Recommendations for live viral and bacterial vaccines in immunodeficient patients and their close contacts

Medical Advisory Committee of the Immune Deficiency Foundation

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The present uncertainty of which live viral or bacterial vaccines can be given to immunodeficient patients and the growing neglect of societal adherence to routine immunizations has prompted the Medical Advisory Committee of the Immune Deficiency Foundation to issue recommendations based on published literature and the collective experience of the committee members. These recommendations address the concern for immunodeficient patients acquiring infections from healthy subjects who have not been immunized or who are shedding live vaccine–derived viral or bacterial organisms. Such transmission of infectious agents can occur within the hospital, clinic, or home or at any public gathering. Collectively, we define this type of transmission as close-contact spread of infectious disease that is particularly relevant in patients with impaired immunity who might have an infection when exposed to subjects carrying vaccine-preventable infectious diseases or who have recently received a live vaccine. Immunodeficient patients who have received therapeutic hematopoietic stem transplantation are also at risk during the time when immune reconstitution is incomplete or while they are receiving immunosuppressive agents to prevent or treat graft-versus-host disease. This review recommends the general education of what

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is known about vaccine-preventable or vaccine-derived diseases being spread to immunodeficient patients at risk for close-contact spread of infection and describes the relative risks for a child with severe immunodeficiency. The review also recommends a balance between the need to protect vulnerable subjects and their social needs to integrate into society, attend school, and benefit from peer education. (J Allergy Clin Immunol 2014;133:961-6.)

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Immunization with live viral or bacterial vaccines is a known hazard to patients with serious immunodeficiencies of T-cell, B-cell, and phagocytic cell origin. Although the risk of acquiring live vaccine–related disease by means of immunization might be well known to families of severely immunocompromised children, the concept of parents, relatives, or nonfamily members (who have not been immunized or who have been recently immunized with live vaccines) serving as a source of infection to an immunodeficient patient has not had sufficient attention. Succinct information on the risk of inadvertent spread of live or attenuated viral or bacterial infection can be found in the *Red Book: 2012 Report of the Committee on Infectious Diseases* section on immunocompromised children,[1] and the previous recommendations of the Centers for Disease Control and Prevention.[2] Recommendations are made for the 4 principal types of primary immunodeficiency: T-cell, B-cell, complement, and polymorphonuclear leukocyte. The appropriate and inappropriate vaccinations of primary immunodeficient children as provided by the *Red Book* (Table I) are reviewed with comments by the Immune Deficiency Foundation Medical Advisory Committee members based on their collective clinical expertise.[1]

For B-cell primary immunodeficiency, such as X-linked agammaglobulinemia and common variable immunodeficiency (CVID), vaccines to be avoided include oral poliovirus, yellow fever, live attenuated influenza, and live bacterial (eg, typhoid [*Salmonella typhi*, *Ty21a*]) vaccines (Table I). Table I mentions the uncertainty of risk and effectiveness of the measles and varicella vaccines for immunodeficient patients because of the lack of specific evidence for protection. Most antibody-deficient patients treated with intravenous immunoglobulin do not have the capacity to generate protective antibody responses. Patients with X-linked agammaglobulinemia have a predilection for central nervous system enteroviral infections, including oral poliovirus vaccine infection,[3] and rarely, this complication has been encountered by patients with CVID with severe hypogammaglobulinemia.[4] A study of 50 patients with X-linked agammaglobulinemia given BCG vaccine as infants did not reveal systemic infection, suggesting this immunization does not pose a major risk (personal communication, Sergio Rosenzweig, MD, October 4, 2013). Although proscribed by the *Red Book: 2012*, there are no reports that patients with CVID who received attenuated live influenza vaccine became infected or spread live virus to others.[1] It is also true that close contacts immunized with the live influenza vaccine rarely, if ever, have transmitted the virus to patients with CVID.[5] On the basis of current recommendations and the variable level of T-cell defects, it is unclear what level of risk for vaccine-acquired disease exists in patients with CVID. This might be related, at least in part, to the later onset of CVID that results in a different pattern of vaccine exposure compared with X-linked agammaglobulinemia. For IgA deficiency and IgG subclass deficiencies, current information suggests that all vaccines are considered safe. It is uncertain that vaccinations will be effective for patients receiving replacement intravenous immunoglobulin therapy.

Abbreviations used
CVID: Common variable immunodeficiency
HCT: Hematopoietic stem cell transplantation
Hib: *Haemophilus influenzae type b*
SCID: Severe combined immunodeficiency disease

For patients with severe T-cell deficiencies before immune reconstitution (eg, severe combined immunodeficiency disease [SCID] and complete DiGeorge syndrome), no live viral (oral poliovirus, measles, mumps, rubella, varicella, yellow fever, herpes zoster, smallpox, rotavirus, or live attenuated influenza virus) or live bacterial (BCG or *S typhi*, *Ty21a*) vaccines should be administered. Immunodeficient patients who have received hematopoietic stem cell transplantation (HCT) but who continue to have incomplete immune reconstitution or are undergoing immunosuppression should not be given live viral or bacterial vaccines.[1] For the patients with HCT with full immunologic reconstitution, individual assessments of the risk/benefit ratio of live viral vaccines should be made by clinical immunology experts.

In patients with partial T-cell deficiencies (eg, partial DiGeorge syndrome or Wiskott-Aldrich syndrome), the *Red Book* states that all live viral vaccines are to be avoided, although inadvertent immunization with the measles, mumps, and rubella vaccine has not produced clinical infection.[6] Individual assessment of a patient's immune status is recommended before consideration of any live viral vaccines in this group of patients. Live measles, mumps, rubella, and varicella vaccines can be considered with the above caveats. The *Red Book: 2012* recommends that a level of 500 CD4 T cells/mm^3 be required for immunization with these vaccines. Children less than 6 years of age must have higher levels of CD4 T cells to consider these immunizations (ie, 1-6 years, 1000 CD4 T cells/mm^3; <1 year, >1500 CD4 T cells/mm^3), as recommended by the Centers for Disease Control and Prevention.[7] Although recommended for HIV-infected children, these levels of CD4 T cells are consistent with the lower range of age-matched healthy children. On the other hand, inactivated viral vaccines can be used safely, but the degree of effectiveness depends on the level of immunocompetence in the patient at the time of vaccination. Pneumococcal, meningococcal, and *Haemophilus influenzae type b (Hib)* vaccines are recommended for these patients because they are T cell–independent antigens. In addition, seasonal killed influenza vaccines are also recommended because they could provide some degree of protection with little or no risk to these patients.

The determination of immune competence in post-HCT children with SCID would include lymphocyte subsets (eg, CD3, CD4, CD8, CD20, and CD56); proliferation of lymphocytes to normal ranges with PHA, anti-CD3 antibody, and recall antigens, such as *Candida* species; and production of antibodies to recall (eg, tetanus) and new (eg, bacteriophage phi-X174) antigens. Parents need to be made aware of the risks of inadvertent