

Vaccination in Primary Immunodeficiency Disorders



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Immunocompromised patients have increased susceptibility to vaccine-preventable infections. Thus, vaccination is a critical issue in this population. Vaccines are usually classified as live versus inactivated or subunit (nonviable) vaccines. In general, inactivated vaccines are safe in immunocompromised patients and should be given per the routine schedule except when they are unlikely to have any benefit as in severe antibody deficiency or combined immunodeficient patients and patients receiving immunosuppressive therapy or immunoglobulin replacement. However, viable vaccines usually carry the risk of causing disease, especially in severely immunocompromised patients. Therefore, much greater caution must be exercised with the use of viable vaccines and administration is individualized on the basis of the estimated risk of infections if not vaccinated versus the potential adverse effects of the vaccine itself. In this review, we make clear recommendations on the basis of available evidence regarding both routine and specialized vaccines, viable and nonviable, and the degree of immune compromise in all the categories of immunodeficiency disorders. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:1066-75)

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Immunocompromised patients have increased susceptibility to vaccine-preventable infections. Thus, vaccination is a critical issue in this population. Preliminary immunogenicity and safety tests of vaccines exclude immunocompromised individuals and the heterogeneity of immunodeficiency disorders makes generalization of recommendations regarding immunization difficult. As a result, primary care clinicians usually have concerns

regarding safety and/or efficacy and appropriate use of vaccination in immunocompromised hosts and these individuals may not be adequately immunized.¹ In this review, we make clear recommendations on the basis of available evidence regarding both routine and specialized vaccines according to the severity of immune compromise in the major categories of immunodeficiency disorders. Where evidence is scant or lacking, we apply general principles regarding vaccine composition and immune function along with anecdotal reports and expert commentaries and reviews to formulate general recommendations presented in an accessible format for all clinicians treating immunocompromised patients.

Immunodeficiency disorders can be broadly classified into low and high levels of infection susceptibility (Table I).² Vaccines are usually classified as live versus inactivated or subunit (nonviable) vaccines (Table II). Nonviable vaccines include toxoids, purified polysaccharides, protein-polysaccharide conjugates, and inactivated whole, fragmented, or modified viruses and bacteria. Inactivated vaccines are generally safe in immunocompromised patients, but may differ in immunogenicity according to the level of immune compromise. Some may be truly unnecessary, especially in patients receiving immunoglobulin therapy.³ However, live vaccines are mostly contraindicated in patients with a high level of infection susceptibility and administration is individualized on the basis of the risk of infection if not vaccinated versus potential adverse effects of the vaccine itself.⁴

Primary immunodeficiencies have been classified into 9 categories by the World Health Organization International Union of Immunological Societies.⁵ More than 300 distinct entities are now recognized and grouped into Combined Immunodeficiencies, Syndromes of Immunodeficiency, Predominantly Antibody Deficiencies, Disorders of Immune Dysregulation, Autoinflammatory Disorders, Innate Immune Defects, Phagocytic Cell Defects, Complement Deficiencies, and the so-called Phenocopies. Of course, it is not possible to make specific recommendations regarding immunization practice in each of these more than 300 entities individually. We have organized our review mainly on the basis of this classification. A separate section on “syndromes” has not been included because these disorders have tremendous variation in their degrees of cellular and/or humoral immune compromise. Individual diagnoses in this group may be considered to fall within the category of “Combined Immunodeficiency” or “Antibody deficiency” as appropriate. We have also included a section on patients receiving immunosuppressive therapy. Recommendations regarding the use of various vaccines in the different categories of immunodeficiency disorders⁵ are summarized in Table III. Specific areas are discussed in more detail below.

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Abbreviations used

HIB- Hemophilus influenza type b

MMR- measles/mumps/rubella

SCID- severe combined immunodeficiency

IMMUNIZATION IN DISTINCT CATEGORIES OF PRIMARY IMMUNODEFICIENCY DISEASE

Combined immunodeficiency

Inactivated vaccines are of no value in children with severe combined immunodeficiency (SCID) not only because there will not be adequate response but also because they are usually on immunoglobulin therapy (see below). Individuals with mild combined immunodeficiency who have residual antibody response and who are not receiving IgG could have benefit from inactivated vaccines, so they are recommended.²

Live vaccines usually carry the risk of causing severe disease in patients with combined immunodeficiency. There are many reported cases of chronic rotavirus infection,⁶⁻⁸ vaccine-associated paralytic polio,⁹ and disseminated BCG¹⁰ after the administration of these vaccines in children with combined immunodeficiency. However, live vaccines may be well tolerated in milder syndromes. For example, some studies^{11,12} have shown safety of measles/mumps/rubella (MMR) and varicella vaccines in children with partial DiGeorge syndrome who have a CD4 T-lymphocyte count of more than 500 cells/mm³. Insufficient data are available for other specific mild combined disorders or vaccines. Some extrapolate data from HIV-infected patients, which suggest that a CD4 T-lymphocyte count of more than 200 cells/mm³ or a percentage of more than 15% in children is safe,^{13,14} which was also supported by a study of patients with DiGeorge syndrome,¹⁵ but this requires further investigation.

Antibody deficiency

Minor antibody deficiency such as selective IgA deficiency, specific antibody deficiency with normal immunoglobulins, or IgG subclass deficiency. Although the antibody response to vaccines may be decreased, these patients often still have some protective antibody response and may be vaccinated safely with both live and inactivated agents, with few exceptions. In a review of 68 cases of vaccine-associated paralytic polio occurring between 1960 and 2012, 57% of cases occurred in patients with predominantly antibody deficiencies.^{2,16} Thus, oral polio vaccine should be avoided in these individuals. In patients with minor antibody deficiencies or some other disorders such as ataxia-telangiectasia, response to pure polysaccharide vaccines is poor, but conjugate vaccines are immunogenic and should be administered.¹⁷

Major antibody deficiency such as common variable immunodeficiency and agammaglobulinemia. These patients have more seriously impaired antibody responses and are almost always receiving immunoglobulin therapy. Thus, most routine inactivated vaccines are not necessary or effective. Patients with some residual antibody response and not receiving immunoglobulin therapy could receive inactivated vaccines. Inactivated influenza vaccine is an exception because (1) immunoglobulin preparations may not contain antibodies to the circulating strains and (2) the vaccine may induce some beneficial cellular immunity. Consequently, influenza vaccine is

recommended even in patients with antibody deficiency receiving IgG.^{18,19} Live vaccines such as MMR or varicella are contraindicated in patients with severe antibody deficiencies either because of a higher risk of developing a disease due to deficient antibody response or because of neutralization of the vaccine by therapeutic IgG in most.²⁰

Immune dysregulation, rheumatic or autoinflammatory diseases

Some have raised concern regarding immunization triggering autoimmunity or a flare up of rheumatic disease in genetically predisposed individuals. Additional concern surrounds the frequent use of immunosuppressive therapy in these populations. The former arises from rare case reports of an initial presentation or flare up of systemic lupus erythematosus or rheumatoid arthritis after vaccination.²¹⁻²³ However, some evidence contrary to this idea has also accumulated. Since 1987, many clinical trials examining the safety and immunogenicity of influenza and pneumococcal vaccines in systemic lupus erythematosus or rheumatoid arthritis have concluded that these are safe, albeit usually generating somewhat lower responses, especially if a patient is on immunosuppressive therapy.²⁴⁻²⁸ Viable vaccines are generally considered to be contraindicated in patients receiving immunosuppressive therapy due to the risk for causing serious infection (this will be discussed in greater detail below).

Phagocytic cell defects

These patients should receive all inactivated vaccines according to routine schedules.^{29,30} Inactivated influenza vaccine is especially important in patients with chronic granulomatous disease (CGD) because influenza mortality is increased with staphylococcal coinfection, which is common in these patients.^{2,31}

Live bacterial vaccines, such as BCG and oral salmonella vaccine, should be avoided in patients with CGD and other phagocytic cell defects. Disseminated BCG infection is reported in many patients after vaccination.^{30,32-34} There are no reported salmonella vaccine complications, but it is well known that these patients are more prone to severe salmonella infection.^{2,29}

Live viral vaccines should be given to patients with CGD or cyclic or congenital neutropenia,² whereas they are contraindicated in patients with leukocyte adhesion defects or cytotoxic granule defects such as Chediak-Higashi syndrome because of associated defects in lymphocyte cytotoxic functions.^{35,36}

Innate immune defects

Innate immune defects are a heterogeneous group of disorders characterized by defective cellular responses, cytokine production, or function. Inactivated vaccines are safe and effective in many of these patients, and should be used according to routine schedules. IRAK4- and MyD88-deficient patients are more susceptible to invasive pneumococcal disease, so pneumococcal vaccination is of great importance in these patients (see below).⁵

Patients with congenital asplenia are at increased risk of invasive infections with encapsulated bacteria, so vaccination against pneumococcal, Hemophilus, and meningococcal infections is strongly recommended as for patients with complement deficiency (see below).²

Patients with defects in the IL-12-INF- γ axis have greater susceptibility to intracellular bacterial infections such as tuberculosis and salmonella, so live bacterial vaccines are contraindicated.³⁷⁻⁴¹ Live viral vaccines are contraindicated in diseases

TABLE I. Disorders and conditions associated with increased infection susceptibility²

High increase in susceptibility
• Primary combined immunodeficiency (CID) disorder (such as severe CID or SCID) • Primary severe antibody deficiency such as agammaglobulinemia • Primary defects of innate immunity (including phagocytic cells) • Cancer chemotherapy • Within 2 mo of solid-organ transplantation • HIV-infected patients with a CD4 T-lymphocyte count of <200 cells/mm³ for adults and adolescents or <15% for infants and children • Patients receiving daily corticosteroid therapy with a dose of ≥20 mg (or > 2 mg/kg for patients whose weight is <10 kg) of prednisone or equivalent for ≥14 d • Patients receiving some biologic immune modulators such as TNF antagonists
Modest increase in susceptibility
• Primary mild antibody deficiency such as specific antibody deficiency • Primary complement deficiency • Primary autoinflammatory disorders • Primary disorders of immune dysregulation • Asymptomatic HIV-infected patients with a CD4 T-lymphocyte count of 200-499 cells/mm³ for adults and adolescents or ≥15%-24% for infants and children • Patients receiving a lower daily dose of systemic steroid than for high-level immunosuppression for ≥14 d or alternate-day corticosteroid therapy • Patients receiving methotrexate ≤0.4 mg/kg/wk, or azathioprine ≤3 mg/kg/d

characterized by defects in type 1 INF- α/β pathways.⁴² It is a consensus that all live vaccines are contraindicated in nuclear factor kappa B pathway defects.⁴³

Complement deficiency

The complement system plays a critical role in protecting the body against serious infections with encapsulated bacteria such as *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Neisseria meningitidis*, in addition to some viruses.⁴⁴ Because patients with complement deficiency have intact specific cellular and humoral immunity, all vaccines are safe and effective in these patients. Also, it is generally considered that additional immunization against the specific organisms they are most vulnerable to is indicated (see below).²

Phenocopies of primary immunodeficiency diseases

This is a heterogeneous group of primary immunodeficiency disorders including conditions that present as inherited immunodeficiency not due to germline genetic mutations, but as a result of acquired somatic mechanisms.⁴⁵ These could include somatic genetic lesions, or autoantibodies to immune system components.

Within this group are diseases resulting from defective lymphocyte apoptosis such as somatic mutations in *FAS*, *NRAS*, or *KRAS*. Vaccination of this group of patients is the same as recommended for the general population, unless they are receiving immunosuppressive therapy or having neutropenia during the course of illness. The same is true for patients with cryopyrinopathy due to somatic mutations in *NLRP3*.

The other subgroup of this category includes diseases due to the presence of autoantibodies to cytokines, other factors, or cell surface glycoproteins. Patients with autoantibodies to INF- γ

should not receive live bacterial vaccines because of increased susceptibility to mycobacterial and salmonella infections.³⁷⁻⁴¹ Patients with autoantibodies to IL-17/IL-22 or with pulmonary alveolar proteinosis due to autoantibodies to GM-CSF should receive vaccines according to routine schedules unless receiving immunosuppressive therapy. Patients with atypical hemolytic uremic syndrome receiving eculizumab (anti-C5 mAb) have the same recommendations as for patients with complement deficiency.²

Vaccination of patients receiving immunosuppressive medication

This represents secondary rather than primary immunodeficiency. We include it in this review because many patients with primary immunodeficiency exhibit autoimmunity and receive immunosuppressive therapy.

Corticosteroids. Inactivated vaccines should be given during corticosteroid therapy as scheduled for normal subjects. With high-dose steroids for long duration, it is better for vaccines to be given before initiating therapy by at least 2 weeks if feasible, or deferred until after stopping therapy.⁴⁶

Administration of live vaccines should be determined according to the route of steroid administration, dose, and duration. For patients receiving topical or local steroids, by skin application, local injection, or aerosol inhalation, live vaccines may be given safely and without concern regarding loss of immunogenicity or safety. The same applies for patients receiving physiologic replacement doses or low dose (<20 mg or 2 mg/kg prednisone or equivalent daily or alternate day for children weighing <10 kg).⁴⁶ Children receiving high-dose steroids for a duration of less than 14 days should not receive vaccines during therapy, but could receive them immediately after termination of therapy or after a delay of 2 weeks, according to some authors. If the duration is more than 14 days, vaccination should be delayed for 4 weeks after termination of therapy.⁴⁶

Other immunosuppressive therapy including biologic agents.

With low-level immune suppression as in patients receiving methotrexate at a dosage of 0.4 mg/kg/wk or less, azathioprine at a dosage of 3 mg/kg/d or less, or 6-mercaptopurine at a dosage of 1.5 mg/kg/d or less, both live and inactivated vaccines may be given safely.⁴⁷ In the setting of a high level of immunosuppression as in patients receiving higher doses of the drugs listed above or TNF- α antagonists, anti-B-lymphocyte mAbs, or cancer chemotherapy, responses to inactivated vaccines are impaired, so it is better to administer vaccines at least 2 weeks before initiating planned immunosuppressive therapy, or during therapy and possibly repeating after terminating therapy. Live vaccines are contraindicated in these cases, so they are given at least 4 weeks before initiating therapy. The interval until immune reconstitution varies greatly according to type and intensity of immunosuppression. Thus, it will be difficult to make a definitive recommendation for the interval after cessation of immunosuppressive therapy whereby viable vaccines may be considered safe and immunogenic.^{46,48,49}

Household contacts of immunodeficient patients

Inactivated vaccines are always recommended according to routine schedules in the close contacts of immunocompromised patients to avoid creating a potential avenue of natural infection. Annual inactivated influenza vaccine is particularly important

TABLE II. Vaccines in current use

Vaccine	Organism	Type
Nonviable vaccines		
DTaP	<i>Corynebacterium diphtheriae</i>	Toxoid
	<i>Clostridium tetani</i>	Toxoid
	<i>Bordetella pertussis</i>	Inactivated toxin plus part of the organism
HAV	Hepatitis A virus	Inactivated virus
HBV	Hepatitis B virus	Recombinant HBsAg
HIB	<i>Hemophilus influenzae</i>	Conjugate
HPV	Human papilloma virus	Recombinant
Inactivated influenza (IM/SC)	Influenza	Inactivated virus
Meningococcal		
MCV4	<i>Neisseria meningitidis</i>	Conjugate
MPSV4		Polysaccharide
Serogroup B meningococcal		Recombinant
Pneumococcal		
PCV13	<i>Streptococcus pneumoniae</i>	Conjugate
PPSV23		Polysaccharide
Polio (IM)	Poliovirus	Inactivated virus
Anthrax	<i>Bacillus anthracis</i>	Inactivated virus
Japanese encephalitis	Japanese encephalitis virus	Inactivated virus
Viable vaccines*		
Live influenza	Influenza virus	
MMR	Measles virus	
	Mumps virus	
	Rubella virus	
Polio (oral)	Poliovirus	
Rotavirus vaccine	Rotavirus	
Varicella	Varicella-zoster virus	
Herpes zoster	Varicella-zoster virus	
Adenovirus	Adenovirus	
Smallpox	Smallpox virus	
Typhoid (oral)	<i>Salmonella typhi</i>	
Yellow fever	Yellow fever virus	
BCG	<i>Mycobacterium bovis</i>	

DTaP, Diphtheria toxoid, tetanus toxoid, and acellular pertussis; HBsAg, Hepatitis B surface antigen; HIB, *Hemophilus influenzae* type b; IM, intramuscular; MCV4, tetravalent meningococcal conjugate vaccine; MPSV4, tetravalent meningococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; SC, subcutaneous.

*Modified or attenuated strains designed to be less virulent than the wild-type agent.

and preferred to live attenuated vaccine, mainly for theoretical reasons, even though there is no documented risk of transmission of the nasal influenza vaccine virus.⁵⁰

Most live vaccines are considered safe in household contacts of immunocompromised patients because there is no evidence of increased risk of transmission of infection. The only exception is oral polio vaccine, which can be transmitted.⁵⁰ If a close contact develops a rash after varicella vaccination, isolation of the immunodeficient patient is recommended with administration of zoster immunoglobulin.⁵⁰

Pregnant women at high risk of having a baby with primary immunodeficiency should receive pneumococcal, *Hemophilus influenzae* type b (HIB), and meningococcal vaccines in addition to routinely given vaccines such as Tdap and influenza. This is to protect the baby via maternal immunoglobulins, which will be transferred across the placenta.⁵⁰

Vaccination in patients receiving immunoglobulin therapy

In patients with antibody deficiency or combined immunodeficiency who receive immunoglobulin therapy, most of the agents in the primary childhood series of immunizations will not be needed because these antibodies are well represented in therapeutic IgG. However, other nonviable vaccines may be considered, especially inactivated influenza and papillomavirus vaccines, because they may induce some cellular immunity. Conjugate polysaccharide vaccines may also be considered (except, perhaps, in patients with agammaglobulinemia) if there is evidence of some antibody response (also see below).^{46,51}

In addition to replacement therapy, immunoglobulin may be given as immune modulatory therapy for patients with immune dysregulation. In most cases, these patients do not have any apparent increased susceptibility to infection or impairment of adaptive immunity, but IgG may also be used as immune modulation in patients with primary immunodeficiency diseases. Regardless of whether or not the patient has a primary immunodeficiency disease, and regardless of whether the IgG is given for replacement or immune modulation, the immunoglobulin may interfere with the immune responses to measles, rubella, and varicella live vaccines (the effect on mumps vaccine is not known).^{46,52} Thus, it is recommended to avoid giving these vaccines for a period between 3 and 11 months after receiving immunoglobulin, depending on the indication and dose given. Immunoglobulin therapy has no effect on other live vaccines such as oral polio and yellow fever, and they may be given as scheduled except where the underlying diagnosis results in a contraindication.^{46,53} In the case of subcutaneous immunoglobulin therapy, the vaccine should be administered at a different anatomical site.⁴⁶

VACCINES

Nonviable vaccines

In general, inactivated vaccines (eg, tetanus and diphtheria toxoids, pertussis, inactivated poliovirus, HIB, and pneumococcal and meningococcal vaccines; Table II) are safe in immunocompromised patients and should be given per the routine schedule, except when they are unlikely to have any benefit as in severe antibody deficiency or combined immunodeficient patients and patients receiving immunosuppressive therapy or immunoglobulin replacement.² Some nonviable vaccines are recommended in specific categories or types of immunodeficiencies or conditions of immunosuppression as discussed below. Note that for patients not receiving immunoglobulin therapy, it is possible to monitor seroconversion for any vaccine. For those who are receiving IgG, it is only possible to monitor conversion reliably for any vaccines that are not within the routine schedule, especially in children aged 1 to 5 years.

Inactivated influenza vaccine. Either live or inactivated influenza vaccine should be given to all healthy individuals 6 months or older. Inactivated influenza vaccine is safe in immunocompromised patients. Some studies have also shown that it

TABLE III. Vaccination in primary immunodeficiency disorders

Vaccine	Combined immunodeficiency and syndromes		Antibody deficiency		Patients receiving IgG			Phagocytic cell disorders		Diseases of innate immunity							
	Severe	Mild*	Severe	Mild	Replacement	Immuno-modulatory	Diseases of immune dysregulation	CGD and neutropenia	LAD and cytotoxic granule defects	Invasive bacterial infections	Invasive viral infections	Mycobacterial infections	Auto-inflammatory disorders	Complement deficiency	Phenocopies	Immune suppression†	
Inactivated/subunit																	
DTaP	B	A	B	A	B	B	A	A	A	A	A	A	A	A	A	B	
HAV	B	A	B	A	B	A	A	A	A	A	A	A	A	A	A	B	
HBV	B	A	B	A	B	B	A	A	A	A	A	A	A	A	A	B	
HIB	B	A	B	A	B	A	A	A	A	E	A	A	A	E	A‡	B	
Human papilloma virus	B	A	A	A	A	A	A	A	A	A	A	A	A	A	A	B	
Influenza (IM/SC)	B	A	A	A	A	A	A	E	A	A	A	A	A	A	A	A	
Meningococcal	B	A	B	A	A	A	A	A	A	E	A	A	A	E	A‡	B	
Serogroup B meningococcal vaccine	B	A	B	A	A	A	A	A	A	E	A	A	A	E	A‡	B	
Pneumococcal conjugate	B	A	B	A	B	A	A	A	A	E	A	A	A	E	A‡	B	
Pneumococcal polysaccharide	B	A	B	A	B	A	A	A	A	E	A	A	A	E	A‡	B	
Polio (IM)	B	A	B	A	B	B	A	A	A	A	A	A	A	A	A	B	
Anthrax	B	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	
JE	B	A	B	A	B	A	A	A	A	A	A	A	A	A	A	B	
Typhoid (IM)	B	A	B	A	B	A	A	A	A	A	A	A	A	A	A	B	
Rabies§	B	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	
Live attenuated																	
Influenza	C	C	C	C	C	A	C	C	C	C	C	C	C	C	C¶	C	
MMR	C	D	C	D	C	B	A	A	C	A	C	A	A	A	D¶	C	
Polio (oral)	C	C	C	C	C	A	A	A	C	A	C	A	A	A	D¶	C	
Rotavirus	C	C	C	D	C	A	A	A	C	A	C	A	A	A	D¶	C	
Varicella	C	D	C	D	C	B	A	A	C	A	C	A	A	A	D¶	C	
Herpes zoster	C	D	C	D	C	B	A	A	C	A	C	A	A	A	D¶	C	
Adenovirus	C	C	C	C	C	D	C	C	C	C	C	C	C	C	C¶	C	
Smallpox	C	C	C	D	C	A	A	A	C	A	C	A	A	A	D¶	C	

[illegible]

Patients with Mendelian susceptibility to mycobacterial disease due to autoantibodies to INF- γ should not receive live bacterial vaccines. Patients with autoantibodies to type I interferon should not receive live viral vaccines.

Typhoid Vi capsular polysaccharide vaccine. Enteric fever is a multisystem disease caused by *Salmonella typhi* and *paratyphi*. It is rare in the United States but endemic in some Asian, African, and Latin American countries. Travelers to these areas should be vaccinated, especially after the development of drug-resistant strains in these endemic areas. Household contacts of a case or carriers who continue to shed the organism in urine for more than 1 year and some laboratory workers who deal with infected samples should also be immunized. There are 2 types of *Salmonella* vaccines, oral live vaccine and nonviable parenteral polysaccharide vaccine. As is the case with most inactivated

vaccines, the polysaccharide vaccine can be administered to immunocompromised patients except in cases in which immune response is not expected.⁶⁴

Rabies vaccine. Rabies vaccine is an inactivated vaccine recommended for preexposure prophylaxis in high-risk occupations, or postexposure to an infected animal together with rabies immune globulin. Because it is inactivated, rabies vaccine is safe in immunodeficient or immunosuppressed patients. Because the immune response may be reduced, especially in severe immunosuppression, the 5-dose vaccine regimen is preferred. Serconversion may be assessed, if desired. Immunosuppressive therapy should be delayed for at least 2 weeks after immunization, if possible.⁶⁵

Some have used rabies vaccine as a neoantigen to assess antibody responses in patients who are receiving IgG therapy. Because immunity to rabies is not widespread in the general population, there is no antibody in pooled human therapeutic IgG. Thus, it is possible to measure the endogenous antibody response in a patient who is receiving IgG replacement. This can avoid the need to discontinue IgG therapy to measure a response to more commonly used vaccines such as tetanus or diphtheria toxoids and pneumococcal vaccines.⁶⁶

Vaccination against *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Neisseria meningitidis*. These organisms are leading causes of serious diseases worldwide, such as pneumonia, meningitis, and sepsis. Vaccination against all should be given to all children and adults according to Advisory Committee on Immunization Practices recommendations, which can be found in reports from the Centers for Disease Control and Prevention and online.^{17,67,68} Additional vaccination against these agents beyond the routine schedule may also be indicated in immunocompromised hosts and individuals who are at increased risk of life-threatening complications of infection due to a wide variety of causes such as chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure), chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy), diabetes mellitus, cerebrospinal fluid leak, cochlear implant, sickle cell disease and other hemoglobinopathies, anatomic or functional asplenia, HIV infection, chronic renal failure, and nephrotic syndrome.^{17,67,68}

Vaccination beyond the routine recommendations for these agents should also be considered for patients with immunodeficiency predisposing to infection with encapsulated bacteria or who are immunosuppressed and who are not receiving immunoglobulin therapy.^{43,67,68} These may include immunization of older children and adults every 5 years with 13-valent pneumococcal conjugate vaccine. The 13-valent pneumococcal conjugate vaccine may be followed 4 to 8 weeks later by 23-valent pneumococcal polysaccharide vaccine to afford increased protection against types not included in 13-valent pneumococcal conjugate vaccine.^{43,67-69} Similar considerations apply to immunization with tetravalent conjugate or nonconjugated meningococcal and monovalent serotype B vaccines.^{43,67-69} Although HIB vaccine is not routinely recommended for patients 5 years or older, at least 1 dose should be given to unimmunized persons aged 5 years or older who are immunocompromised or have anatomic or functional asplenia (including sickle cell disease).^{43,67-69}

IgG replacement therapy has been shown to provide variable but usually protective levels of passive immunity to pneumococcus, HIB, and somewhat more variably to meningococcus.^{51,70,71} Nevertheless, some patients receiving IgG therapy can make at least partial responses to polysaccharide and/or conjugate vaccines, and some have suggested that there is therapeutic benefit for some patients with supplemental immunization with these agents.^{51,71} This is not considered a component of standard care at this time.⁴³

Viable vaccines

Viable vaccines usually carry the risk of causing disease, especially in severely immunocompromised patients. Therefore, much greater caution must be exercised with the use of these vaccines.

Live influenza vaccine. Cold-adapted viable nasal spray influenza vaccine has been studied in some groups of stable HIV-infected patients and has shown efficacy and safety comparable to the immunocompetent population.^{72,73} Because a (presumably) safer and effective inactivated influenza vaccine exists, the viable influenza vaccine is considered to be generally contraindicated in all immunocompromised patients and their household contacts.²

Oral polio vaccine. Oral polio vaccine carries the risk of vaccine-associated paralytic poliomyelitis. Furthermore, there are reported cases of poliomyelitis following vaccination in children with severe combined immunodeficiency or hypogammaglobulinemia. Oral polio vaccine is contraindicated in cases affecting immunity to viral infections including combined immunodeficiency, major antibody deficiency, and phagocytic cell dysfunction. Also, patients with innate immune defects affecting immunity to viruses such as signal transducer and activator of transcription 1 or signal transducer and activator of transcription 2 deficiencies and patients receiving immunosuppressive therapy should not receive oral polio vaccine. This contraindication also extends to household contacts of these patients.^{2,9,20,74-76}

BCG. The BCG vaccine is a live attenuated bovine strain of *Mycobacterium tuberculosis* (*M bovis*) used in areas where it is endemic or in individuals at high risk. There are many reported cases of disseminated mycobacterial disease after BCG vaccination in severely immunocompromised hosts. Therefore, it is contraindicated in combined immunodeficiency, phagocytic cell defects, and in patients receiving immunosuppressive therapy.^{32,77-80} Several diseases characterized by increased susceptibility to mycobacterial infection (typical and atypical) are grouped together under the designation "Mendelian susceptibility to mycobacterial disease." These include 7 autosomal (*IFNGR1*, *IFNGR2*, *STAT1*, *IL12B*, *IL12RB1*, *ISG15*, and *IRF8*) and 2 X-linked (*NEMO* and *CYBB*) genes.⁷⁸⁻⁸² Thus, BCG is contraindicated in all these disorders. Because TB is a major problem in developing countries and in patients with HIV infection, there is great interest and need for an inactivated vaccine. Some early trials in monkeys have been promising.⁸³

Rotavirus vaccine. Rotavirus vaccine is the only live oral vaccine given to infants in the United States. It is contraindicated in severe combined immunodeficiency disorders because of some reports of severe gastroenteritis in these infants. Early identification of infants with SCID and other forms of severe T-cell lymphopenia by newborn screening can prevent inadvertent

administration of the vaccine and avoid its potentially life-threatening complications. There are no reports of disease caused by this vaccine in other populations, but it is also generally considered to be contraindicated in other severe immune defects such as severe antibody deficiency, HIV infection, and severe immune suppression due to steroid or other immunosuppressive therapies.^{2,6}

Adenovirus vaccine. Adenovirus is a common cause of respiratory, ocular, and gastrointestinal infections in children. These are usually mild and self-limited diseases, but in immunocompromised hosts may cause severe disease with a high fatality rate, especially in SCID and agammaglobulinemia. The available vaccine is approved only in military personnel and safety has not been investigated among immunocompromised hosts.^{84,85}

Smallpox vaccine. Because smallpox has been eradicated, smallpox vaccine is given only to high-risk personnel such as laboratory workers or the military. There is no absolute contraindication to the vaccine in the case of exposure because the risk of dying from the disease is the same as having a serious complication after vaccination. The vaccine would not be used for preexposure prophylaxis in patients with severe immune compromise such as SCID, severe antibody deficiency, or severe immunosuppression by steroid or other therapy.⁸⁶ Exposure is unlikely other than in a terrorist attack or similar catastrophic event. Postexposure prophylaxis could be considered on the basis of individual risk.

Live typhoid vaccine. Live attenuated typhoid vaccine, as are most live vaccines, is contraindicated in SCID, severe antibody deficiency, phagocytic cell dysfunction, and during steroid or other immunosuppressive therapy. Also, patients with Mendelian susceptibility to mycobacterial disease who have increased susceptibility to intracellular organisms including salmonella should not receive the vaccine. If needed in any of these conditions, the inactivated vaccine is given.⁶⁴

Yellow fever vaccine. Although there are no data regarding the safety of yellow fever vaccine in immunocompromised patients, it is expected to cause severe side effects in this population. Thus, it is contraindicated in patients with humoral, cellular, and severe phagocytic immunodeficiency. Also, patients undergoing immunosuppression should not receive this vaccine.^{46,87}

Varicella and zoster vaccines. Varicella vaccine may cause severe or fatal infection in children with SCID. Zoster vaccine is indicated for people aged 60 years and older to reduce the risk of shingles and the long-term pain from postherpetic neuralgia. Varicella and zoster vaccines are contraindicated in patients with combined immune deficiency or in those undergoing severe immunosuppression. Immune globulin therapy interferes with the effect of live viral vaccines. These vaccines should not be given during administration of immune globulin therapy or for a period between 3 and 11 months after cessation of such therapy.^{46,88,89}

MMR. MMR is a combination of live vaccines against measles, mumps, and rubella, which are diseases with serious sequelae. As is the case with most live vaccines, there are several reports of serious side effects of measles vaccination in immunodeficient patients.⁹⁰⁻⁹² Thus, it is contraindicated in SCID, and major

antibody and phagocytic cell defects. Also, patients with severe immunosuppression should not receive the vaccine. Immune globulin therapy is known to interfere with MMR vaccine immunogenicity, so it is contraindicated in patients receiving IgG therapy and should be delayed for 3 to 11 months depending on the dose and indication of the IgG. MMRV is a new vaccine containing live varicella vaccine in addition to the MMR components. It has the same precautions as MMR and varicella vaccines do separately. In cases of mild immunodeficiency, giving MMR and varicella separately is preferred to MMRV, as MMRV is not studied in immunocompromised hosts and it causes more fever and febrile seizures than the vaccines given separately in immunocompetent hosts.^{2,93,94}

CONCLUSIONS

The safety and immunogenicity of vaccines is an important and frequent question during the routine care of patients with primary immunodeficiency. These patients have increased susceptibility to infections, and at the same time, vaccines may be nonprotective for them or have serious complications. Generally, live vaccines are contraindicated in patients with severe immunodeficiency, but could be given in mild combined immunodeficiency on the basis of some studies on patients with HIV or DiGeorge syndrome. Inactivated vaccines are safe with some concerns about immunogenicity in cases of severe immunodeficiency, whereas they should be given to patients with mild immunodeficiency. Some categories of primary immunodeficiency require special additional schedules of vaccination such as patients with complement deficiency and asplenia (and others). Further studies of vaccine efficacy and safety in specific types of primary immunodeficiency are needed to establish better evidence-based guidelines.

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