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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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Abstract

The present uncertainty of which live viral or bacterial vaccines may be given to immune deficient 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 upon published literature and the collective experience of the committee members. These recommendations address the concern for immunodeficient patients acquiring infections from healthy individuals who have not been immunized or who are shedding live vaccine-derived viral or bacterial organisms. Such transmission of infectious agents may occur within the hospital, clinic, home, or at any public gathering. Collectively, we define this type transmission as close-contact spread of infectious disease that is particularly relevant in patients with impaired immunity who may develop infection when exposed to individuals 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 on immunosuppressive agents to prevent or treat graft-versus-host disease.

This review recommends the general education of what 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 individuals with their social needs to integrate into society, attend school, and benefit from peer education.

Keywords

Live Viral and Bacterial Vaccines; Primary Immunodeficiency Disease; Severe Combined Immunodeficiency Disease; Cellular Immune reconstitution

Introduction

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. While the risk of acquiring live vaccine-related disease by immunization may be well known to families of severely

immunocompromised children, the concept of parents, relatives, or non-family members (not immunized or who have been recently immunized with live vaccines) serving as a source of infection to an immune deficient 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 four 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 (IDF) Medical Advisory Committee members based upon 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 (e.g. typhoid [*Salmonella typhi*, *Ty21a*]) vaccines (See Table I). Table 1 mentions the uncertainty of risk and effectiveness of the measles and varicella vaccines for immunodeficient patients due to the lack of specific evidence for protection. Most antibody deficient patients treated with IVIG 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 CVID patients with severe hypogammaglobulinemia[4]. A study of 50 patients with X-linked agammaglobulinemia given Bacille Calmette-Guérin (BCG) vaccine as infants did not reveal systemic infection suggesting this immunization does not pose a major risk (Personal communication, Sergio Rosenzweig, M.D., October 4, 2013). Although proscribed by the Red Book 2012, there are no reports that CVID patients who received attenuated live influenza vaccine became infected or spread live virus to others.[1]. The reverse is also true, that close-contacts immunized with the live influenza vaccine rarely, if ever, have transmitted the virus to CVID patients[5]. Based on current recommendations and the variable level of T cell defects, it is unclear what level of risk for vaccine acquired disease exists in CVID patients. This may be at least in part related to the later onset of CVID that results in a different pattern of vaccine exposure compared to XLA. For IgA deficiency and IgG subclass deficiencies current information suggests that all vaccines are considered safe. For patients on replacement IVIG therapy, it is uncertain that vaccinations will be effective.

For severe T cell deficiencies prior to immume reconstitution, (e.g. severe combined immunodeficiency disease [SCID], 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, *Salmonella typhi*, [*Ty21a*]) vaccines should be given. Immunodeficient patients who have received hematopoietic stem cell transplantation (HCT) but who remain with incomplete immune reconstitution or are under immunosuppression should not be given live viral or bacterial vaccines.[1] For the HCT patients 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 (e.g., partial DiGeorge syndrome, 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 prior to consideration of any live viral vaccines in this group of patients. Live measles, mumps, rubella, and varicella vaccines may 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 under 6 years of age must need higher levels of CD4 T cells to consider these immunizations, i.e., >1 year to 6 years, 1000 CD4 T cells/mm^3 and <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 may be used safely, but the degree of effectiveness depends upon 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, since they are T cell independent antigens. In addition, seasonal killed influenza vaccines are also recommended as this could provide some degree of protection with little or no risk to these patients.

The determination of immune competence in post-HCT SCID children would include lymphocyte subsets (e.g. CD3, CD4, CD8, CD20, CD56); proliferation of lymphocytes to normal ranges with phytohemagglutinin, anti-CD3 antibody, and recall antigens such as Candida; and production of antibodies to recall (e.g. tetanus) and new antigens (e.g. bacteriophage phi-X174). Parents need to be made aware of the risks of inadvertent vaccine-related infections and give signed consent for the child to receive live attenuated vaccines.

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

For white blood cell disorders (e.g. neutropenias, chronic granulomatous disease, leukocyte adhesion deficiency), all routine childhood vaccines may 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 due to their predilection to acquire these infections.[9]

Close-Contacts

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

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

The only vaccines pregnant women should routinely receive are Tdap vaccine and inactivated influenza vaccine. 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 maternally transferred IgG antibodies can protect the potentially immunodeficient newborn child during the first few months of life while definitive diagnosis and treatment can be undertaken.

If a varicella rash develops in a close-contact after immunization with the varicella or zoster vaccines, the risk of transmission to the immune compromised individual 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 (VZIG) 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 due to its low rate of transmission to other individuals[1].

Examples of Inadvertent Transmission of Live Viral Vaccine-Related Infection

Vaccine-Derived Poliovirus

In 2010, an infant in South Africa prior to identification of his diagnosis of SCID received 3 doses of poliovirus vaccine (oral vaccine at birth, and inactivated at 10 and 14 weeks of life).[10] At 10 months of life, the child developed 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 prior to diagnosis of SCID, developed fever, respiratory 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 suffered no flaccid paralysis and a successful bone marrow transplant cleared the vaccine-derived poliovirus from her stool. An extensive investigation of the child's Amish community of several hundred people 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 virological 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 under-vaccinated community, vaccine-derived virus can spread to others and in the case of the child with SCID, may 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] Since 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 undiagnosed SCID children 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 6–8 weeks of life, a time prior to SCID infants typically having serious problems and thus, an affected infant would likely be undiagnosed. 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 SCID infants.

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 may provide a shorter interval of protection compared with older vaccines that had 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 in 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 fell from hundreds of thousands annually to an average of 5,000 cases per year.[17] However, starting in the 1990s, the number of pertussis cases began to rise with a recent peak of 41,000 cases per year in the U.S. 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 due to increasing rates of vaccine refusal and in some circumstances more rapid loss of immunity, increases potential exposure of immunodeficient children. The immunosuppressed individual is particularly at risk in crowded living conditions owing to the spread of these diseases by aerosol droplets or 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 SCID infants treated with HCT reported a significant deficit of mental development and psychomotor validated scale index in the first few years post HCT.[18] Titman et al[19] in a larger number of SCID infants receiving HCT in the UK 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 to national control scores of 100 or sibling control IQ score 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 these children prior to HCT or to 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 non-immunized persons could lead to a return of the epidemics that were seen in the past. While the benefits of immunization to the general population have been enormous, special caution and considerations must be made for individuals with primary immunodeficiency disorders. Individuals 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 may prevent them from halting the growth and spread of the vaccine-derived live infectious agent. Close-contacts may carry vaccine-derived virus and cause the horizontal spread of the virus to a child with primary immunodeficiency. Special precautions must be taken with the 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 may have sufficient T cell responses to protect against exposures to horizontal viral infection but careful evaluation of the degree of immune reconstitution of a HCT-treated immunodeficient patient must be made before live viral vaccines are administered. This precaution for proper immunological evaluation has been reinforced recently by the development of central nervous system vasculopathy secondary to vaccine strain varicella in an undiagnosed child with DOCK-8 deficiency.[21] Immunodeficient children who have successfully reconstituted immune function after HCT, however, 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 (e.g. XLA, partial DiGeorge, IgA deficiency) or with narrow infection phenotype (e.g., 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 prior to immunization regarding the risk vs. the benefit. Education of families with immunodeficiencies is a must to avoid complications of live viral vaccines. Further information on the management of immune deficient children and other patients can be found at the following web links: Online Mendelian Inheritance in Man (OMIM), website (www.ncbi.nlm.nih.gov/omin/); European Society for Immune Deficiencies (ESID), website (www.esid.org/), Immune Deficiency Foundation, website (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 polio virus).
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 circles (TREC 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 TREC 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 prior to live vaccine treatment. Vaccinate only following consultation with a clinical immunologist proficient in diagnosis and management of primary immune deficiency who can explain the risk/benefit ratio for parents or patients.

4. Balance the need of the immune reconstituted 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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Abbreviations

HCT	hematopoietic stem cell transplant
PID	primary immunodeficiency disease
SCID	severe combined immunodeficiency disease

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Table 1

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[a]	Observations of PID Physicians[g]
Primary[b]				
B lymphocyte (humoral)	Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)	OPV,[c] smallpox, LAIV, yellow fever (YF), and most live-bacteria vaccines[d]; consider measles vaccine; no data for varicella or rotavirus vaccines	Effectiveness of any vaccine is uncertain if it depends only on humoral response (e.g., PPSV23 or MPSV4); IGIV therapy interferes with measles and possibly varicella immune response. Efficacy of pneumococcal vaccination 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 CVID
	Less severe antibody deficiencies (e.g., selective IgA deficiency and IgG subclass deficiencies)	OPV,[c] BCG, YF vaccines; other live vaccines[e] appear to be safe, but caution is urged.	All vaccines probably effective; immune response may be attenuated. Pneumococcal vaccine and *Hib* recommended.	Agreement
T lymphocyte (cell-mediated and humoral)	Complete defects (e.g., severe combined immunodeficiency, complete DiGeorge syndrome)	All live vaccines[d,e,f]	All vaccines probably ineffective. Pneumococcal vaccine and *Hib* recommended.	Agreement
	SCID given HCT	Live-virus and – bacteria vaccines, depending on immune status.[d,e]	Effectiveness of any vaccine depends on degree of immune suppression. Pneumococcal, meningococcal, and *Hib* vaccines recommended.	Careful assessment of immune competence required prior to any live virus vaccination
	Partial defects (e.g., most patients with DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia telangiectasia)	Selected live vaccines[d,e]	Effectiveness of any vaccine depends on degree of immune suppression. Pneumococcal and *Hib* and meningococcal vaccines 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 number (>500 CD4+ T cells/mm^3)
Complement	Persistent complement component, properdin, or factor B deficiency	None	All routine vaccines probably effective. Pneumococcal and meningococcal vaccines recommended.	Agreement
Phagocytic function	Chronic granulomatous disease, leukocyte adhesion defects, myeloperoxidase deficiency	Live-bacterial vaccines[d]	All inactivated vaccines safe and probably effective. Live-virus vaccines probably safe and effective.	Agreement
IFN-γ-IL-12 pathway defects	Predilection for BCG vaccine in acquired infections	BCG[d]	No reported live attenuated viral vaccine induced infection, but caution is urged.	Very little data on live vaccine other than that of BCG.

OPV indicates oral poliovirus; LAIV, live-attenuated influenza vaccine; IGIV, Immune Globulin Intravenous; Ig, immunoglobulin; BCG, Bacille Calmette-Guérin; *Hib*, *Haemophilus influenzae* type b; MMR, measles-mumpsrubella.

J Allergy Clin Immunol. Author manuscript; available in PMC 2015 April 01.

[a] Other vaccines that are recommended universally or routinely should be given if not contraindicated.

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

[c] OPV vaccine no longer is available in the United States.

[d] Live-bacteria vaccines: BCG and Ty21a *Salmonella typhi* vaccine.

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

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

[g] Opinions of consensus of PID experts who authored this policy statement

Age-related levels of immunocompetence proposed by the CDC are <1 yr, 1500, 1–5 yr 1000, >6 yr, 500 CD4+ T cells/mm^3 for HIV may also be used.

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