

Update: Vaccines in primary immunodeficiency



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Vaccines were originally developed to prevent or ameliorate infectious disease. As knowledge of immune function and appreciation of immunodeficiency has developed, researchers have used vaccine responses as a tool to characterize the phenotypes of patients exhibiting various syndromes. Thus it has become possible for a clinician to evaluate individual responses to vaccines to interrogate the immunocompetence of their patients. Although there have been many advances in these areas, we still have much to learn about the quantity and quality of humoral and cellular vaccine responses in healthy and immunodeficient subjects and how that knowledge can then be extrapolated to diagnostic purposes. Adverse effects of vaccines have been recognized for many years, especially the occurrence of infections caused by viable vaccine organisms in immunodeficient hosts. Nevertheless, vaccines are essential for disease prevention in immunodeficient patients, just as they are for healthy subjects. Clinicians must understand the appropriate and safe use of vaccines in patients with immunodeficiency. This review highlights some recent advances and ongoing challenges in application of vaccines for the diagnosis and treatment of immunodeficiencies. (*J Allergy Clin Immunol* 2018;141:474-81.)

Key words: Immunology, primary immunodeficiency, vaccines

Active immunization is one of the most ancient medical practices and is still being developed and refined today.¹ Of course, the first clinical use of vaccines was for the prevention of infectious diseases, and this remains the predominant use today (for a general review of clinical vaccination concepts, see Best²). As knowledge of the function of the immune system in host defense has evolved, we have begun to appreciate heritable defects in its function (primary immunodeficiencies [PIDs]), as well as those arising from secondary processes (iatrogenic and

Abbreviations used

CVID: Common variable immunodeficiency
HIB: *Haemophilus influenzae* type B
HPV: Human papillomavirus
MMR: Measles, mumps, rubella
PCV: Pneumococcal conjugate vaccine
PID: Primary immunodeficiency
PPSV: Pneumococcal polysaccharide vaccine
SCID: Severe combined immunodeficiency
WHIM: Warts, hypogammaglobulinemia, infections, myelokathexis, *CXCR5* mutation
WILD: Disseminated warts, immunodeficiency, lymphedema, anogenital dysplasia

other processes impacting immune mechanisms). Immune defects affect not only response to natural infection but also to immunization. Thus the clinical use of vaccines has expanded to include a role in the diagnosis of PIDs. In addition, immunodeficiency requires alterations in vaccine use to avoid potential adverse consequences. Principal among these are infections caused by viable vaccine organisms.

Vaccines can be broadly classified as viable or nonviable (Table I). Viable vaccine microbes are attenuated with respect to virulence so that they do not cause clinically significant disease in healthy hosts while they generate protective cellular and humoral immunity. However, in hosts with PIDs, even attenuated organisms can cause disease, ranging from mild to fatal. Thus these vaccines must be used with caution in these subjects.³⁻⁵ Nonviable vaccines consist of inactivated organisms or subunits or components of organisms or their disease-causing products (toxins). These agents are incapable of causing infection or illness in any recipient, even those with the most severe immune dysfunction. Depending on the specific vaccine and PID, the immune response might be normal, absent, or intermediate. The efficacy and safety of vaccines in patients with PIDs and those receiving immunosuppressive therapy have been recently reviewed.^{3,4,6}

Viable vaccines generate cytotoxic cellular and humoral immune responses in a manner analogous to the wild-type counterpart organism. Nonviable vaccines induce T cell–dependent humoral responses but less cytotoxic T-cell response. Pure polysaccharide vaccines are among the least immunogenic because they are not efficient activators of T-cell help for antibody production. The immunogenicity of vaccines that induce polysaccharide-specific antibody responses is enhanced by coupling the polysaccharide hapten to a protein or glycoprotein carrier (conjugate vaccine, Table I). By doing so, the immunogen is processed and presented by antigen-presenting cells, leading to recruitment of T-cell help and a more robust response and longer-lasting memory.⁷

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Disclosure of potential conflict of interest: F. A. Bonilla has a board membership with the Louis August Jonas Foundation; has consultant arrangements with Grand Rounds Health, the Immune Deficiency Foundation, Charles River Associates International, Green Cross, Parexel, Sarepta Inc, Cowen Group, Gerson-Lehrman Group, Grifols, and Huron Consulting Group; has received a grant from Shire, Inc; has received payment for lectures from Albany Medical College and Drexel University; and has received royalties from UpToDate.

Received for publication August 1, 2017; revised December 19, 2017; accepted for publication December 19, 2017.

Available online December 27, 2017.

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0091-6749/\$36.00

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<https://doi.org/10.1016/j.jaci.2017.12.980>

TABLE I. Vaccines in current use

Vaccine	Type
Nonviable vaccines	
Anthrax	Inactivated virus
Diphtheria toxin	Toxoid
Hepatitis A	Inactivated virus
Hepatitis B	Recombinant HBsAg
HIB	Conjugate
HPV	Recombinant
Influenza (inactive)	Inactivated virus
Japanese encephalitis	Inactivated virus
Meningococcus A, C, Y, W-135	Conjugate, 4-valent
	Polysaccharide, 4-valent
Meningococcus B	Recombinant
Pertussis (acellular)	Bacterial components
Pneumococcus	Conjugate, 13-valent
	Polysaccharide, 23-valent
Polio (inactive)	Inactivated virus
Rabies	Inactivated virus
Tetanus toxin	Toxoid
Typhoid (inactive)	Polysaccharide
Viable vaccines	
Adenovirus	Attenuated virus
Influenza (viable)	Attenuated virus
Measles	Attenuated virus
Mumps	Attenuated virus
Polio (oral)	Attenuated virus
Rotavirus vaccine	Human/bovine reassortant virus
Rubella	Attenuated virus
Smallpox*	Attenuated virus
Typhoid (oral)	Attenuated virus
Varicella/zoster	Attenuated virus
Yellow fever	Attenuated virus
BCG	Attenuated mycobacteria

*This vaccine is no longer in routine use because the disease is considered to have been eradicated worldwide.

Therapeutic and diagnostic vaccine uses have been reviewed recently, and general guidelines have been developed.^{3-5,8-10} This review will highlight some of the recent developments and ongoing challenges regarding use of vaccines in patients with PIDs. Note that secondary immunodeficiencies caused by the effects of other disorders and medical therapies can also affect vaccine use. Similarly, immunization practice after stem cell therapy for PIDs follows the same recommendations as in other settings. These considerations are beyond the scope of this review; recommendations can be found in the literature.^{3,4,6,11,12}

DIAGNOSTIC USE OF VACCINES FOR PIDs

Vaccine efficacy is established through reduction of the incidence of infection in vaccine recipients. The predominant surrogate marker for vaccine efficacy is production of specific IgG. This is appropriate in most cases because neutralizing or opsonizing antibody represents a principal protective mechanism induced by natural infection. This is also convenient because measurement of blood antibody levels is technically (relatively) simple and inexpensive.

The predictive value of diminished antibody response for immunodeficiency diagnosis depends on the normal seroconversion rate, which is usually defined for clinical purposes as the proportion of immunocompetent vaccine recipients that achieve a level of antibody that is considered protective. It should be noted that the designated level might not be protective for all subjects,

but clinical tools are lacking to detect this in practice. Threshold protective levels are often defined according to correlation with a criterion of vaccine efficacy and have been established for many vaccines (Table II). Knowing the immunization history of the patient is essential for interpreting vaccine response.

One might interrogate the response to any vaccine as a potential diagnostic tool for immunodeficiency. The key is to know the normal seroconversion rate and the rate in an immunodeficient population (not well-established for any vaccine) to determine the predictive value of a negative result. Thus, the predictive value of diminished specific antibody determination for immunodeficiency diagnosis is poorly defined. Another dimension of antibody response is the fold increase in antibody levels after immunization. This is often not well defined in the healthy population. Of course, antibody measurement is irrelevant for diagnosis of many forms of immunodeficiency (eg, phagocytic cell defects, some innate deficiencies, autoinflammatory disorders, and complement) in which adaptive humoral immunity is not impaired.

Tetanus and diphtheria toxoid vaccines

Antibody responses to tetanus and diphtheria toxoids are often used as one component of the diagnosis of humoral immunodeficiency.^{5,13} These are potent immunogens with high seroconversion rates, and therefore an initial low determination in a fully immunized subject should have good predictive value for immunodeficiency diagnosis, depending on the time since the last immunization. For example, if a patient is due for his or her routine 10-year booster, the value might be low. It is often not routine practice to revaccinate a patient for diagnostic purposes if the initial level is greater than the protective threshold. However, this might be a missed opportunity to interrogate responsiveness to these vaccines through the fold increase in levels after booster immunization. Healthy subjects can have up to 20- to 30-fold increases in antibody levels.¹³ The lower end of the normal fold response range is not well defined and depends in part on the level before booster immunization. Furthermore, current standard clinical measurements might not be suitable because assays often are not read at greater than an upper limit of 7 IU/mL. It might be fruitful to design an assay specifically for the purpose of diagnosing immunodeficiency.

Pneumococcal conjugate and polysaccharide vaccines

Ninety serotypes of pneumococcus have been described. Some are more common than others, and there is some geographic variation in the prevalence of each type. The 23 types that are considered most important for human disease have been included in the pure pneumococcal polysaccharide vaccine (PPSV). The most widely used pneumococcal conjugate vaccine (PCV) currently contains 13 serotypes. Because these distinct types of vaccine stimulate immune responses somewhat differently, the criterion for protection from invasive disease is not the same for both. After PCV, a level of 0.35 $\mu\text{g/mL}$ is considered protective for a particular serotype,¹⁴ whereas a level of 1.3 $\mu\text{g/mL}$ is considered protective after PPSV.¹⁴⁻¹⁶

Pneumococcal antibodies can cross-react across many serotypes or bind to only 1 serotype (type specific). The response to 1 type is evaluated both according to the fold increase in level

TABLE II. Vaccine seroconversion rates*

Vaccine	Protective level	Seroconversion rate (%)
Tetanus toxoid	>0.1-0.2 IU/mL (ELISA)	Approaching 100%, 1 mo after second or third dose, all ages
Diphtheria toxoid	>0.1-0.2 IU/mL (ELISA)	Approaching 100%, 1 mo after second or third dose, all ages
HBS antigen	10 mIU/mL	After 3 doses: 98% to 100% in adolescents, 96% in age 20-29 y, 94% in age 30-39 y, 89% in age >40 y
Polio (inactivated)	Titer >1:4	95% to 100% after 2 doses (varies by type)
Measles	≥255 mIU/mL	95% to 99% single dose, age 15 mo (2 doses recommended for long-lasting immunity)
Mumps	≥10 ELISA U/mL	95% to 99% single dose, age 15 mo (2 doses recommended for long-lasting immunity)
Rubella	≥10 ELISA U/mL	95% to 99% single dose, age 15 mo (2 doses recommended for long-lasting immunity)
Varicella	≥5 ELISA units	99% to 100%, 1 or 2 doses (2 doses recommended for long-lasting immunity)
HIB	1 µg/mL	83% to 97% after 3 doses
Pneumococcal conjugate (13-valent)	0.35 µg/mL	63.5% to 98.4% after 3 doses, varies with serotype
Pneumococcal polysaccharide (23-valent) not <2 y	1.3 µg/mL ^{15,16}	Varies widely with serotype
Meningococcal conjugate (4-valent)	Titer >1:8	85% to 100%, 2 doses at 12 and 15 mon, varies with serotype
	>4-fold increase in titer	73.5% to 89.4%, single dose, adults, varies with serotype

*Data from individual vaccine-prescribing information, unless otherwise noted.

after immunization and whether a protective level is attained and is usually measured 4 weeks after immunization. A 2- or 4-fold increase is considered normal depending on the preimmunization level; that is, a 4-fold increase is less likely if the preimmunization level is high. Antibody response at less than 2 years of age is often good but very unpredictable.¹⁷ Response after age 5 years is more consistent, and most subjects will respond to a majority of serotypes. The response between the ages of 2 and 5 years is intermediate.^{9,15,16,18}

An impaired response to PPSV is widespread in patients with PIDs with a component of humoral deficiency.⁵ Unfortunately, the tremendous variability in the normal response to PPSV is such that the predictive value of an abnormal response in a subject under evaluation for PIDs is often uncertain. The problem has been studied extensively, and there is still no solid consensus on what clearly constitutes an abnormal response.^{5,9,15,16,18} One might consider both aggregate (not type-specific) and type-specific responses for PID diagnosis.^{19,20} For clinical diagnostic purposes, attention has been focused more on type-specific responses.

These complexities are further compounded by several factors, including the following: (1) some studies measure responses to a small number of serotypes, and the choice of serotypes varies between studies; (2) different assay methods (eg, ELISA vs other solid-phase multiplex platforms) yield different results; and (3) immunization with PCV enhances subsequent response to PPSV administered within several months, whereas PPSV can inhibit subsequent responses to PCV or PPSV.^{21,22} All of these issues must be studied further to derive more robust criteria for a normal response.

Recommendations for routine pneumococcal (and other) immunizations can be found on the Web site of the US Centers for Disease Control and Prevention.²³ Only PCV is used at less than 2 years of age. At greater than 65 years of age, both vaccines are recommended, with PCV given first and PPSV given a few months to a year later. Between these extremes of age, pneumococcal immunization is recommended for a variety of health conditions (chronic metabolic or hematologic diseases, immunodeficiencies, and others; see the full list on the US Centers for Disease Control and Prevention Web site²³ and see Sobh and Bonilla⁴). In these situations the PCV-first and PPSV-second strategy is also recommended. In circumstances in which

PPSV might have been administered first, it is recommended to wait 1 full year before subsequent PCV administration. These approaches take advantage of the priming effect of PCV and avoid the suppressing effect of PPSV mentioned above. The current state of the use of pneumococcal vaccines in PID diagnosis is discussed extensively and summarized in 2 recent guidelines.^{5,9}

Another dimension of the normal antibody response is not well understood, and its importance for PID diagnosis requires much additional study: the matter of antibody quantity versus quality. The concentration of antibody in blood (quantity) is an important determinant of protective immunity. However, the avidity of antibody for antigen and its ability to opsonize an organism (measures of quality) are equally important. A high concentration of antibody of poor quality will not be protective, and this has been demonstrated in individual patients with invasive pneumococcal infections in spite of having protective blood levels measured in clinical immunoassays.^{24,25} Lower pneumococcal antibody avidity can correlate with clinical features, such as infection susceptibility.²⁴ Clinical assays of pneumococcal avidity are available, whereas opsonophagocytic assays remain more labor intensive and have not yet seen general clinical application. Both modalities require more extensive study before they will have routine use for PID diagnosis.

The vast majority of vaccine response literature focuses on the production of IgG antibody. However, it is possible that measurement of other isotypes (IgA and IgM) could also have predictive value for PID diagnosis. These assays could be used readily in patients receiving IgG replacement. Assays have been developed for measurement of aggregate IgA and IgM responses to PPSV, although these are not yet in routine clinical use.^{26,27} These responses peak somewhat earlier than IgG responses: 2 weeks for IgA and 3 weeks for IgM.²⁷ Diminished IgA and IgM pneumococcal polysaccharide responses have been documented in patients with common variable immunodeficiency (CVID) and transient hypogammaglobulinemia of infancy.^{27,28}

Typhoid vaccine

In a recent study, measurement of responses to injectable (nonviable) *Salmonella typhi* polysaccharide vaccine performed better than aggregate (not type-specific) pneumococcal antibody

responses for discrimination of patients with CVID and hypogammaglobulinemia from healthy control subjects.²⁹ A 10-fold increase in IgG antibody to *S typhi* served to distinguish patients with CVID from control subjects with 90.9% sensitivity and 62.5% specificity. Inferior performance of the pneumococcal vaccine in this study was due in large part to a high level of preimmunization pneumococcal IgG in healthy subjects, which skewed the fold increase in titer heavily downward in this group. Furthermore, 27.8% of healthy subjects did not meet the 10-fold response criterion.

Another study using the same vaccine and comparing a research assay and the same commercial assay used above found that a response ratio of only 2 had both 100% sensitivity and specificity for distinguishing control subjects from a previously diagnosed group of patients with antibody deficiency (also similar to the prior study).³⁰ These authors also showed that responses could be measured reliably in patients receiving IgG therapy and that commercial preparations of IgG did not contain measurable typhoid polysaccharide antibody. These studies suggest that measurement of *S typhi* antibody could be useful for PID diagnosis.

Another recent study compared pneumococcal PPSV response, *S typhi* response, and isohemagglutinin titers in a cohort of 100 older children and adults aged 10 to 55 years.³¹ Only 2 of the 100 subjects were less than the fifth percentile of response for both pneumococcus and *S typhi*. These authors suggest that using a combination of responses might have better predictive value than either alone. Interestingly, those with low levels of isohemagglutinins did not exhibit poor response to either of the polysaccharide vaccines. This suggests that isohemagglutinin titers might not serve as a useful surrogate for polysaccharide immunization for the diagnosis of PIDs, as had been stated in some guidelines.⁵

Vaccine failure

Vaccine failure is defined as disease caused by an organism against which the host was fully immunized. There are few studies examining the implications of vaccine failure for immunodeficiency diagnosis. In one such study, a cohort of patients who received routine childhood immunization with conjugated *Haemophilus influenzae* type B (HIB) vaccine and subsequently had invasive infection with HIB were evaluated for humoral immunodeficiency.³² Nineteen (11.2%) of 170 children had low IgA levels, low IgM levels, or panhypogammaglobulinemia (low IgG, IgA, and IgM levels) a median of 4 years after infection. Hypogammaglobulinemia was associated with an earlier age of infection and a history of frequent (>2 times per year) antibiotic use. The more frequent finding of hypogammaglobulinemia in younger patients suggested that a significant fraction (50%) might have had transient hypogammaglobulinemia. Interestingly, the proportion of subjects with protective levels of HIB antibody at follow-up did not differ between those with normal immunoglobulin levels and those with hypogammaglobulinemia.

A similar situation has been reported in association with pneumococcal infection. A fully immunized 4-year-old boy with necrotizing pneumonia caused by a vaccine-type pneumococcus was subsequently found to have dyskeratosis congenita.³³

Invasive pneumococcal disease can occur in fully immunized healthy subjects. In most cases this does not represent actual

vaccine failure. Recall that there are approximately 90 known serotypes of pneumococcus, whereas PCV contains 13 types and PPSV contains 23. In areas in which vaccine coverage is high, cases of disease caused by nonvaccine strain serotypes increase.^{34,35} When an invasive pneumococcal infection occurs in a fully immunized subject, typing the infecting strain can determine whether vaccine failure has occurred.

Patients receiving immunoglobulin therapy

Measuring an antibody response in a subject who is receiving regular infusions of immunoglobulin might be desired if one wishes to determine whether (1) a transient antibody deficiency has improved or (2) a patient might be receiving the therapy unnecessarily. Such a determination is complicated by the fact that passively acquired pathogen or vaccine-specific IgG confounds the results of the most commonly used assays (tetanus and diphtheria toxoids and pneumococcal polysaccharide). In this circumstance, it is desirable to measure a response to an antigen not commonly encountered by plasma donors and to which the patient has never been exposed.

Several options exist. The bacteriophage X174 has been used for this purpose for a few decades.³⁶ There is no natural human exposure to this virus, and therefore it fulfills both requirements. It is also possible to measure primary and secondary antibody responses. The main drawback of this approach is a lack of convenience. The immunogen and measurement of the response is available only through a research protocol at a single institution (University of Washington, Seattle, Washington). Rabies virus vaccine has been used for this purpose.³⁷ Although not routine, this approach has the advantage that both the vaccine and assays for measuring IgG are readily available. Typhoid vaccine has also been demonstrated recently to be useful for assessing antibody responses in patients receiving IgG therapy (see the section on typhoid vaccine above).³⁰ Tick-borne encephalitis virus vaccine has also been used to measure antibody production in patients receiving IgG therapy.³⁸

THERAPEUTIC USE OF VACCINES IN PATIENTS WITH PIDs

Human papillomavirus vaccine

A variety of innate and adaptive cellular immunodeficiencies are associated with increased susceptibility to human papillomavirus (HPV) infection.³⁹ These include severe combined immunodeficiency (SCID); Wiskott-Aldrich syndrome; ataxia-telangiectasia; nuclear factor κ B essential modulator deficiency; leukocyte adhesion deficiency (*CD18* mutation); X-linked hyper-IgM syndrome; disseminated warts, immunodeficiency, lymphedema, anogenital dysplasia (WILD) syndrome; epidermodysplasia verruciformis (mutations of *TMC6* or *TMC8*); GATA-2 deficiency; warts, hypogammaglobulinemia, infections, myelokathexis, *CXCR5* mutation (WHIM) syndrome; autosomal recessive hyper-IgE syndrome (*DOCK8* mutation); Netherton syndrome (*SPINK5* mutation); and *MST1* and *RhoH* mutations. Note that a recent support suggests that at least some cases of WILD syndrome are due to mutations in *GATA-2*.⁴⁰ Although conventional therapies might be effective, they might not be sufficient to control the sometimes exuberant disease exhibited by patients with these diagnoses.⁴¹

In one study, the HPV vaccine was quite immunogenic (89% to 100% type-specific seroconversion rates) in immunosuppressed children, including those who had recently received solid-organ or stem cell transplantation or were being treated with immunomodulators for autoimmune conditions.⁴² HPV vaccine has also been shown to be immunogenic and possibly protective in patients with WHIM syndrome and HIV infection.⁴¹ The vaccine should be used routinely in patients with PIDs, except in situations in which there is no capacity for response.^{4,41}

Immunosuppressed patients might exhibit improvement in cutaneous warts after HPV vaccine administration.⁴¹ One patient with WILD syndrome has been reported to have cleared cutaneous warts after administration of HPV vaccine.⁴³ Interestingly, the papillomavirus types infecting that patient were not contained in the vaccine. Another patient with persistent neutropenia and T-cell lymphopenia of unknown cause also was reported to have had disappearance of cutaneous warts after HPV vaccine administration.⁴⁴ These are examples of an uncommon therapeutic use of a vaccine to treat an established infection rather than as prophylaxis.

Influenza virus vaccine

Annual immunization with nonviable influenza vaccine is recommended for all patients with PIDs unless they are considered incapable of any response.^{4,45} Nevertheless, it is expected that most patients will not exhibit normal antibody production. This has been documented in patients with a mixed group of humoral defects (mostly CVID).⁴⁶ The same group of authors subsequently showed decreased cellular immune responses in patients with predominantly humoral defects and suggested that additional measures (eg, medication prophylaxis during outbreaks) might be necessary to prevent influenza morbidity, even in patients with PIDs with predominantly humoral defects.⁴⁷

Patients receiving immunoglobulin therapy

Passive immunization through infusion of polyclonal human IgG is a mainstay of therapy for any PIDs with impaired adaptive humoral immunity. Protective levels of antibody toward the most commonly used routine vaccines have been documented in IgG recipients.⁴⁸⁻⁵¹ These include (at least) antibodies toward tetanus and diphtheria toxoids, measles, varicella, pertussis, pneumococci, and 3 of the common meningococcal serotypes (not type C). These vaccines are known to induce persisting (sometimes lifelong) humoral immunity (measles, varicella, and meningococcus), or booster doses of vaccines (toxoids) are administered to maintain levels among healthy subjects who are the plasma donors. Pertussis and pneumococcal antibodies are probably maintained through a combination of immunization and natural infection.

There are few studies of vaccine responses in patients already established on IgG replacement. One study of 23 patients with CVID receiving IgG examined responses to tetanus and diphtheria toxoids, HIB conjugate, hepatitis A and B, and pneumococcal polysaccharide.⁵² These authors documented positive responses to peptide or conjugate vaccines in 23% and to polysaccharide in 18% of all immunizations. Another study of 23 patients with CVID established reduced but protective responses to meningococcal polysaccharide vaccine in 65%.⁵³ Note that administration of the polysaccharide meningococcal vaccine is no longer recommended because conjugate vaccines are available.

The clinical utility or efficacy of routine administration of any of these vaccines in patients with CVID is not established. All of these antibodies are generally well represented in therapeutic IgG, with the possible exceptions of HIB and hepatitis A virus. Toxoids and other nonviable vaccines can be used in any immunocompromised host because they are nonviable and largely incapable of harm beyond hypersensitivity reactions. One important unanswered question would be whether routine use of these vaccines would be cost-effective. Of course, viable vaccines must be applied more cautiously (see below). Furthermore, measles, mumps, rubella (MMR) and varicella vaccines are neutralized by antibodies present in therapeutic IgG, and routine use in these patients is considered to be contraindicated for that reason.^{3,4}

ADVERSE EFFECTS OF VACCINES IN PATIENTS WITH PIDs BCG

In patients with PIDs, most attention related to adverse events related to immunization involve administration of viable vaccines (Table 1). This is borne out in one retrospective study of all vaccine-related adverse events in a fairly large cohort of 379 patients at a single center.⁵⁴ In this report 15 definite or probable vaccine adverse events were recorded. Nine (60%) of these involved live agent vaccines. Among these, 7 involved BCG.

The attenuated tuberculosis vaccine BCG (*Mycobacterium bovis*) was among the first recognized as causing serious complications in patients with PIDs with impaired cell-mediated immunity. Prominent among these are SCID and defects of the IFN- γ /IL-12 axis.⁵⁵⁻⁵⁸ The latter disorders are often designated Mendelian susceptibility to mycobacterial disease. Unfortunately, the complications of disseminated BCG infection in these patients can be fatal. The occurrence of significant localized disease (eg, axillary lymphadenopathy) should be considered a potential warning sign of an underlying PID.⁵⁸ Similarly, a family history of serious complications of BCG immunization might be an important historical clue to the possibility of PIDs.⁵⁹

Clark and Cameron⁶⁰ sought to define thresholds for tuberculosis infection rates and SCID incidence to determine when use of BCG led to increases or decreases of quality-adjusted life years. They determined that the use of BCG is favorable if the annual tuberculosis incidence is between 0.1% and 1% and the incidence of SCID is between 0 and 5:100,000. In this analysis of vaccine benefit, the incidence of tuberculosis is directly related to the incidence of SCID; that is, a high rate of tuberculosis supports use of the vaccine, even if the incidence of SCID is high. If the rate of tuberculosis is low, then the occurrence of SCID must also be low to support vaccine use. The incidence of SCID in the United States is 1.7:100,000.^{61,62} The incidence of tuberculosis reported in the United States for 2015 was 3:100,000 or 0.003%.⁶³ In this analysis BCG use would not be supported in the United States. Note that this does not take into account the incidence of Mendelian susceptibility to mycobacterial disease, which would make vaccination even more unfavorable.

MMR and varicella vaccines

Serious infections caused by vaccine strain measles and varicella viruses have long been recognized as potential

complications in patients with severe defects of cellular immunity.⁶⁴⁻⁶⁷ However, several studies have demonstrated safety and efficacy in cohorts of children with (usually) milder forms of T-cell defects, such as DiGeorge syndrome,⁶⁸⁻⁷¹ although some cases of severe disease have also been reported in these patients.^{72,73} Case reports of complications of measles vaccine are not abundant, arguing for its judicious use among patients with mild immune compromise. Criteria for live vaccine use in patients with DiGeorge syndrome have been proposed as follows: (1) good response to nonviable vaccines, (2) normal/near-normal *in vitro* T-cell response to mitogens and recall antigens, (3) CD8 T-cell counts of greater than 300 cells/mm³, and (3) CD4 cell counts of greater than 500 cells/mm³.^{68,73,74} A late complication of rubella vaccine in immunodeficient hosts has been appreciated recently.⁷⁵⁻⁷⁷ Cutaneous granulomatous inflammation (granuloma annulare, occasionally with ulceration) occurs in patients with a variety of immunodeficiencies, including those with predominantly cellular dysfunction, as well as those with some mainly humoral defects. In some patients, vaccine strain rubella has been detected in biopsy specimens of these skin lesions. Some patients also exhibit visceral (liver) granulomata containing vaccine rubella. Underlying diagnoses include activated phosphoinositide 3-kinase δ syndrome, ataxia-telangiectasia, cartilage-hair hypoplasia, recombination-activating gene 1 (*RAG1*) or *RAG2* mutation, and unspecified combined immunodeficiency. Unfortunately, many of these diagnoses would not be evident at the time of routine MMR administration. However, newborn screening for SCID through the T-cell receptor excision circle assay could raise suspicion of a non-SCID T-cell deficiency in some of these children at birth, potentially avoiding live vaccine administration.⁶² An effective therapy for these lesions has not yet been described.

Oral polio vaccine

Oral (viable) polio vaccine has long been recognized as causing severe diarrheal and paralytic disease in patients with severely impaired cellular and humoral immunity.⁷⁸ This has led to a change in vaccination procedures in many countries such that only the inactivated vaccine is administered by means of injection to young infants. However, beyond the individual risk for patients with PIDs, the problem is actually of much greater magnitude and has implications for the eradication of polio worldwide.⁷⁹⁻⁸¹

Oral polio vaccine is much more widely used in developing countries. Vaccine-derived polioviruses can persist in patients with PIDs, undergo genetic drift, and be excreted (sometimes for years) to cause outbreaks of clinically significant (often fatal) disease in areas where vaccine coverage is low. Detected or reported immunodeficiency-associated cases are relatively rare (68 cases in 26 countries in 52 years),⁷⁹ but prolonged excretion of poliovirus in a small proportion of subjects is sufficient to seriously hamper attempts toward global eradication.

Rotavirus vaccine

The human/bovine reassortant pentavalent rotavirus vaccine has been in routine use for only a decade. Soon after it was introduced, the first case reports of vaccine infections were reported in patients with SCID.⁸²⁻⁸⁴ These patients exhibited persistent diarrhea that resolved after stem cell therapy. No deaths

have been reported. Newborn screening for SCID should largely mitigate the risk of disease caused by this vaccine.⁸⁵

CONCLUSION

Educated and judicious vaccine use for immunoprophylaxis and in some cases for disease treatment are as critical for health maintenance in patients with PIDs as for all persons. Systematic study of normal vaccine responses will help refine their diagnostic use for PIDs. This is especially so for polysaccharide antigen responses, which remain challenging to characterize clinically, even in healthy subjects. It might be necessary to modify existing assays or develop new ones to realize this goal. These include refined measurements of antibody quality with respect to affinity/avidity and opsonophagocytic activity. Ongoing large-scale collection of data regarding vaccine complications and failures will be invaluable to inform PID diagnosis and cost-effective use. Vaccinology is a very active field of study not only with respect to well-known diseases but also for emerging infections worldwide. Providers who care for patients with PIDs must remain abreast of developments to provide optimal care.

Key messages

- Assessment of antibody responses to routine and supplementary vaccine administration is critical for immunodeficiency diagnosis.
- Vaccine management is an essential component of therapy for immunodeficiency.
- Early recognition of immunodeficiency reduces the likelihood of harm from live-agent vaccines.

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