Vaccination in Primary Immunodeficiency Disorders

Ali Sobh, MD[a], and Francisco A. Bonilla, MD, PhD[b] *Boston, Mass*

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. Prelicensure 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 disorders[5] are summarized in Table III. Specific areas are discussed in more detail below.

[a]Mansoura University Children's Hospital, Faculty of Medicine, Mansoura University, Mansoura, Egypt
[b]Boston Children's Hospital, Harvard Medical School, Boston, Mass
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Corresponding author: Francisco A. Bonilla, MD, PhD, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115. E-mail: Francisco.bonilla@childrens.harvard.edu.
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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 BCG[10] 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/mm^3. 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/mm^3 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