Vaccination of immune compromised children—an overview for physicians

Laure F. Pittet1,2,3 · Klara M. Posfay-Barbe2,3

Received: 29 May 2020 / Revised: 9 February 2021 / Accepted: 17 February 2021 / Published online: 5 March 2021
© The Author(s) 2021

Abstract
Immune compromised children are threatened by a higher risk of infections; some of these are preventable by vaccination. Primary care physicians play a fundamental role in optimising vaccination status. In this narrative review, we present the evidence on vaccine safety and immunogenicity in immune compromised children and discuss in which conditions live-attenuated vaccines can possibly be used. Vaccination schedules differ in some of these conditions, including the use of vaccines with higher antigenic contents (e.g. high-dose hepatitis B vaccine), additional vaccine doses (e.g. 2-dose schedule meningococcal vaccine), more frequent booster doses (e.g. life-long pneumococcal vaccine booster), supplementary vaccines (e.g. meningococcal B vaccine) and use of vaccines beyond the age of usual recommendation (e.g. Haemophilus influenzae type b vaccine after 5 years of age). Serological monitoring is a useful tool for customizing vaccination schedule in immune compromised children, confirming adequate vaccine response and documenting seroprotection (especially against measles and varicella). Finally, verification of vaccination status of all household members can prevent them being vector of transmission of an infection to the immune compromised children. Conclusion: Intensified information strategies are needed to improve trust, rectify perceived risks and improve vaccine acceptability; primary physicians can play a critical role in the latter.

What is Known:
• Physician’s awareness is key to success, since it repeatedly correlates with higher vaccination rates

What is New:
• The vaccination status of immunocompromised children is rarely up-to-date
• Knowing the latest vaccine recommendations is challenging, as they differ for each medical condition and change periodically
• This review summarises the vaccine recommendations for children with compromised immune systems and highlights how paediatricians play a key role in coordinating their application

Keywords Immunosuppression · Immunization · Vaccine-preventable diseases · Paediatrician

Communicated by Nicole Ritz

Abbreviations
IBD Inflammatory bowel disease
HBV Hepatitis B virus
HIV Human immunodeficiency virus
HPV Human papilloma virus
LAV Live-attenuated vaccine
MCV Meningococcal conjugate vaccine
MMR Measles-mumps-rubella
PCV Pneumococcal conjugate vaccine
RSV Respiratory syncytial virus

1 Infectious Diseases Unit, Royal Children’s Hospital Melbourne, Parkville, Victoria, Australia
2 Unit of Pediatric Infectious Diseases, Division of General Pediatrics, Department of Pediatrics, Gynecology & Obstetrics, Children’s Hospital, University Hospitals of Geneva, 6 Rue Willy Donzé, 1211 Geneva, Switzerland
3 Faculty of Medicine, University of Geneva, Rue Michel-Servet 1, 1211 Geneva, Switzerland
Introduction

Protecting immune compromised children against infections is challenging and is a problem of growing importance. Indeed, paediatricians are dealing with more and more patients with deficient immune system, as (i) immunosuppressive therapies are increasingly used in various medical conditions and (ii) the life expectancy of patients with these conditions has substantially raised. The quality of life of these children has also improved over the years: they are able to attend school, travel and be active in their community. This inevitably puts them in contact with others and a variety of infectious pathogens. Moreover, the frequent hospital admission and outpatient visits associated with chronic diseases inevitably increase their risk of nosocomial exposure to pathogens.

Vaccination has repeatedly been recognised as one of the most important and most cost-efficient invention in healthcare [1]. Vaccine-preventable diseases occur more frequently and have a worse outcome in immunocompromised individuals. In a retrospective cohort study of nearly 7000 paediatric solid organ recipients, 15.6% were hospitalised for a vaccine-preventable diseases in the first 5 years following transplantation, an 87-fold higher rate compared with the general population [2]. Worst outcomes are well illustrated by the severity of measles infection, which carries a 40% to 70% fatality rate among immunocompromised patients, despite adequate treatment, up to 35-fold higher compared with immunocompetent hosts [3]. Measles and other vaccine-preventable diseases have recently re-emerged in many regions, mostly due to declining vaccine uptake [4, 5]. As herd protection cannot be relied on, prevention of vaccine-preventable diseases in vulnerable population is key.

The aim of this review is to present an overview of the knowledge in the field, provide tables and references that could help primary care physicians when managing immune compromised children. The following questions are addressed: Which fundamental role do primary care physicians play? Who are immune compromised children? Why are their vaccinations status not up-to-date? Are vaccines immunogenic and safe in immune compromised children? Is the vaccination schedule the same than for healthy children? Which additional vaccines are recommended? Why/when should vaccine-preventable diseases serology be monitored? In which situation can live-attenuated vaccine be administrated? Recommendation for passive immunisation are beyond the scope of this review, but details can be find elsewhere [6, 7].

Which fundamental role does the primary care physician play

The primary care physician plays a critical role in optimising their patients’ protection against vaccine-preventable diseases. The first step is to identify within all their patients which are the ones who could benefit from an enhanced protection. When a child has a new diagnosis, and the immune system is likely to be affected, a quick review of the patient’s vaccination history should be automatic. The ascertainment of the patient’s protection status should rely on checking their records or serologies, as trusting oral recall only can lead to undervaccination or overimmunization [44]. Primary care physicians have a key role to play in discussing with families on the importance of vaccination and reassurance on their safety. In collaboration with a specialist team, a customised vaccination schedule could be planed and anticipated, aiming to immunise, for example, early in the disease process, anticipating periods of higher immunosuppression. This schedule should catch up missing vaccination and add the supplementary vaccines when needed. If recommended, vaccine seroresponses should be checked following vaccination and during follow-up visits.

Another fundamental role of the primary care physician is to ensure that all household members have their vaccinations updated. This “cocooning” strategy is a form of indirect protection for non-immune children, or for those who are unable to be vaccinated. Cocooning is, however, usually not sufficient to fully protect these children, especially those with normal lifestyles.

Who are immune compromised children

Immunodeficiency can be primary or acquired, secondary to a disease, infection, medication, chronic organ failure or other state (e.g. malnutrition, young age) [8]. 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 autoimmune disorders and immune-mediated diseases, allergic disorders or solid organ transplant. The most common conditions encountered in daily practice are listed in Table 1.

Why are immune compromised children’s vaccination status not up-to-date

Although vaccinations seem particularly indicated in this high-risk population, immune compromised children are often less adequately vaccinated than healthy children [9–11]. As vaccines and booster doses are given regularly throughout childhood, most children may not have completed their schedule before the onset of immunosuppression. But the main reasons underlying non-vaccination are summarised in Fig. 1 [11–13]. Moreover, as vaccination guidelines change frequently, and differ for each different medical condition, it is
| Medical condition | How is the immune system affected | Non-live vaccines recommendation | Live-attenuated vaccines recommendation | Additional vaccine(s) recommendation | Serological monitoring | Guidelines, references |
|-------------------|----------------------------------|---------------------------------|----------------------------------------|--------------------------------------|------------------------|-----------------------|
| Primary immunodeficiency disorders | Genetic abnormality affecting various pathway of the immune response | Routine | Permitted in certain situations only | IIV, PCV (± PPSV23), MCV4, MenB if complement deficiency | “Regularly”, but no guidance on how often | ACIP [29], Reviews [43, 51–54] |
| Oncological diseases | Most cancers and their treatment affect the immune system | Routine during chemotherapy | Permitted as of 3m after completion of chemotherapy | IIV (even during chemotherapy), PCV (± PPSV23), MCV | No indication | Could be useful to monitor seroprotection against measles and varicella | CCLG [48], IDSA [22], ACIP [29], AIEOP [55] |
| Hematopoietic stem-cell transplantation | Impaired and immature immune cells, loss of Ig | Revaccination starting 3m to 6m after HSCT (including Hib, regardless of age) | Revaccination permitted in certain condition as of 1.5y to 2y after HSCT | IIV, PCV, 3d (± PPSV23), MCV, 2d | No indication | Could be useful to monitor seroprotection against measles and varicella | CCLG [48], EBMT [49], IDSA [22], ACIP [29] |
| Solid organ transplantation | Immunosuppressive treatment | Accelerated schedule before SOT. Continue after SOT (as of 2m to 6m post-SOT) | Accelerated schedule if > 4w before SOT. Permitted in certain situation after SOT, as of 1y post-SOT | IIV, PCV (± PPSV23) | No indication | Frequent monitoring to guide vaccination; it can also inform on protection against measles and varicella | AST, IPTA [47], IDSA [22], ACIP [29] |
| Asplenia/hyposplenia | Higher risk of fulminant infection with encapsulated bacteria and parasite (highest risk in the first 2y of asplenia but persist life-long) | Routine, catch-up Hib vaccination regardless of age, HBV vaccination highly recommended if frequent transfusion, Anticipate 2w between vaccination and elective splenectomy | Permitted, as of a few days after splenectomy | IIV, PCV (± PPSV23), MCV4 2d 2m apart, then every 5y, MenB | Frequent monitoring of serotype-specific pneumococcal IgG to guide booster doses | IDSA [22], ACIP [29] |
| Sickle cell disease | | | | | | |
| Human immunodeficiency virus infection | Lower CD4+ T-cell | Delay vaccination until viral load < 50 copies/mL and CD4 > 15% for 6m. Use high-dose HBV vaccine (40 μg) in adolescents. Give Hib vaccine regardless of age if not immune. DT booster at least 1×/10y. | Permitted only if CD4 > 200 cells/μL (or > 15–24% in infants and children) for > 6m | IIV, PCV (± PPSV23), MCV4 2d 2m apart | Anti-HBs Ig periodically (if ongoing exposure) | Anti-tetanus, anti-diphtheria | Anti-measles, anti-rubella | PENTA [56], CHIVA, IDSA [22], ACIP [29] |
### Table 1 (continued)

| Medical condition                                      | How is the immune system affected                                                                 | Non-live vaccines recommendation | Live-attenuated vaccines recommendation | Additional vaccine(s) recommendation | Serological monitoring                                                                 | Guidelines, references |
|--------------------------------------------------------|------------------------------------------------------------------------------------------------------|----------------------------------|----------------------------------------|---------------------------------------|----------------------------------------------------------------------------------------|------------------------|
| **Immunosuppressive treatment for rheumatologic, renal, neurologic, gastrointestinal conditions** | Underlying disease with dysregulated immune system, immunosuppressive treatment to control disease activity | Accelerate schedule before immunosuppression, but continue during and after | Permitted if low immunosuppression | IIV PCV (± PPSV23) | No indication but monitoring could guide booster doses and inform on protection, in particular against measles and varicella | IDSA [22] Review [16] |
| **Complement inhibitors** (eculizumab)                | Medication inhibiting the deployment of the terminal complement system, high risk of meningococcal disease | Routine                          | Permitted                               | IIV PCV PCV MCV4 MenB                  | No indication                                                                                   | Review [57]            |
| **Inflammatory bowel disease**                         | Underlying defect in immune system, immunosuppressive treatment                                   | Accelerate schedule before immunosuppression, but continue during and after | Permitted if low immunosuppression | IIV PCV (± PPSV23) | No indication, but monitoring could guide booster doses and inform on protection, in particular against measles and varicella | IDSA [22] Reviews [13, 16] |
| **Nephrotic syndrome**                                | Urinary loss of IgG, oedema, immunosuppressive treatment                                         | Accelerate schedule before immunosuppression, but continue during and after | Permitted if low immunosuppression, VZV vaccine highly recommended | IIV PCV (± PPSV23) | Monitoring of serotype-specific pneumococcal antibody useful to guide booster. Monitor seroprotection against measles and varicella could be useful as well. | ACIP [29] Review [18] |
| **Prematurity**                                        | Immune cell immaturity Low IgG level (not had time to transfer from the mother)              | Accelerated schedule, based on chronological age | Accelerated schedule, based on chronological age | IIV PCV PCV MCV RSV (cf country) | No indication                                                                                   | Review [58] AAP (RSV) [7] |
| **Diabetes mellitus**                                 | Impaired phagocytic and neutrophil function, worsened with inadequate glycaemic control       | Routine, HBV vaccination highly recommended | Permitted                               | IIV PCV (± PPSV23) | Documentation of protection against HBV. No other indication, antibody response to vaccinations seems to be normal overall | ACIP [29] Review [59] CDA (adults) [60] |
| **Renal failure, chronic kidney disease** (including dialysis) | Mild defects in T cell function, immune response impaired by various factor; Ig loss in dialysate | Accelerate schedule before dialysis, but continue during and after, HBV vaccination highly recommended | Permitted                               | IIV PCV (± PPSV23) | No indication, but monitoring could guide booster doses and inform on protection (vaccine responses likely to be impaired) | ACIP [29] Review [18] |
| Medical condition | How is the immune system affected | Non-live vaccines recommendation | Live-attenuated vaccines recommendation | Additional vaccine(s) recommendation | Serological monitoring | Guidelines, references |
|--------------------|----------------------------------|----------------------------------|----------------------------------------|--------------------------------------|------------------------|------------------------|
| Chronic liver disease | Impaired phagocyte function and defects in opsonising antibody, Ig loss in ascites, hyposplenism (with severe liver disease), higher risk of severe superimposed viral hepatitis | Routine, HAV and HBV vaccination highly recommended | Permitted | IIV PCV (± PPSV23) | No indication, but monitoring could guide booster doses and inform on protection | ACIP [29] |
| Chronic heart disease or malformation | Infections may precipitate cardiac decompensation | Routine | Permitted | IIV PCV (± PPSV23) RSV (cf country and underlying disease) | No indication | ACIP [29], AAP (RSV) [7] |
| Chronic lung disease | Increased risk of severe respiratory infections. Severe lung diseases lead to poor mucociliary clearance, bronchiectasis, defects in pulmonary macrophage function | Routine | Permitted | IIV PCV (± PPSV23) RSV (cf country and underlying disease severity) | No indication | ACIP [29], AAP (RSV) [7] |
| Cystic fibrosis Bronchopulmonary dysplasia Asthma | | | | | | |
| Haemophilia | Historical increased risk of transfusion-related transmission of viral infection | Routine, d HAV and HBV vaccination highly recommended | Permitted d | IIV? Insufficient data to date | No indication, adequate response to HBV vaccine could be documented | WFH [61] |
| Malnutrition Anorexia nervosa | Immune response impaired due to malnutrition | Routine | Permitted | IIV | No indication | Review [62] |
| Obesity | Immune response slightly impaired due to overweight (and insulin resistance), higher risk of respiratory infection | Routine | Permitted | IIV | No indication, few studies reported lower vaccine responses | Reviews [63–65] |
| Coeliac disease | Functional hyposplenism (reversible), impaired immune response | Routine, HBV vaccination highly recommended | Permitted | IIV PCV (± PPSV23) ± MCV if hyposplenism confirmed | HBV serology (data suggest poor response to HBV vaccine administered prior to gluten-free diet) | Review [66, 67] |
## Table 1 (continued)

| Medical condition                                      | How is the immune system affected                                                                 | Non-live vaccines recommendation | Live-attenuated vaccines recommendation<sup>a</sup> | Additional vaccine(s) recommendation | Serological monitoring | Guidelines, references |
|--------------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------------------------|---------------------------------------------------|-------------------------------------|-----------------------|------------------------|
| Chronic neurological disease and neurodevelopmental disorder | Decreased protection of airways increases risk of infection, higher risk of complication for some VPD (e.g., influenza, pneumococcus, varicella, pertussis) | Routine                          | Permitted, VZV vaccination highly recommended (higher risk of neurological complications) | IIIV PCV                           | No indication          | Recent article [68]    |
| Inborn errors of metabolism                            | Neurological defect, concomitant immunodeficiency, metabolic decompensation                     | Routine                          | Permitted                                         | IIIV? PCV?                         | Unpredictable vaccine responses, depending on underlying immune defect | Review [21]            |
| CNS anatomic barrier defect (e.g. CSF leak, inner ear dysplasia, or cochlear implant) | Deficient anatomical barrier leads to higher risk of CNS infection                                 | Routine                          | Permitted PCV (± PPSV23)                          | No indication                      | IDSA [22] ACIP [29]    |
| Severe dermatologic conditions (severe eczema, psoriasis) | Chickenpox particularly prone to bacterial superinfection; severe dermatologic possibly require immunosuppressive treatment | Routine                          | Permitted if low immunosuppression, VZV vaccination highly recommended | No indication                      | Review [69]            |
| Parents, close contact of immune compromised individuals | ‘Cocooning’ strategy, to decrease the risk to transmit VPD to the immunocompromised children | Routine                          | Highly recommended if not immune; OPV and smallpox vaccine are the only LAV contra-indicated in close contact | IIIV or LAIV                       | Documentation of immunity against measles and varicella if disease/vaccination history uncertain (or immunise regardless) | IDSA [22] Review [53] |

The table summarises the vaccine recommendations available for various health conditions. Recommendations can differ between guidelines and between countries. In some countries, the cost of some vaccines may not be reimbursed. Recommendation for serological monitoring is rarely discussed in guidelines and the ones presented in this table summarise experts’ advice.

<sup>a</sup>The live-attenuated influenza vaccine should never be given to immune compromised children as they can receive the inactivated influenza vaccine

<sup>b</sup>Effectiveness doubtful, depend on underlying disease and whether IVIG are given regularly

<sup>c</sup>Postpone if lymphocyte count < 1.0 × 10⁹/L. Non-live vaccine permitted during chemotherapy but will not be considered as “valid dose”

<sup>d</sup>Reduce the risk of bleeding by subcutaneous injection, use smallest gauge needle and applying pressure and/or ice for 3–5 min after injection

AAP American Academy of Paediatrics, ACIP Advisory Committee on Immunization Practices, AIEOP Italian Association Paediatric Haematology Oncology, CDA Canadian Diabetes Association, CHIVA Children’s HIV Association, CSP cerebrospinal fluid, d dose, DtaP diphtheria-tetanus-pertussis vaccine, EBMTh European Society for Blood and Marrow Transplantation, HAV hepatitis A virus, HBV hepatitis B virus, Hib Haemophilus influenzae type b, HSC T hematopoietic stem cell transplantation, IDSA Infectious Disease Society of America, Ig immunoglobulin, IIIV inactivated influenza vaccine, IPTA International Paediatric Transplant Association, IPV inactivated poliovirus vaccine, IVIG intravenous immunoglobulins, LAIV live-attenuated influenza vaccine, LAV live-attenuated vaccine, m month, MCV meningococcal conjugated vaccine, MenB meningococcus type B vaccine, MMR measles-mumps-rubella vaccine, NVL non-live vaccine, OPV oral polio vaccine, PCV pneumococcal conjugate vaccine, PPSV23 23-valent pneumococcal polysaccharide vaccine, PENTA Paediatric European Network for Treatment of AIDS, RSV respiratory syncytial virus, SOT solid organ transplantation, VPD vaccine-preventable disease, VZV varicella vaccine, w week, WFH World Federation of Hemophilia, y year
challenging to stay up-to-date with the most recent, specific recommendations [14]. As an example, it was recently reported in patients with inflammatory bowel disease (IBD) that vaccination was the least frequently followed quality of care recommendation [15]. 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% to 90%) [11]. Information and better communication appear to be key components for increasing vaccination uptake; primary care physician usually excels in both, being trusted by and close to the patient’s family (Fig. 2).

Are vaccines immunogenic in immune compromised children

Concern on vaccine effectiveness is often an obstacle to vaccination in immune compromised children; immune response to vaccination can be suboptimal [16]. Vaccine responses may be reduced in both magnitude and durability, explaining the need for repeated monitoring of antibody levels during follow-up. However, even in highly immunocompromised hosts, vaccination may induce at least some immune response that could be beneficial in case of further encounter with the pathogen. Vaccines should therefore be administered despite possible non-responsiveness; in some medical conditions, monitoring of antibody concentration is recommended (Table 1).

Are vaccines safe in immune compromised children

Whereas immunogenicity is an important aspect, vaccine safety is often the main concern of parents and healthcare practitioners. Live-attenuated vaccines (LAV), in particular, are usually avoided in the immunocompromised hosts as they could theoretically induce vaccine-strain infections; these are discussed in detail in a section below. In contrast, non-live vaccines are incapable of causing infection, since they consist in inactivated toxins (protein), in pathogen that have been killed (inactivated) or in only specific segments of the pathogen (subunit, polysaccharides) that may be conjugated to a protein (conjugate vaccine) to enhance the immunological response (Table 2). These vaccines can be given to immunocompromised patient without any safety concerns, as demonstrated in many studies in patients with chronic diseases, e.g. in HIV-infected individuals [17], patients with immunemediated diseases [16], chronic kidney diseases [18] and solid organ transplantation recipients [19]. Therefore, information is critical to clearly explain the expected benefit to the patient.

Proper communication is particularly important for patients with immune-mediated diseases, inborn error of metabolism or solid organ transplantation, for which questions about the inflammation induced by vaccination could play a role in modulating the auto-immune response or inducing a metabolic crisis. Moreover, since the medical conditions of these children will be lifelong, vaccinations cannot be postponed indefinitely. Therefore, in these children, while it is important as for all children to monitor possible side effects of vaccination, the effect of the vaccine on the underlying condition should also be reported, such as signs of graft rejection or flare in disease activity. However, there is increasing data suggesting that concerns regarding the risk of disease exacerbation are unfounded, with numerous studies showing that immunization did not induce significant worsening of underlying disease [16, 19–21].

Is the vaccination schedule the same than for healthy children

The vaccination schedules are usually the same; they slightly differ from those of healthy children in that they may include supplementary vaccinations (for example usually not given beyond a certain age), accelerated schedule, extra doses for primary vaccination, extra boosters, as well as specific
| Pathogen                  | Vaccine type | Vaccine recommendation                                                                 | Rational for serological monitoring                | Test used to measure seroprotection | Level required | Mechanism prevented |
|--------------------------|--------------|----------------------------------------------------------------------------------------|-----------------------------------------------------|-------------------------------------|----------------|---------------------|
| Diphtheria               | Protein      | Booster doses may be required more frequently; accelerated schedule in preterm or before onset of immunosuppression; effectiveness doubtful during cancer treatment and in children with primary immunodeficiency | Monitor vaccine response and guide for booster indication | Toxin neutralisation               | 0.01–0.1 IU/mL | Toxin production |
| Tetanus                  | Protein      |                                                                                        |                                                     | Toxin neutralisation               | 0.1–0.1 IU/mL | Toxin production |
| Pertussis                | Protein      |                                                                                        | No indication                                       | ELISA                              | Not defined   | Mucosal replication |
| Polio                    | Inactivated  | Catch-up regardless of age in some high-risk situation (hypo-/asplenia, HIV, after chemotherapy, after HSCT) | Not routinely indicated                             | Serum neutralisation               | 1/4–1/8 dilution | Viremia |
| Haemophilus influenza b  | Conjugate    |                                                                                        | Could be used to document protection in high-risk situation | ELISA                              | 1 ng/mL (polysaccharide) | Viremia |
| Polio                    | Subunit      |                                                                                        |                                                     | ELISA                              | >100–1000 IU/L (optimal) | Bacteremia |
| Hepatitis A              | Inactivated  | Mainly recommended in travellers or if high risk of hepatitis                           | Not routinely indicated                             | ELISA                              | 20 IU/L        | Viremia |
| Hepatitis B              | Subunit      | Particularly recommended in cases of increased risk of needle-/transfusion-related transmission; supplementary vaccine doses and/or use of vaccine with higher antigenic dose may be required | Monitor vaccine response as poorly immunogenic in immunocompromised individuals | ELISA                              | 10 IU/L (protective) | Viremia |
| Human papillomavirus     | Subunit      | Strongly recommended in all immunocompromised conditions, with a 3-dose schedule regardless of age | No indication                                       | ELISA                              | Not defined   | Mucosal replication |
| Influenza                | Inactivated  | Recommended in all chronic diseases and immunocompromised conditions; clinical studies are ongoing to evaluate the need of high-dose vaccine in certain conditions | No indication                                       | HAI                                 | 1/40 dilution (1/320 dilution in children) | Mucosal replication |
| Pneumococcus             | Conjugate    | Recommended in all chronic diseases and immunocompromised conditions; indication for booster is less clear, mainly indicated in hypo-/asplenic patients | Could be used to guide for booster indication       | Serotype-specific ELISA            | 0.35 μg/mL     | Bacteremia |
| Meningococcus            | Conjugate    | Mainly recommended when complement is affected, in oncological, HSCT, HIV-infected and hypo-/asplenic individuals, with a 2-doses schedule | No indication                                       | ELISA                              | 2 μg/mL        | Bacteremia |
| Measles                  | Live-attenuated | Accelerated schedule finishing at least 4 weeks before onset of immunosuppression. Permitted in some situations during immunosuppression (low immunosuppression, specific criteria for HIV and SOT) | Could be used to document protection in high risk situation | Microneutralisation assay ELISA | 120 mIU/mL | Viremia |

**Table 2** Summary of recommendation for vaccine administration and serological monitoring
conditions for administration of LAV. These are detailed in Tables 1 and 2, and in the following sections.

Recommendations are somewhat different between immunocompromising conditions: they are determined by the individual risk of infection and the data available. Among the various guidelines available, the Infectious Diseases Society of America provides a good overview of the current evidence available and covers most medical conditions (Table 1) [22]. The different national immunisation schedules can also be found online [23].

Which supplementary non-live vaccines are indicated in which situation

Most immune compromised children benefit from protection against pneumococcus, influenza, meningococcus and human papilloma virus (HPV). These vaccines are included in many national guidelines for healthy children as well, so may not necessarily be considered as “supplementary vaccines”.

Invasive *pneumococcal* diseases carry a high mortality rate (11–30%) [24] and are more frequent in immunocompromised individuals, or those with chronic diseases, such as IBD [25], nephrotic syndrome [26] or a-/hypoplastic conditions [27, 28]. The pneumococcal conjugate vaccine (PCV) is usually recommended in healthy children before the age of 5, but also in all medical conditions with immunosuppression, regardless of age. Although some guidelines also recommend to subsequently administer the 23-valent polysaccharide vaccine (PPSV23) to those at high risk [29], many experts disagree, since PPSV23 do not induce memory cells and become less effective after repeated administrations (hyporesponsiveness) [30].

*Influenza* is probably the most common vaccine-preventable diseases leading to hospitalisation, accounting for 3.4% of all critical care admissions in the USA during the flu season [31]. In a retrospective cohort study in paediatric solid organ transplantation recipient, 40% of the hospitalisation for vaccine-preventable diseases were due to influenza infection [2]. Given the high burden of influenza disease, the vaccine is recommended in virtually all immune compromised children, as of 6 months of age. Moreover, preventing influenza also helps preventing secondary pneumococcal infection. Immune compromised children should always receive the inactivated vaccine and not the live-attenuated influenza vaccine (in Europe, the latter is only available in the UK).

*Meningococcal* vaccines are recommended to asplenic patients, HIV-infected individuals, those with complement deficiencies or receiving a treatment affecting the complement (such as eculizumab) [32]. Most guidelines recommend a 2-dose schedule of the 4-valent conjugate vaccine (MCV4), and, when available, vaccination against serogroup B as well (Table 1).
As the risk of malignancy related to HPV is highly increased (up to 100-fold) in immunocompromised individuals [33], a 3-dose schedule is strongly recommended for all. The 2-dose schedule—used routinely in immunocompetent 11–15-year-old individuals—may not be sufficiently immunogenic, reason why the 3-dose schedule should be preferred [34].

**Do immune compromised children need more or higher doses**

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

**High-dose vaccine** For vaccination against HBV per example, use of high-dose vaccine is recommended by some experts in HIV-infected adolescents (and adult), haemodialysis adult, and studies involving adults suggest it could be beneficial for oncological patients, or those with immune-mediated diseases [22]. Another example is the high-dose influenza vaccine being currently evaluated in immunocompromised individuals, including oncological patients, solid organ transplantation recipients and haemodialysis patients [35–37]. Data in paediatric patients, however, is scarce.

**More vaccine doses** Regarding schedule, 3-dose (rather than 2-doses) schedule are recommended for HPV in all immunocompromised condition, and a 2-dose (rather than single dose) schedule is recommended for MCV4 [22].

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

**The rationale behind serological monitoring**

One of the most useful tools for customization of vaccination schedule in immune compromised children is to regularly monitor their serologies [38]. In children receiving chemotherapy for example, there is strong evidence to suggest that antibody concentrations wane more rapidly during treatment [39]. Cut-off values for seroprotection (i.e. correlates of protection) are available for most vaccine-preventable diseases (Table 2), but may vary slightly between laboratories. These measures allow to (i) confirm adequate vaccine response, (ii) guide when to administer a booster dose and (iii) document current protection against vaccine-preventable diseases. The latter is of particular importance for varicella and measles viruses, for which the reported mortality rates in infected immunocompromised hosts are up to 25% and 70%, respectively [3, 40, 41]. For both viruses, absence of seroprotection would require prompt management following contact (intravenous immunoglobulins and/or antiviral therapy), whereas documentation of highly seroprotective titres could suggest a “wait and see” attitude [42]. Physician can therefore inform individually on the risk of severe disease following contact with varicella or measles and provide guidance on what to do if this situation occurs. Regular monitoring of serologies against vaccine-preventable diseases has been adopted by many as an important part of the regular follow-up of immunocompromised patient. Although this test does not measure the other actors of the immune response, it is the only indirect measure of protection available. There is, however, no clear recommendation on when, in whom and how often should serology be assessed (Tables 1 and 2). Annual monitoring of serologies may be indicated in highly immunocompromised patients, or when the immunosuppressing regimen has recently been increased, whereas less frequent monitoring (i.e. once every 5 years) should probably be enough in well-controlled HIV-infected individuals, for example.

**In which situation can live-attenuated vaccines be administered**

When vaccinating immunocompromised individuals, the most important safety issue concerns LAV. They consist in live pathogens that have been ‘weakened’ so that they can still replicate but with difficulty and without having the capacity to cause the disease in an immunocompetent host. Given the fear of a theoretical uncontrolled replication that could lead to severe vaccine-induced disease, LAV are mostly contraindicated in immune compromised children. In patients with severe primary immunodeficiency disease (e.g. severe combined immunodeficiency), LAV carry a significant risk of vaccine-strain infections, which have been reported following the oral rotavirus or poliovirus vaccines, measles-mumps-rubella(MMR) vaccine and bacille Calmette-Guérin vaccine [43, 44]. However, there is growing evidence documenting the safety of immunising immunocompromised hosts with different types of LAV in carefully selected settings.

MMR and varicella vaccines are usually well tolerated in case of milder immunosuppression, such as in children with DiGeorge syndrome (if lymphocyte count is > 500 cells/μL) [43], HIV-infected individuals (if CD4 count is > 200 cells/μL) [45, 46], liver or kidney transplant recipients (strict conditions [47]), after hematopoietic stem cell transplantation [48, 49], or in individuals with immune-mediated diseases on low/no immune suppression [16, 22], including children with nephrotic...
syndrome [50]. MMR and varicella vaccine have indeed the potential to protect patients against threatening pathogen that are endemic or linked with epidemics in many places around the world. However, extra caution should be taken and close safety monitoring is highly recommended following the administration of LAV in any situation when the immune system is affected [22, 47]. In the setting of solid organ transplantation, a consensus of worldwide experts has recommended the following surveillance: (i) education on urgency to seek medical attention in case of new onset of rash or fever within 4 weeks following vaccination and (ii) at least one contact with the patient’s caregiver in the month following vaccination to identify any adverse event that might have occurred [47].

Concluding discussion

As many questions remain, clinical trials are still needed to refine the study of the immune response induced by each vaccine in all immunocompromising conditions to determine whether, when and for whom there is a need for a specific immunisation schedule. Moreover, additional guidance regarding the serological monitoring of vaccine response and persistence of protection is required.

As new vaccines become available and the epidemiology of vaccine-preventable diseases evolves, it is increasingly important for all those caring for children to be up to date with the recent changes to guidelines, in order to improve the usual low uptake of additional immunisations in high-risk groups [51]; physician’s awareness is key, since it repeatedly correlates with higher vaccination rates [11].

Author contribution LFP drafted the initial manuscript. KMPB critically revised the manuscript and both authors approved the final version as submitted.

Funding Open Access funding provided by Université de Genève. LFP is supported by the Swiss National Science Foundation (Early Postdoc.Mobility grant number P2GEP3_178155).

There is no funding source for this review.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare that they have no conflict of interest.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. van Wijhe M, McDonald SA, de Melker HE, Postma MJ, Wallinga J (2016) Effect of vaccination programmes on mortality burden among children and young adults in the Netherlands during the 20th century: a historical analysis. Lancet Infect Dis 16:592–598
2. Feldman AG, Beaty BL, Curtis D, Juarez-Colunga E, Kempe A (2019) Incidence of hospitalization for vaccine-preventable infections in children following solid organ transplant and associated morbidity, mortality, and costs. JAMA Pediatr 173:260–268
3. Kaplan LJ, Daum RS, Smaron M, McCarthy CA (1992) Severe measles in immunocompromised patients. JAMA 267:1237–1241
4. Pittet LF, Abbas M, Siegrist CA, Pittet D (2020) Missed vaccinations and critical care admission: all you may wish to know or rediscover—a narrative review. Intensive Care Med 46:202–214
5. VanderEnde K, Gacic-Dobo M, Diaioso LS, Conklin LM, Wallace AS (2018) Global routine vaccination coverage – 2017. MMWR Morb Mortal Wkly Rep 67:1261–1264
6. Luna MS, Manzoni P, Paes B, Baraldi E, Cossey V, Kugelman A, Chawla R, Dotta A, Rodriguez Fernandez R, Resch B, Carbouelli-Estrany X (2020) Expert consensus on palivizumab use for respiratory syncytial virus in developed countries. Paediatr Respir Rev 33:35–44
7. American Academy of Pediatrics Committee on Infectious Diseases, American Academy of Pediatrics Bronchiolitis Guidelines Committee (2014) Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics 134:415–420
8. Chinen J, Shearer WT (2010) Secondary immunodeficiencies, including HIV infection. J Allergy Clin Immunol 125:S195–S203
9. Feldman AG, Curtis DJ, Moore SL, Kempe A (2020) Underimmunization of pediatric transplant recipients: a call to action for the pediatric community. Pediatr Res 87:277–281
10. Martinelli M, Giugliano FP, Strisciglio C, Uribonas V, Serban DE, Banaszkiewicz A, Assa A, Hojsak I, Lerchova T, Navas-Lopez VM, Romano C, Sladek M, Veres G, Aloj M, Kucinskiene R, Miele E (2019) Vaccinations and immunization status in pediatric inflammatory bowel disease: a multicenter study from the Pediatric IBD Porto Group of the ESPGHAN. Inflamm Bowel Dis
11. Giannattasio A, Squeglia V, Lo Vecchio A, Russo MT, Barbarino A, Carlomagno R, Guarino A (2010) Pneumococcal and influenza vaccination rates and their determinants in children with chronic medical conditions. Ital J Pediatr 36:28
12. Doherty M, Schmidt-Ott R, Santos JI, Stanberry LR, Hofstetter AM, Rosenthal SL, Cunningham AL (2016) Vaccination of special populations: Protecting the vulnerable. Vaccine 34:6681–6690
