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.)

Key words: *Live viral and bacterial vaccines, primary immunodeficiency disease, severe combined immunodeficiency disease, cellular immune reconstitution*

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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

TABLE I. Immune Deficiency Foundation Medical Advisory Committee recommendations for immunization of children and adolescents with primary immune deficiencies

Category	Example of specific immunodeficiency	Vaccine contraindications, *Red Book: 2012*	Effectiveness and comments, including risk-specific vaccines*	Observations of PID physicians#
Primary†				
B lymphocyte (humoral)	Severe antibody deficiencies (eg, X-linked agammaglobulinemia and CVID)	OPV,‡ smallpox, LAIV, YF, and most live bacteria vaccines§; consider measles vaccine. There are no data for varicella or rotavirus vaccines.	Effectiveness of any vaccine is uncertain if it depends only on humoral response (eg, PPSV23 or MPSV4). IGIV therapy interferes with measles and possibly varicella immune response. Efficacy of pneumococcal vaccination is not documented in severe antibody deficiency. Consider measles and varicella vaccines.	Agree with statements on XLA but little vaccine-related viral infection is seen in patients with CVID.
	Less severe antibody deficiencies (eg, selective IgA deficiency and IgG subclass deficiencies)	OPV,‡ BCG, YF vaccines; other live vaccines‖ appear to be safe, but caution is urged.	All vaccines are probably effective; immune response might be attenuated. Pneumococcal vaccine and *Hib* are recommended.	Agreement
T lymphocyte (cell-mediated and humoral)	Complete defects (eg, severe combined immunodeficiency, complete DiGeorge syndrome)	All live vaccines§‖¶	All vaccines are probably ineffective. Pneumococcal vaccine and *Hib* are recommended.	Agreement
	SCID given HCT	Live virus and live bacteria vaccines, depending on immune status§‖	Effectiveness of any vaccine depends on degree of immune suppression. Pneumococcal, meningococcal, and *Hib* vaccines are recommended.	Careful assessment of immune competence is required before any live virus vaccination.
	Partial defects (eg, most patients with DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia telangiectasia)	Selected live vaccines§‖	Effectiveness of any vaccine depends on degree of immune suppression. Pneumococcal and *Hib* and meningococcal vaccines are recommended. Consider *Hib* vaccine if not administered during infancy.	Weight of clinical evidence does not support strict avoidance of all live viral vaccines. Documentation of adequate T-cell numbers (>500 $CD4^+$ T cells/mm^3) is required.
Complement	Persistent complement component, properdin, or factor B deficiency	None	All routine vaccines are probably effective. Pneumococcal and meningococcal vaccines are recommended.	Agreement
Phagocytic function	Chronic granulomatous disease, leukocyte adhesion defects, myeloperoxidase deficiency	Live bacterial vaccines§	All inactivated vaccines are safe and probably effective. Live virus vaccines are probably safe and effective.	Agreement
IFN-γ–IL-12 pathway defects	Predilection for BCG vaccine in acquired infections	BCG§	No reported live attenuated viral vaccine–induced infection, but caution is urged.	There are very few data on live vaccine other than that for BCG.

Adapted from Pickering LK, Baker CJ, Kimberlin DW, Long SS, editors. Red Book: 2012 Report of the Committee on Infectious Diseases. 29th ed. Elk Grove Village (IL): American Academy of Pediatrics; 2012.

Age-related levels of immunocompetence proposed by the CDC are as follows: <1 year, 1500 $CD4^+$ T cells/mm^3; 1-5 years, 1000 $CD4^+$ T cells/mm^3; and >6 years, 500 $CD4^+$ T cells/mm^3. These can also be used for patients with HIV.

IGIV, Immune globulin, intravenous; *LAIV*, live attenuated influenza vaccine; *MMR*, measles, mumps, and rubella; *OPV*, oral poliovirus; *PID*, primary immunodeficiency disease; *XLA*, X-linked agammaglobulinemia; *YF*, yellow fever.

*Other vaccines that are recommended universally or routinely should be given if not contraindicated.

†All children and adolescents should receive an annual age-appropriate inactivated influenza vaccine. LAIV is indicated only for healthy subjects 2 through 49 years of age.

‡OPV vaccine is no longer available in the United States.

§Live bacteria vaccines: BCG and Ty21a *S typhi* vaccine.

‖Live virus vaccines: LAIV, MMR, measles-mumps-rubella-varicella (MMRV), herpes zoster (ZOS), OPV, varicella, YF, vaccinia (smallpox), and rotavirus.

¶Regarding T-lymphocyte immunodeficiency as a contraindication to rotavirus vaccine, data only exist for severe combined immunodeficiency syndrome.

#Opinions of consensus of PID experts who authored this policy statement.

vaccine-related infections and provide signed consent for the child to receive live attenuated vaccines.

For complement deficiencies, early components (eg, C1, C2, and C4) and the late components C5 to C9, all viral vaccines, can be administered, and pneumococcal, *Hib*, and meningococcal vaccines for the early- and late-acting complement components, respectively, are strongly recommended because of the predilection of complement-deficient patients to acquire these bacterial infections. Therefore all childhood vaccines can be given to complement-deficient patients, with special emphasis on the pneumococcal and meningococcal vaccines using both the unconjugated and conjugated forms, as appropriate, to retain protection levels of antibodies.[8]

For white blood cell disorders (eg, neutropenias, chronic granulomatous disease, and leukocyte adhesion deficiency), all routine childhood vaccines can be given. Patients with chronic granulomatous disease should not be given the live bacterial vaccines, BCG, and *Salmonella Ty21a*. Similarly, patients with IFN-γ–IL-12 pathway defects should not receive BCG and *Salmonella Ty21a* vaccination because of their predilection for these infections.[9]

CLOSE CONTACTS

Close contacts of patients with compromised immunity should not receive live oral poliovirus vaccine because they might shed the virus and infect a patient with compromised immunity. Close contacts can receive other standard vaccines because viral shedding is unlikely and these pose little risk of infection to a subject with compromised immunity.[1]

Particularly important are annual immunizations with inactivated influenza vaccine; scheduled periodic pertussis vaccine (Tdap); pneumococcal vaccine; measles, mumps, and rubella vaccine; and varicella vaccine for older contacts whose routine immunizations might not be up to date.

The only vaccines pregnant women should routinely receive are the Tdap and inactivated influenza vaccines. However, mothers at high risk for a child with primary immunodeficiency and without an up-to-date immunization history should also receive pneumococcal, *Hib*, and meningococcal vaccines so that maternally transferred IgG antibodies can protect the potentially immunodeficient newborn child during the first few months of life while definitive diagnosis and treatment are undertaken.

If a varicella rash develops in a close contact after immunization with the varicella or zoster vaccines, the risk of transmission to the immunocompromised subject is minimal unless blisters develop at the site of the vaccine administration. In this case isolation of the patient is recommended, and varicella zoster immune globulin could be given prophylactically. Treatment of the close contact or the patient, if infected, would consist of intravenous acyclovir or oral valacyclovir. Killed trivalent influenza vaccine is preferred for close contacts, although live attenuated influenza vaccine can be given to close contacts because of its low rate of transmission to other subjects.[1]

EXAMPLES OF INADVERTENT TRANSMISSION OF LIVE VIRAL VACCINE–RELATED INFECTION

Vaccine-derived poliovirus

In 2010, an infant in South Africa received 3 doses of poliovirus vaccine (oral vaccine at birth and inactivated vaccine at 10 and 14 weeks of life) before identification of his diagnosis of SCID.[10] At 10 months of life, the child had fever, vomiting, tonic-clonic seizures, and acute flaccid paralysis. Poliovirus 3 was identified in a stool sample and cerebrospinal fluid. Viral analysis revealed vaccine-derived poliovirus, and the child was left with lower limb paralysis.

In 2005, an Amish infant in Minnesota who had not been immunized with oral poliovirus before diagnosis of SCID had fever, respiratory tract infections, failure to thrive, bloody diarrhea, and anemia.[11] A stool specimen revealed the presence of live oral polio vaccine–derived poliovirus. Fortunately, the child had no flaccid paralysis, and a successful bone marrow transplantation cleared the vaccine-derived poliovirus from her stool. An extensive investigation of the child's Amish community of several hundred persons revealed the presence of high-titer neutralizing antibodies to poliovirus 1, and many of these subjects had stool specimens that were positive for vaccine-derived poliovirus. Altogether, 35% of this isolated community had serologic or virologic evidence of the vaccine-derived poliovirus, including the patient's 3 siblings, who had never been immunized with either the oral poliovirus vaccine or the inactivated poliovirus vaccine. This outbreak of a vaccine-derived poliovirus infection shows how in an undervaccinated community vaccine-derived virus can spread to others and, in the case of the child with SCID, might lead to vaccine-derived poliovirus infection and clinical disease. Beginning in 2000, only the inactivated poliovirus vaccine was available for routine use in the United States and Canada.[12]

Vaccine-acquired rotavirus

Since 2009, 9 cases have been published describing rotavirus vaccine–derived infections that have threatened the health of children later discovered to have SCID.[13] Because rotavirus infection is a diarrheal disease causing high morbidity in infants, efforts to produce a vaccine that reduces the incidence of acute viral gastroenteritis in infants older than 3 months of life were certainly warranted. The reports of acute illness associated with vaccination in children with undiagnosed SCID led to a modification in the package insert to warn against use in immunosuppressed infants so as to avoid vaccine-related disease in infants with SCID. However, the American Academy of Pediatrics has recommended that all infants be given this vaccine at 6 to 8 weeks of life, a time before infants with SCID typically have serious problems, and thus an affected infant would likely not receive a diagnosis. Fortunately, the implementation of newborn screening for SCID should identify infants with SCID early enough to prevent the accidental administration of rotavirus vaccine to these affected infants.[14] There have been no reports of household contacts spreading rotavirus disease to infants with SCID.

LOSS OF HERD IMMUNITY IN THE GENERAL POPULATION: IMPLICATIONS FOR CHILDREN WITH PRIMARY IMMUNODEFICIENCY

For many decades, the public has grown complacent with the rare occurrence of potential deadly childhood infections, such as pertussis (whooping cough), measles, mumps, and rubella. The advent of effective immunization is most certainly the reason that these former scourges of pediatric infection became rare. The public has a mistaken belief that these diseases are gone and will not return, resulting in more children not receiving standard childhood vaccines. In addition, some parents have a suspicion that childhood immunizations have severe side effects, including

the development of autism, despite overwhelming scientific evidence to the contrary. Clinical and epidemiologic research has witnessed a disturbing resurgence of these childhood illnesses. Adding to this potentially dangerous situation is the evidence that newer vaccines with extremely rare side effects might provide a shorter interval of protection compared with older vaccines with a higher rate of untoward reactions, even though reactions were confined to a very small proportion of the pediatric population (generally 2 per 100,000 injections).[15] Without herd immunity to the infectious epidemics of the past, unimmunized members of society not only fall prey to morbid and possibly lethal infections that will spread from children to adults but also the reverse. Herd immunity to poliovirus, for example, protects against wild-type poliovirus transmitted by newly arrived immigrants from other countries where poliovirus infection still exists. Herd immunity also protects against the spread of vaccine-derived live poliovirus infections. Parents who elect not to vaccinate their children are actually placing themselves and their children at increased risk of serious infection and even death.[16] A case in point is that pertussis infections are now being seen in tens of thousands of young infants from largely unvaccinated communities. In the 1940s, when the pertussis vaccine was first introduced, the number of US pertussis cases decreased from hundreds of thousands annually to an average of 5000 cases per year.[17] However, starting in the 1990s, the number of pertussis cases began to increase, with a recent peak of 41,000 cases per year in the United States. This has prompted new recommendations regarding reimmunization schedules for children and adults.

The threat of pertussis and other childhood communicable diseases to children with immunodeficiency is particularly alarming. The increased risk of disease in the pediatric population, in part because of increasing rates of vaccine refusal and in some circumstances more rapid loss of immunity, increases potential exposure of immunodeficient children. The immunosuppressed subject is particularly at risk in crowded living conditions because of the spread of these diseases by aerosol droplets or through the oral-fecal route.

INTEGRATION OF THE IMMUNORECONSTITUTED IMMUNODEFICIENT CHILD INTO SOCIETY

The protective instincts of parents for the child who has an immunodeficiency must maintain a balance with the needs of the child to develop socially and educationally. A limited study of 16 infants with SCID treated with HCT reported a significant deficit in mental development and psychomotor validated scale index scores in the first few years after HCT.[18] In a larger number of infants with SCID receiving HCT in the United Kingdom, Titman et al[19] reported an increase in behavioral disorders and neurocognition problems. A related study of cognitive and psychosocial outcomes in 21 children treated with HCT for hemophagocytic lymphohistiocytosis found that affected children had a lower full-scale IQ score of 81 compared with national control scores of 100 or sibling control IQ scores of 99.[20] A high level of support at school was necessary to prevent affected children from falling further behind their classmates. Whether these problems are only a consequence of the chemotherapy given to these children before HCT or infections is not known. Regardless, development of the child as a social being is extremely important, and the child cannot remain housebound for fear of infectious susceptibility. The authors urged long-term systematic follow-up of these patients to make possible early recognition, effective measurement, and proper school interventions to address these conditions.

SUMMARY

The development of immunizations for common bacterial and viral infections has represented a major advance in the battle against microbial organisms that constantly threaten the welfare of humankind and particularly the pediatric population. However, the alarming increase in nonimmunized persons could lead to a return of the epidemics seen in the past. Although the benefits of immunization to the general population have been enormous, special caution and considerations must be made for subjects with primary immunodeficiency disorders. Subjects who lack adaptive and some cases of defective innate immunity are at considerable risk when immunized with live or attenuated viral or bacterial vaccines because their complete or partial lack of immunity might prevent them from halting the growth and spread of the vaccine-derived live infectious agent. Close contacts might carry vaccine-derived virus and cause the horizontal spread of the virus to a child with primary immunodeficiency. Special precautions must be taken with family members to avoid live poliovirus immunizations, but almost all other vaccines can be given with appropriate explanation of the risks and benefits of immunizations and the very low transmission rate to immunodeficient subjects.[1]

Killed vaccines will not cause infection in immunodeficient or any other children. The fear of increased community-acquired vaccine-preventable diseases should lead to adherence to and completion of recommended immunization schedules in the community to reinforce herd immunity, such that all vaccine-preventable diseases become exceedingly rare.

Immunodeficient children who have attained full immune reconstitution after bone marrow, blood, or cord blood stem cell transplantation might have sufficient T-cell responses to protect against exposures to horizontal viral infection, but careful evaluation of the degree of immune reconstitution of an HCT-treated immunodeficient patient must be made before live viral vaccines are administered. This precaution for proper immunologic evaluation has been reinforced recently by the development of central nervous system vasculopathy secondary to vaccine strain varicella in an undiagnosed child with dedicator of cytokinesis 8 (DOCK-8) deficiency.[21] However, immunodeficient children who have successfully reconstituted immune function after HCT should not be isolated from society because of their equally important need to become part of normal society. School attendance is essential for their neuropsychological adjustment.

Children with some of the common immune deficiencies (eg, X-linked agammaglobulinemia, partial DiGeorge, and IgA deficiency) or with a narrow infection phenotype (eg, X-linked thrombocytopenia) can be immunized with live viral vaccine (other than poliovirus), but the advice of a clinical immunologist who cares for immunodeficient children is strongly recommended before immunization regarding the risk versus the benefit. Education of families with immunodeficiencies is a must to avoid complications of live viral vaccines. Further information on the management of immunodeficient children and other patients can be found at the following Web links: the Online Mendelian Inheritance in Man Web site (www.ncbi.nlm.nih.gov/omin/); the European Society for Immune Deficiencies Web site

(www.esid.org/), and the Immune Deficiency Foundation Web site (www.primaryimmune.org).

RECOMMENDATIONS

1. Educate parents and physicians about the critical need for maintenance of herd immunity in the population at large. It is particularly important for family members of patients with defective T and B lymphocyte–mediated immunity to receive all of the available standard immunizations (excluding live poliovirus).
2. Avoid live viral and bacterial vaccines in all patients with significant T- and B-cell deficiencies. Early diagnosis afforded by newborn screening for low numbers of T cells with the T-cell receptor excision circle assay will alert physicians and parents of the need to avoid live viral and bacterial vaccines, including the live rotavirus vaccine, which can produce severe diarrhea in infants with serious T-cell compromise. For any infants born into an extended family with a history of infants with life-threatening immune deficiency, defer all live viral and bacterial vaccines until the infant has been tested to rule out a serious T-cell immunodeficiency. This precaution is particularly important for high-risk families living in states that do not have T-cell receptor excision circle–based newborn screening for serious T-cell deficiencies.
3. Determine the degree of immune reconstitution in patients treated with HCT, enzyme therapy, or gene therapy before live vaccine treatment. Vaccinate only after consultation with a clinical immunologist proficient in the diagnosis and management of primary immune deficiency who can explain the risk/benefit ratio for parents or patients.
4. Balance the need of the immunoreconstituted child to be protected from exposure to infection from live vaccines and close contact–transmitted vaccine-derived infection with the need of the child to integrate into society and develop social and learning skills in group environments.

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