if they have undergone therapy for less than 14 days, or 4 weeks if they have undergone therapy for more than 14 days.

In individuals using:

- steroids at low or moderate doses (<2 mg/kg) for less than 2 weeks
- steroids physiological maintenance doses (replacement therapy)
- topical, intra-articular, conjunctival steroids or steroid aerosol (unless it is suspected systemic immunosuppression), all the necessary vaccinations can be carried out during treatment, including those with live attenuated viruses[27].

6.6. HIV

HIV disease is currently the most frequent secondary immunodeficiency and is characterized by profound T-cell lymphopenia, which is due to several mechanisms: HIV-induced apoptosis, viral cytopathic effect, and apoptosis secondary to immune activation. The immunological profile of HIV infection is peculiar. In fact, patients show a condition of hypergammaglobulinemia and a T cell defect that negatively affects the development of specific antibody responses to various T cell dependent antigens, in particular encapsulated bacteria [102]. In HIV patients, especially those with CD4+

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T-cell count lower than 200 cells/mmc, opportunistic infections as *Pneumocystis jiroveci* pneumonia, histoplasmosis, toxoplasmosis and coccidioidomycosis are common. Recommendations differ according to the severity of the clinical condition of each patient. In particular, live vaccines should be considered in HIV asymptomatic patients with CD4+ T >200 cells/μl, if older than 5 years, or ≥15% of lymphocytes if children below the age of 5 years.

Conversely, live vaccine are contraindicated in HIV patients showing high immune suppression, namely: CD4+ T <200 cells/μl, if older than 5 years, or <15% of lymphocytes, if children below the age of 5 years. All inactivated vaccines should be given according to schedule for immunocompetent people, vaccines against *Haemophilus influenzae*, PCV, PPSV23 inactivated influenza, HBV and *Neisseria meningitidis* are recommended [27].

6.7. Lymphoproliferative diseases

Lymphoproliferative diseases, such as Chronic Lymphocytic Leukemia (CLL) and Multiple Mieloma (MM), mainly affect adult people and are associated with higher risk to develop infections, observed in roughly 50% of these patients, with a mortality rate accounting for up to 20–25% [103]. Susceptibility to infections is multifactorial and may be related to both intrinsic immunological impairment (hypogammaglobulinemia, T- and NK-cells defect, innate immunity dysfunctions) and chemo-immunotherapy treatment regimens. Hypogammaglobulinemia, whose prevalence ranges from 20 to 70%, is the most common immune defect in patients with CLL and worsens even in the absence of disease progression [104]. Similar to B-cell defects, T-cell defects are related to the stage of disease and become more pronounced in advanced stage [105]. Most of the infections are caused by Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Escherichia coli, Klebsiella pneumoniae and Pseudomonas aeruginosa and involve the respiratory tract (bronchitis and pneumonia), the skin, the genito-urinary and the gastrointestinal tract. The use of purine analogues and monoclonal antibodies, such as rituximab and alemtuzumab, has changed the spectrum of involved pathogens so that infections by protozoa, fungi and viruses have become frequent. To date, two main strategies are used in patients with hypogammaglobulinemia who develop recurrent bacterial infections: antibiotic prophylaxis and IgG replacement therapy [104,106,107]. Vaccine guidelines for patients affected by lymphoproliferative disease are not available [108]. Different schedules of vaccination have been suggested in studies carried out on small cohorts of patients. The immunological response is more adequate if patients receive protein, conjugate and adjuvant vaccines. However, it is not clear whether vaccination response differs in patients with active disease in comparison to patients in remission [109,110]. Vaccines containing purified antigens or inactivated organisms, including pneumococcal or seasonal influenza vaccine, have a good safety profile and are not associated with increased risk of side effects compared to healthy patients. Thus, they should be recommended. Live vaccines are generally contraindicated and may be considered only during remission, after stopping chemotherapy and if the level of immunosuppression is low.

6.8. Biological drugs

Biologic response modifiers, such as etanercept, infliximab, anakinra, tocilizumab, are antibodies against proinflammatory cytokines or proteins that target cytokine receptors on lymphocytes. These drugs are used to treat several immune-mediated or autoinflammatory diseases and are often used in combination with other immunosuppressive drugs, such as methotrexate or corticosteroids. Biologic response modifiers are considered highly immunosuppressivetheir immune-modulating effects can last for weeks to months after discontinuation. Other biological drugs such as monoclonal antibodies anti CD-20 (rituximab) and anti CD-52 (alemtuzumab) were firstly introduced for the treatment of hematological malignancies. They were later used to treat refractory autoimmune and inflammatory disorders as well. However, they are also thought to induce secondary immune deficiencies. Removal of CD20+ cells induces an impairment of B cells regulatory function, which results in a severe iatrogenic hypogammaglobulinemia. The acquired hypogammaglobulinemia occurs early after the start of the therapy and affects 15–40% of patients; it is usually transient but in some cases can be prolonged over time. Alemtuzumab induces neutropenia and T, B and NK-cells reduction at the start of the treatment. Such changes can last up to one year after discontinuation of the therapy. Patients treated with biological drugs are at increased risk of infections; they become highly susceptible to specific types of pathogens in relation to the mechanism of action of the drug: viral, bacterial, and/or opportunistic infections may be very common. Vaccination status should be assessed pretreatment and recommended vaccines should be administered.

Recommended vaccines include inactivated influenza vaccine and either PPSV23 for patients aged 2 years or older, after completing PCV13 doses on the routine schedule, or PCV13 for patients aged 6 years or older who had never received PCV13. Inactivated vaccines are recommended during therapy according to the annual immunization schedule. Live virus vaccines are contraindicated during the therapy and for weeks to months after discontinuation [6,27]. Varicella vaccine is strongly recommended for patients in whom alemtuzumab might be planned but it can be given only before starting the therapy.

6.9. Vaccines for international travel

6.9.1. Rabies vaccine

Rabies vaccine is an inactivated vaccine, safe in immunocompromised patients for preexposure prophylaxis in high-risk occupations and postexposure to an infected animal, together with rabies immune globulin or when travelling to endemic area [11]. It is appropriate for use also in HCT recipients. Preexposure rabies vaccination should probably be delayed until 12–24 months after HCT, whereas postexposure administration of rabies vaccine with human rabies Ig can be done any time after HCT [101].

6.9.2. Yellow fever vaccine

There are limited data regarding safety and efficacy of this live attenuated vaccine. It should not be administered to patients with severe humoral, cellular and phagocytic immune defect. Also subjects undergoing to immunosuppressive therapy should not receive this vaccine [27]. When the risk–benefit balance may favor use of the vaccine, it can be considered in patients with minor antibody deficiencies or minimally immunocompromised HIV-infected individuals [6].

6.9.3. Japanese B encephalitis

Although there are no data regarding the safety or immunogenicity of inactivated Japanese encephalitis vaccine in immunocompromised subjects, it is expected to be generally used as with most inactivated vaccines [19].

7. Vaccinations for household members and caregivers of the immunocompromised host

We recommend that all close contacts of a patient with immunodepression are immunized against all vaccine preventable diseases, whenever this is possible. In fact, when the patient is

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forbidden to receive any vaccine, the only way to protect him is through protection of the related people. It is then mandatory to verify that all the contacts are vaccinated: if not already protected, they can receive all killed, inactivated and recombinant vaccines. In particular, in older household members, it is suggested to administer a booster of anti-pertussis vaccine, since protection obtained through a previous infection is likely to decrease over time. The booster should be repeated every ten years [19]. In the case of bacterial infection, such as pertussis or meningitis, the patient has probably been vaccinated, although with less efficacy, or may be protected by replacement therapy. However, isolating the patient, observing all the hygienic measures and, in case of meningitis due to *Neisseria meningitidis or Haemophilus influenzae*, administering antibiotic prophylaxis to the subject are advised.

Regarding live attenuated vaccines, it is important to have some cautions depending on the specific immune defect: if the immunosuppression is high, the risk of transmission of vaccine virus and of development of the disease is real. As reported by the ACIP, live attenuated influenza vaccine should not be administered in people who care for PID patients. Otherwise, the contact with immunosuppressed patients within 7 days after vaccination should be avoided due to the risk of virus transmission [111]. Inactivated influenza vaccine is recommended in household contacts and a booster is required when a long time has passed since last dose [21]. Furthermore, in household contacts, live attenuated polio vaccine is contraindicated, although this vaccine is no longer used in Europe. Measles, mumps, rubella, chickenpox and rotavirus can be administered to family members or other close contacts susceptible to infection, since the risk of developing the disease is extremely rare [21]. Particularly, adults with primary immune deficiency should avoid changing the diaper to children vaccinated with rotavirus in the 4 weeks following the immunization [6]. It is also recommended to verify the immune status against varicella in adult contacts, since they could be not vaccinated and not protected by natural immunization. If a household member had a rash after varicella vaccine, the risk of transmission of infection to an immunosuppressed patient would be very low. The only risky case would be if blisters appeared in correspondence of the inoculation site: in that case it would be better to isolate the patient and to treat him with prophylactic specific immunoglobulins (a single dose within 96 h after exposure) and to treat the contact with antiviral therapy. In the rare case of measles in a household member, patient must receive specific immunoglobulins within 6 days from exposure [6].

In summary:

- *There are no contraindications* for family members to make or continue the vaccinations recommended by the health care system. There is no evidence of human-to-human transmission of the live attenuated virus vaccine strain MMR
- Vaccination against *influenza (inactivated vaccine)* is recommended for the entire duration of the patient care. Live attenuated influenza vaccine should not be administered
- Vaccination against *varicella zoster virus is recommended* for relatives with no personal history
- Vaccination with live polio is contraindicated: *only inactivated vaccine IPV should be administered* [76,101].

8. Conclusions

Whether or not to vaccine immunocompromised patients is a still open question. In the case of many of these disorders, there is a lack of information concerning the immunogenicity and safety of vaccines, mainly because of the variability of the immune defects among subjects with the same disease. The present uncertainty of which vaccines can be given to immunodeficient patients, the fear of adverse events following immunization and the growing social distrust on vaccination, has inevitably lead to a reduced use of vaccines, even in subjects who could safely receive them. Collaborative efforts are needed among healthcare professionels to increase vaccine coverage. Specialists who care for immunocompromised patients share responsibility with the primary care provider for recommending appropriate vaccinations to these patients and their household members. Significant campaigns of education should be provided by specialty centers to the several subspecialists and primary care providers to favour physician's adherence to vaccine recommendations. The vaccination schedule in people with immune deficiency should always contemplate a precise assessment of risk-benefits and specific immunization program should be performed according to the clinical and immunological status for each of these conditions. This document recommends a balance between the need to protect immunocompromised subjects and to avoid the potential adverse effects of the vaccine itself, in order to improve the health and care of these patients. Further studies of vaccine efficacy and safety in specific types of immunodeficiency will be needed to support decisions on indications for vaccination in immunodeficient people.

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