2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host

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An international panel of experts prepared an evidenced-based guideline for vaccination of immunocompromised adults and children. These guidelines are intended for use by primary care and subspecialty providers who care for immunocompromised patients. Evidence was often limited. Areas that warrant future investigation are highlighted.

Keywords. vaccination; immunization; immunocompromised patients; immunosuppression; asplenic patients; immunodeficiency patients

EXECUTIVE SUMMARY

These guidelines were created to provide primary care and specialty clinicians with evidence-based guidelines for active immunization of patients with altered immunocompetence and their household contacts in order to safely prevent vaccine-preventable infections. They do not represent the only approach to vaccination. Recommended immunization schedules for normal adults and children as well as certain adults and children at high risk for vaccine-preventable infections are updated and published annually by the Centers for Disease Control and Prevention (CDC) and partner organizations. Some recommendations have not been addressed by the Advisory Committee on Immunization Practices (ACIP) to the CDC or they deviate from recommendations. The goal of presenting these guidelines is to decrease morbidity and mortality from vaccine-preventable infections in immunocompromised patients. Summarized below are the recommendations made by the panel. Supporting tables that provide additional information are available in the electronic version. The panel followed a process used in the development of other Infectious Diseases Society of America guidelines, which included a systematic weighting of the quality of the evidence and the grade of the recommendation (Table 1). The key clinical questions and recommendations are summarized in this executive summary. A detailed description of the methods,

Received 4 October 2013; accepted 5 October 2013; electronically published 4 December 2013.

It is important to realize that guidelines cannot always account for individual variation among patients. The guidelines are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

An asterisk (*) indicates recommendation for a course of action that deviates from recommendations of the Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention.

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Clinical Infectious Diseases 2014;58(3):e44–100

DOI: 10.1093/cid/cit684

Table 1. Classification System for Assessing Strength of Recommendations and Quality of the Supporting Evidence

Strength of Recommendation and Quality of Evidence	Clarity of Balance Between Desirable and Undesirable Effects	Methodological Quality of Supporting Evidence (Examples)	Implications
Strong recommendation, high-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research is unlikely to change our confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, low-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence	Recommendation may change when higher-quality evidence becomes available. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Strong recommendation, very low-quality evidence (very rarely applicable)	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher-quality evidence becomes available; any estimate of effect for at least 1 critical outcome is very uncertain.
Weak recommendation, high-quality evidence	Desirable effects closely balanced with undesirable effects	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances, patients, or societal values. Further research is unlikely to change our confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Alternative approaches likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak recommendation, low-quality evidence	Uncertainty in the estimates of desirable effects, harms, and burden; desirable effects, harms, and burden may be closely balanced	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Weak recommendation, very low-quality evidence	Major uncertainty in the estimates of desirable effects, harms, and burden; desirable effects may or may not be balanced with undesirable effects	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Other alternatives may be equally reasonable. Any estimate of effect, for at least 1 critical outcome, is very uncertain.

Abbreviation: RCT, randomized controlled trial.

background, and evidence summaries that support each recommendation can be found in the full text of the guidelines.

RECOMMENDATIONS FOR RESPONSIBILITY FOR VACCINATION

I. Who Is Responsible for Vaccinating Immunocompromised Patients and Members of Their Household?

1. Specialists who care for immunocompromised patients share responsibility with the primary care provider for ensuring that appropriate vaccinations are administered to immunocompromised patients (strong, low).*
2. Specialists who care for immunocompromised patients share responsibility with the primary care provider for recommending appropriate vaccinations for members of immunocompromised patients' household (strong, very low).*

RECOMMENDATIONS FOR TIMING OF VACCINATION

II. When Should Vaccines Be Administered to Immunocompetent Patients in Whom Initiation of Immunosuppressive Medications Is Planned?

3. Vaccines should be administered prior to planned immunosuppression if feasible (strong, moderate).
4. Live vaccines should be administered ≥4 weeks prior to immunosuppression (strong, low) and should be avoided within 2 weeks of initiation of immunosuppression (strong, low).*
5. Inactivated vaccines should be administered ≥2 weeks prior to immunosuppression (strong, moderate).

RECOMMENDATIONS FOR VACCINES FOR HOUSEHOLD MEMBERS OF IMMUNOCOMPROMISED PATIENTS

III. Which Vaccines Can Be Safely Administered to Individuals Who Live in a Household With Immunocompromised Patients? What Precautions Should Immunocompromised Patients Observe After Vaccination of Household Members?

6. Immunocompetent individuals who live in a household with immunocompromised patients can safely receive inactivated vaccines based on the CDC–ACIP's annually updated recommended vaccination schedules for children and adults (hereafter, CDC annual schedule; strong, high) or for travel (strong, moderate).
7. Individuals who live in a household with immunocompromised patients age ≥6 months should receive influenza vaccine annually (strong, high). They should receive either:
   (a) Inactivated influenza vaccine (IIV; strong, high) or
   (b) Live attenuated influenza vaccine (LAIV) provided they are healthy, not pregnant, and aged 2–49 years (strong, low). Exceptions include individuals who live in a household with an immunocompromised patient who was a hematopoietic stem cell transplant (HSCT) recipient within 2 months after transplant or with graft vs host disease (GVHD) or is a patient with severe combined immune deficiency (SCID).* In these exceptions, LAIV should not be administered (weak, very low) or, if administered, contact between the immunocompromised patient and household member should be avoided for 7 days (weak, very low).
8. Healthy immunocompetent individuals who live in a household with immunocompromised patients should receive the following live vaccines based on the CDC annual schedule: combined measles, mumps, and rubella (MMR) vaccines (strong, moderate); rotavirus vaccine in infants aged 2–7 months (strong, low); varicella vaccine (VAR; strong, moderate); and zoster vaccine (ZOS; strong, moderate). Also, these individuals can safely receive the following vaccines for travel: yellow fever vaccine (strong, moderate) and oral typhoid vaccine (strong, low).
9. Oral polio vaccine (OPV) should *not* be administered to individuals who live in a household with immunocompromised patients (strong, moderate).
10. Highly immunocompromised patients should avoid handling diapers of infants who have been vaccinated with rotavirus vaccine for 4 weeks after vaccination (strong, very low).
11. Immunocompromised patients should avoid contact with persons who develop skin lesions after receipt VAR or ZOS until the lesions clear (strong, low).

VACCINES FOR INTERNATIONAL TRAVEL

IV. Which Vaccines Can Be Administered to Immunocompromised Persons Contemplating International Travel?

12. Clinicians may administer inactivated vaccines indicated for travel based on the CDC annual schedule for immunocompetent adults and children (strong, low).
13. Yellow fever vaccine generally should *not* be administered to immunocompromised persons (strong, moderate). If travel to an endemic area cannot be avoided, vaccination can be considered in the following minimally immunocompromised human immunodeficiency virus (HIV)–infected individuals:
   (a) asymptomatic HIV-infected adults with CD4 T-cell lymphocyte count ≥200 cells/mm^3 (weak, low)
   (b) asymptomatic HIV-infected children aged 9 months–5 years with CD4 T-cell lymphocyte percentages of ≥15 (weak, very low).
14. With certain exceptions (eg, yellow fever vaccine and MMR vaccine in certain HIV-infected patients [see recommendation 13 and "Recommendations for vaccination of HIV-infected adults, adolescents, and children" section] and in certain HSCT patients [see "Recommendations for vaccination of hematopoietic stem cell transplant patients"]), live vaccines should *not* be given to immunocompromised persons (strong, low).

RECOMMENDATIONS FOR VARICELLA AND ZOSTER VACCINES IN IMMUNOCOMPROMISED PATIENTS

VAR

V. Should Immunocompromised Patients or Those Scheduled to Receive Immune Suppressive Therapy Receive VAR?

15. VAR should be given to immunocompetent patients without evidence of varicella immunity (ie, age-appropriate varicella vaccination, serologic evidence of immunity, clinician-diagnosed or -verified history of varicella or zoster, or laboratory-proven varicella or zoster; strong, moderate) if it can be administered ≥4 weeks before initiating immunosuppressive therapy (strong, low).

16. A 2-dose schedule of VAR, separated by >4 weeks for patients aged ≥13 years and by ≥3 months for patients aged 1–12 years, is recommended if there is sufficient time prior to initiating immunosuppressive therapy (strong, low).
17. VAR should *not* be administered to highly immunocompromised patients. However, certain categories of patients (eg, patients with HIV infection without severe immunosuppression or with a primary immune deficiency disorder without defective T-cell–mediated immunity, such as primary complement component deficiency disorder or chronic granulomatous disease [CGD]) should receive VAR, adhering to a 2-dose schedule separated by a 3-month interval (strong, moderate).
18. VAR can be considered for patients without evidence of varicella immunity (defined in recommendation 16) who are receiving long-term, low-level immunosuppression (weak, very low).*
19. VAR should be administered to eligible immunocompromised patients as the single antigen product, not VAR combined with MMR vaccine (strong, low).

VI. Should Immunocompromised Patients or Those Who Will Undergo Immunosuppression Receive Herpes Zoster Vaccine?

20. ZOS should be given to patients aged ≥60 years if it can be administered ≥4 weeks before beginning highly immunosuppressive therapy (strong, low).
21. ZOS should be considered for varicella-positive patients (ie, persons with a history of varicella or zoster infection or who are varicella–zoster virus [VZV] seropositive with no previous doses of VAR) aged 50–59 years if it can be administered ≥4 weeks before beginning immunosuppressive therapy (weak, low).*
22. ZOS should be administered to patients aged ≥60 years who are receiving therapy considered to induce a low level of immunosuppression (strong, low).
23. ZOS should *not* be administered to highly immunocompromised patients (strong, very low).

RECOMMENDATIONS FOR INFLUENZA VACCINE IN THE IMMUNOCOMPROMISED HOST

VII. Should Immunocompromised Persons Receive Influenza Vaccine?

24. Annual vaccination with IIV is recommended for immunocompromised patients aged ≥6 months (strong, moderate) except for patients who are very unlikely to respond (although unlikely to be harmed by IIV), such as those receiving intensive chemotherapy* (strong, low) or those who have received anti–B-cell antibodies within 6 months* (strong, moderate).
25. LAIV should *not* be administered to immunocompromised persons (weak, very low).

RECOMMENDATIONS FOR VACCINATION OF PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISORDERS

VIII. Which Vaccines Should Be Administered to Patients With Primary (Congenital) Complement Deficiencies?

26. Patients with primary complement deficiencies should receive all routine vaccines based on the CDC annual schedule; none are contraindicated (strong, low).
27. Patients with primary complement deficiencies and who are
    (a) aged 2–5 years should receive 1 dose of 13-valent pneumococcal conjugate vaccine (PCV13) if they have received 3 doses of PCV (either 7-valent PCV [PCV7] or PCV13) before age 24 months and 2 doses of PCV13 (8 weeks apart) if they have received an incomplete schedule of ≤2 doses of PCV7 (PCV7 or PCV13) before age 24 months (strong, low).
    (b) aged 6–18 years with a classic pathway (C1, C2, C3, C4), alternate pathway, or severe mannan-binding lectin (MBL) deficiency who have not received PCV13 should receive a single dose of PCV13 (strong, very low).
    (c) aged ≥19 years with a classic pathway (C1, C2, C3, C4), alternate pathway, or severe MBL deficiency who are PCV13 naive should receive a single dose of PCV13 (strong, very low). For those who received pneumococcal polysaccharide vaccine-23 (PPSV23), PCV13 should be administered ≥1 year after the last PPSV23 dose (weak, low)
28. Patients aged ≥2 years with an early classic pathway, alternate pathway, or severe MBL deficiency should receive PPSV23 ≥8 weeks after PCV13, and a second dose of PPSV23 should be given 5 years later (strong, low).
29. Patients with primary complement deficiencies should receive conjugate meningococcal vaccine. A 4-dose series of bivalent meningococcal conjugate vaccine and *Haemophilus influenzae* type b conjugate vaccine (HibMenCY; MenHibrix, GlaxoSmithKline) should be administered at age 2, 4, 6, and 12–15 months for children aged 6 weeks–18 months (strong, low) or a 2-dose primary series of meningococcal conjugate vaccine, quadrivalent (MCV4) should be administered to patients with primary complement component deficiency at age 9 months–55 years (MCV4-D [Menactra, Sanofi Pasteur] for those aged 9–23 months; MCV4-D or MCV4-CRM [Menveo, Novartis; CRM, diphtheria CRM_{197} protein] for those aged 2–54 years; strong, low). For persons aged >55 years, MPSV4 (meningococcal polysaccharide vaccine, quadrivalent) should be administered if they have not received MCV4 and MCV4 should be administered if they have received MCV4 (strong, low). For patients aged 9–23 months, the doses should be administered 3 months apart; for patients aged ≥2 years, the doses should be administered 2 months apart. MCV4-D should be administered ≥4

weeks after a dose of PCV13 because of a reduced antibody response to some pneumococcal serotypes when MCV4-D and PCV7 are administered simultaneously (strong, low).

30. Patients with a primary complement component deficiency should be revaccinated with MCV4 (or MPSV4 for those aged >55 years who have not received MCV4) every 5 years (strong, low).

IX. Which Vaccines Should Be Administered to Patients With Phagocytic Cell Deficiencies (eg, CGD, Leukocyte Adhesion Deficiency, Chediak–Higashi Syndrome)?

31. Patients with phagocytic cell deficiencies should receive all inactivated vaccines based on the CDC annual schedule (strong, low). Children aged 2–5 years should receive PCV13 as in recommendation 27a (weak, very low).
32. Patients aged ≥6 years with phagocytic cell deficiencies other than CGD (unless patient with CGD is receiving immunosuppressive medication) should receive PCV13 as in recommendations 27b and 27c (weak, very low).
33. Patients aged ≥2 years with phagocytic cell deficiencies other than CGD (unless patient with CGD is receiving immunosuppressive medication) should receive PPSV23 ≥8 weeks after receipt of PCV13, and a second dose of PPSV23 should be given 5 years later (weak, low).
34. Live bacterial vaccines, such as bacillus Calmette–Guérin (BCG) or oral typhoid vaccine, should *not* be administered to patients with a phagocytic cell defect (strong, moderate).
35. Live viral vaccines should be administered to patients with CGD and to those with congenital or cyclical neutropenia (weak, low).
36. Live viral vaccines should *not* be administered to patients with leukocyte adhesion deficiency, defects of cytotoxic granule release such as Chediak–Higashi syndrome, question XIII, recommendations 50-or any other undefined phagocytic cell defect (strong, low).

X. Which Vaccines Should Be Administered to Patients With Innate Immune Defects that Result in Defects of Cytokine Generation/Response or Cellular Activation (eg, Defects of the Interferon-gamma/Interleukin-12 Axis)?

37. Patients with innate immune defects that result in defects of cytokine generation/response or cellular activation should receive all inactivated vaccines based on the CDC annual schedule (strong, very low).
38. For patients with innate immune defects that result in defects of cytokine generation/response or cellular activation, PCV13 should be administered as in recommendations 27a–c (weak to strong, very low to low).
39. The advice of a specialist should be sought regarding individual conditions concerning use of live vaccines in patients with innate immune defects that result in defects of cytokine generation/response or cellular activation/inflammation generation (strong, low).
40. Live bacterial vaccines should *not* be administered to patients with defects of the interferon-gamma/interleukin-12 (IFN-γ/IL-12) pathways (strong, moderate).
41. Live viral vaccines should *not* be administered to patients with defects of IFN (alpha or gamma) production (strong, low).

XI. Which Vaccines Should Be Administered to Patients With Minor Antibody Deficiencies?

42. Patients with immunoglobulin (Ig)A deficiency or specific polysaccharide antibody deficiency (SPAD) should receive all routine vaccinations based on the CDC annual schedule, provided that other components of their immune systems are normal (strong, low).
43. Children with SPAD or ataxia–telangiectasia should receive PCV13 as described in recommendations 27a–c (weak to strong, very low to low). Those aged ≥2 years should receive PPSV23 ≥8 weeks after indicated doses of PCV13, and a second dose should be given 5 years later (strong, low).
44. Monitoring of vaccine responses can be useful for assessing the degree of immunodeficiency of patients with minor antibody deficiencies and level of protection (weak, moderate).
45. OPV should *not* be administered to IgA-deficient patients (strong, low).

XII. Which Vaccines Should Be Administered to Patients With Major Antibody Deficiencies Who are Receiving Immunoglobulin Therapy?

46. Inactivated vaccines other than IIV are *not* routinely administered to patients with major antibody deficiencies during immunoglobulin therapy (strong, low).
    (a) For patients with suspected major antibody deficiencies, all inactivated vaccines can be administered as part of immune response assessment prior to immunoglobulin therapy (strong, low).
47. IIV can be administered to patients with major antibody deficiencies and some residual antibody production (weak, low).
48. Live OPV should *not* be administered to patients with major antibody deficiencies (strong, moderate).
49. Live vaccines (other than OPV) should *not* be administered to patients with major antibody deficiencies (weak, low).*

XIII. Which Vaccines Should Be Administered to Patients With Combined Immunodeficiencies?

50. For patients with suspected combined immunodeficiencies, all inactivated vaccines can be administered as part immune response assessment prior to commencement of immunoglobulin therapy (strong, low).

(a) For patients with combined immunodeficiencies who are receiving immunoglobulin therapy, inactivated vaccines should *not* be routinely administered (strong, low).

51. For patients with combined immunodeficiencies and residual antibody production potential, IIV can be administered (weak, very low).
52. Children with partial DiGeorge syndrome (pDGS) should undergo immune system assessment with evaluation of lymphocyte subsets and mitogen responsiveness in order to determine whether they should be given live viral vaccines. Those with ≥500 CD3 T cells/mm^3, ≥200 CD8 T cells/mm^3, *and* normal mitogen response should receive MMR vaccine and VAR (weak, low).*
53. Patients with SCID, DGS with a CD3 T-cell lymphocyte count <500 cells/mm^3, other combined immunodeficiencies with similar CD3 T-cell lymphocyte counts, Wiskott–Aldrich syndrome, or X-linked lymphoproliferative disease and familial disorders that predispose them to hemophagocytic lymphohistiocytosis should *avoid* all live vaccines (strong, moderate).

RECOMMENDATIONS FOR VACCINATION OF HIV-INFECTED ADULTS, ADOLESCENTS, AND CHILDREN

XIV. Which Inactivated Vaccines Should Be Administered to HIV-Infected Patients?

54. HIV-infected patients should be vaccinated according to the CDC annual schedule for the following inactivated vaccines: IIV (strong, high); PCV13 in patients aged <2 years (strong, moderate); *H. influenzae* type b conjugate (Hib) vaccine (strong, high); diphtheria toxoid, tetanus toxoid, acellular pertussis (DTaP) vaccine (strong, moderate); tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis (Tdap) vaccine (strong, very low); tetanus toxoid, reduced diphtheria toxoid (Td) vaccine (strong, low); hepatitis B (HepB) vaccine (strong, moderate); hepatitis A (HepA) vaccine (strong, moderate); inactivated poliovirus (IPV) vaccine (strong, moderate); and quadrivalent human papillomavirus (HPV4) vaccine* in females and males aged 11–26 years (strong, very low) with additions noted below.
55. PCV13 should be administered to HIV-infected patients aged ≥2 years as in recommendations 27a–c (strong, low to moderate).
56. PPSV23 should be administered to HIV-infected children aged ≥2 years of age who have received indicated doses of PCV (strong, moderate), HIV-infected adults with CD4 T-lymphocyte counts of ≥200 cells/mm^3 (strong, moderate), and HIV-infected adults with CD4 T-lymphocyte counts of <200 cells/mm^3 (weak, low). PPSV23 should be given ≥8 weeks after indicated dose(s) of PCV13, and a second dose of PPSV23 should be given 5 years later (strong, low).
57. HIV-infected children who are aged >59 months and have not received Hib vaccine should receive 1 dose of Hib vaccine (strong, low). Hib vaccine is *not* recommended for HIV-infected adults (weak, low).
58. HIV-infected children aged 11–18 years should receive a 2-dose primary series of MCV4 2 months apart (strong, moderate). A single booster dose (third dose) should be given at age 16 years if the primary series was given at age 11 or 12 years and at age 16–18 years if the primary series was given at age 13–15 years (strong, low). If MCV4 is administered to HIV-infected children aged 2–10 years because of risk factors for meningococcal disease, a 2-dose primary series of MCV4 should be administered with a 2-month interval between doses, and a booster dose should be given 5 years later (strong, very low).
59. HIV-infected patients should receive the HepB vaccine series (strong, moderate), with consideration of high-dose HepB vaccine (40 μg/dose) for adults (weak, moderate) and adolescents* (weak, low). One to 2 months after completion, patients should be tested for anti-HBs (antibodies to HepB surface antigen; strong, low). If a postvaccination anti-HB concentration of ≥10 mIU/mL is not attained, a second 3-dose series of HepB vaccine (strong, low; alternative: 1 dose of HepB vaccine after which anti-HBs is tested*), using standard dose (strong, moderate) or high dose (40 μg*; weak, low) for children and high dose for adolescents* and adults (strong, low), should be administered.
60. HepB vaccine containing 20 μg of HepB surface antigen (HBsAg) combined with HepA vaccine (HepA–HepB; Twinrix), 3-dose series, can be used for primary vaccination of HIV-infected patients aged ≥12 years (strong, moderate).*
61. Internationally adopted HIV-infected children who have received doses of OPV should receive a total of 4 doses of a combination of OPV and IPV vaccine (strong, low).
62. HPV4 vaccine is recommended over bivalent human papillomavirus (HPV2) vaccine because HPV4 vaccine prevents genital warts (strong, low),* although there are no data on differences between the vaccines for preventing cervical dysplasia in HIV-infected women.

XV. Should Live Vaccines Be Administered to HIV-Infected Patients?

63. HIV-exposed or -infected infants should receive rotavirus vaccine according to the schedule for uninfected infants (strong, low).
64. HIV-infected patients should *not* receive LAIV (weak, very low).
65. MMR vaccine should be administered to clinically stable HIV-infected children aged 1–13 years without severe immunosuppression (strong, moderate) and HIV-infected

patients aged ≥14 years without measles immunity and with a CD4 T-cell lymphocyte count ≥200/mm^3 (weak, very low).

66. HIV-infected children with a CD4 T-cell percentage <15 (strong, moderate) or patients aged ≥14 years with a CD4 T-cell lymphocyte count <200 cells/mm^3 should *not* receive MMR vaccine (strong, moderate).
67. HIV-infected patients should *not* receive quadrivalent MMR-varicella (MMRV) vaccine (strong, very low).
68. Varicella-nonimmune, clinically stable HIV-infected patients aged 1–8 years with ≥15% CD4 T-lymphocyte percentage (strong, high), aged 9–13 years with ≥15% CD4 T-lymphocyte percentage (strong, very low), and aged ≥14 years with CD4 T-lymphocyte counts ≥200 cells/mm^3 should receive VAR (strong, very low). The 2 doses should be separated by ≥3 months (strong, moderate).

RECOMMENDATIONS FOR VACCINATION IN PATIENTS WITH CANCER

XVI. What Vaccines Should Be Given to Patients With Cancer?

69. Patients aged ≥6 months with hematological malignancies (strong, moderate) or solid tumor malignancies (strong, low) *except* those receiving anti–B-cell antibodies* (strong, moderate) or intensive chemotherapy, such as for induction or consolidation chemotherapy for acute leukemia (weak, low), should receive IIV annually.*
70. PCV13 should be administered to newly diagnosed adults with hematological (strong, very low) or solid malignancies (strong, very low) and children with malignancies (strong, very low) as described in recommendations 27a-c. PPSV23 should be administered to adults and children aged ≥2 years (strong, low) at least 8 weeks after the indicated dose(s) of PCV13.
71. Inactivated vaccines (other than IIV) recommended for immunocompetent children in the CDC annual schedule can be considered for children who are receiving maintenance chemotherapy (weak, low). However, vaccines administered during cancer chemotherapy should *not* be considered valid doses (strong, low) unless there is documentation of a protective antibody level (strong, moderate).
72. Live viral vaccines should *not* be administered during chemotherapy (strong, very low to moderate).
73. Three months after cancer chemotherapy, patients should be vaccinated with inactivated vaccines (strong, very low to moderate) and the live vaccines for varicella (weak, very low); measles, mumps, and rubella (strong, low); and measles, mumps, and rubella– varicella (weak, very low) according to the CDC annual schedule that is routinely indicated for immunocompetent persons. In regimens that included anti–B-cell antibodies, vaccinations should be delayed at least 6 months (strong, moderate).

RECOMMENDATIONS FOR VACCINATION OF HEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS

XVII. Should HSCT Donors and Patients Be Vaccinated Before Transplantation?

74. The HSCT donor should be current with routinely recommended vaccines based on age, vaccination history, and exposure history according to the CDC annual schedule (strong, high). However, administration of MMR, MMRV, VAR, and ZOS vaccines should be avoided within 4 weeks of stem cell harvest (weak, very low). Vaccination of the donor for the benefit of the recipient is *not* recommended (weak, moderate).
75. Prior to HSCT, candidates should receive vaccines indicated for immunocompetent persons based on age, vaccination history, and exposure history according to the CDC annual schedule if they are not already immunosuppressed (strong, very low to moderate) and when the interval to start of the conditioning regimen is ≥4 weeks for live vaccines (strong, low) and ≥2 weeks for inactivated vaccines (strong, moderate).
76. Nonimmune HSCT candidates aged ≥12 months should receive VAR (as a 2-dose regimen if there is sufficient time) if they are not immunosuppressed and when the interval to start the conditioning regimen is ≥4 weeks (strong, low).

XVIII. Which Vaccines Should Be Administered to Adults and Children After HSCT?

77. One dose of IIV should be administered annually (strong, moderate) to persons aged ≥6 months starting 6 months after HSCT (strong, moderate) and starting 4 months after if there is a community outbreak of influenza as defined by the local health department (strong, very low). For children aged 6 months–8 years who are receiving influenza vaccine for the first time, 2 doses should be administered (strong, low).
78. Three doses of PCV13 should be administered to adults and children starting at age 3–6 months after HSCT (strong, low). At 12 months after HSCT, 1 dose of PPSV23 should be given provided the patient does not have chronic GVHD (strong, low). For patients with chronic GVHD, a fourth dose of PCV13 can be given at 12 months after HSCT (weak, very low).*
79. Three doses of Hib vaccine should be administered 6–12 months after HSCT (strong, moderate).
80. Two doses of MCV4 should be administered 6–12 months after HSCT to persons aged 11–18 years, with a booster dose given at age 16–18 years for those who received the initial post-HSCT dose of vaccine at age 11–15 years (strong, low).
81. Three doses of tetanus/diphtheria–containing vaccine should be administered 6 months after HSCT (strong, low). For children aged <7 years, 3 doses of DTaP should be administered (strong, low). For patients aged ≥7 years, administration of 3 doses of DTaP should be considered (weak, very low).* Alternatively, a

dose of Tdap vaccine should be administered followed by either 2 doses of diphtheria toxoid combined with tetanus toxoid (DT) (weak, moderate)* or 2 doses of Td vaccine (weak, low).

82. Three doses of HepB vaccine should be administered 6–12 months after HSCT (strong, moderate). If a postvaccination anti-HBs concentration of ≥10 mIU/mL is not attained, a second 3-dose series of HepB vaccine (strong, low; alternative: 1 dose of HepB vaccine after which anti-HBs is tested*), using standard dose (strong, moderate) or high dose (40 μg*; weak, low) for children and high dose for adolescents* and adults (strong, low), should be administered.
83. Three doses of IPV vaccine should be administered 6–12 months after HSCT (strong, moderate).
84. Consider administration of 3 doses of HPV vaccine 6–12 months after HSCT for female patients aged 11–26 years and HPV4 vaccine for males aged 11–26 years (weak, very low).
85. Do *not* administer live vaccines to HSCT patients with active GVHD or ongoing immunosuppression (strong, low).
86. A 2-dose series of MMR vaccine should be administered to measles-seronegative adolescents and adults (strong, low) and to measles-seronegative children (strong, moderate) 24 months after HSCT in patients with neither chronic GVHD nor ongoing immunosuppression and 8–11 months (or earlier if there is a measles outbreak) after the last dose of immune globulin intravenous (IGIV).
87. A 2-dose series of VAR should be administered 24 months after HSCT to varicella-seronegative patients with neither GVHD nor ongoing immunosuppression and 8–11 months after the last dose of IGIV (strong, low).

RECOMMENDATIONS FOR VACCINATION OF SOLID ORGAN TRANSPLANT RECIPIENTS

XIX. For Adult and Child Solid Organ Transplant Candidates and Living Donors, Which Vaccines Should Be Administered During Pretransplant Evaluation?

88. Living donors should be current with vaccines based on age, vaccination history, and exposure history according to the CDC annual schedule (strong, high); MMR, MMRV, VAR, and ZOS vaccine administration should be avoided within 4 weeks of organ donation (weak, very low). Vaccination of donors solely for the recipient's benefit is generally not recommended (weak, low).
89. Adults and children with chronic or end-stage kidney, liver, heart, or lung disease, including solid organ transplant (SOT) candidates, should receive all age-, exposure history-, and immune status-appropriate vaccines based on the CDC annual schedule for immunocompetent persons (strong, moderate).
90. Adult SOT candidates; adults with end-stage kidney disease; and pediatric patients who are SOT candidates; are aged <6 years and have end-stage kidney, heart, or lung disease; or are aged 6–18 years and have end-stage kidney disease should receive PCV13 as in recommendations 27a-c (strong, very low).
91. Adults and children aged ≥2 years who are SOT candidates or have end-stage kidney disease should receive PPSV23 if they have not received a dose within 5 years and have not received 2 lifetime doses (strong, moderate). Patients with end-stage kidney disease should receive 2 lifetime doses 5 years apart (strong, low). Adults and children aged ≥2 years with end-stage heart or lung disease as well as adults with chronic liver disease, including cirrhosis, should receive a dose of PPSV23 if they have never received a dose (strong, low). When both PCV13 and PPSV23 are indicated, PCV13 should be completed 8 weeks prior to PPSV23 (strong, moderate).
92. Anti-HBs–negative SOT candidates should receive the HepB vaccine series (strong, moderate) and, if on hemodialysis and aged ≥20 years, they should receive the high-dose (40 μg) HepB vaccine series (strong, moderate). If a postvaccination anti-HBs concentration of ≥10 mIU/mL is not attained, a second 3-dose series of HepB vaccine (strong, low; alternative: 1 dose of HepB vaccine after which anti-HBs is tested*) should be administered, using standard dose (strong, moderate) or high dose* for children (weak, low) and high dose for adolescents* and adults (strong, low). HepA-unvaccinated, -undervaccinated, or -seronegative SOT candidates (particularly liver transplant candidates) aged 12–23 months (strong, moderate) and ≥2 years (strong, moderate) should receive a HepA vaccine series.
93. Combined HepA–HepB vaccine can be used for SOT candidates aged ≥12 years of age* in whom both vaccines are indicated (strong, moderate).
94. The HPV vaccine series should be administered to SOT candidates aged 11–26 years (strong, low-moderate).
95. SOT candidates aged 6–11 months can receive MMR vaccine if they are not receiving immunosuppression and if transplantation is not anticipated within 4 weeks (weak, very low). If transplantation is delayed (and the child is not receiving immunosuppression), the MMR vaccine should be repeated at 12 months (strong, moderate).
96. The VAR should be administered to SOT candidates without evidence of varicella immunity (as defined in recommendation 16) if they are not receiving immunosuppression and if transplantation is not anticipated within 4 weeks (strong, moderate). The VAR can be administered to varicella-naive SOT candidates aged 6–11 months who are not immunosuppressed provided the timing is ≥4 weeks prior to transplant (weak, very low).* Optimally, 2 doses should be administered ≥3 months apart (strong, low).
97. SOT candidates aged ≥60 years (strong, moderate) and varicella-positive candidates (as defined in recommendation

22) aged 50–59 years (weak, low)* who are not severely immunocompromised should receive ZOS if transplantation is *not* anticipated within 4 weeks.

XX. Which Vaccines Should Be Administered to SOT Recipients?

98. Vaccination should be withheld from SOT recipients during intensified immunosuppression, including the first 2-month posttransplant period, because of the likelihood of inadequate response (strong, low). However, IIV can be administered ≥1 month after transplant during a community influenza outbreak (weak, very low).
99. Standard age-appropriate inactivated vaccine series should be administered 2 to 6 months after SOT based on the CDC annual schedule (strong, low to moderate), including IIV (strong, moderate).
100. PCV13 should be administered 2 to 6 months after SOT if not administered before SOT, with the timing based on the patient's degree of immunosuppression, as described in recommendations 27a–c (strong, very low to moderate).
101. For SOT patients aged ≥2 years, 1 dose of PPSV23 should be administered 2 to 6 months after SOT, with the timing based on the patient's degree of immunosuppression, and ≥8 weeks after indicated doses of PCV13, if not given within 5 years and if the patient has received no more than 1 previous lifetime dose (strong, moderate).
102. HepB vaccine should be considered for chronic HepB-infected recipients 2 to 6 months after liver transplant in an attempt to eliminate the lifelong requirement for HepB immune globulin (HBIG; weak, low).*
103. MMR vaccine and VAR should generally *not* be administered to SOT recipients because of insufficient safety and effectiveness data (strong, low), except for varicella in children without evidence of immunity (as defined in recommendation 15) who are renal or liver transplant recipients, are receiving minimal or no immunosuppression, and have no recent graft rejection (weak, moderate).*
104. Vaccination should *not* be withheld because of concern about transplant organ rejection (strong, moderate).

RECOMMENDATIONS FOR VACCINATION OF PATIENTS WITH CHRONIC INFLAMMATORY DISEASES ON IMMUNOSUPPRESSIVE MEDICATIONS

XXI. Which Vaccines Should Be Administered to Patients With Chronic Inflammatory Diseases Maintained on Immunosuppressive Therapies?

105. Inactivated vaccines, including IIV, should be administered to patients with chronic inflammatory illness treated (strong, low-moderate) or about to be treated (strong, moderate) with immunosuppressive agents as for immunocompetent persons based on the CDC annual schedule.
106. PCV13 should be administered to adults and children with a chronic inflammatory illness that is being treated with immunosuppression as described in the standard schedule for children and in recommendations 27a–c (strong, very low-moderate).
107. PPSV23 should be administered to patients aged ≥2 years with chronic inflammatory illnesses with planned initiation of immunosuppression (strong, low), low-level immunosuppression (strong, low), and high-level immunosuppression (strong, very low). Patients should receive PPSV23 ≥8 weeks after PCV13, and a second dose of PPSV23 should be given 5 years later (strong, low).
108. VAR should be administered to patients with chronic inflammatory diseases without evidence of varicella immunity (defined in recommendation 15; strong, moderate) ≥4 weeks prior to initiation of immunosuppression (strong, low) if treatment initiation can be safely delayed.
109. VAR should be considered for patients without evidence of varicella immunity (defined in recommendation 15) being treated for chronic inflammatory diseases with long-term, low-level immunosuppression (weak, very low).*
110. ZOS should be administered to patients with chronic inflammatory disorders who are aged ≥60 years prior to initiation of immunosuppression (strong, low) or being treated with low-dose immunosuppression (strong, very low) and those who are aged 50–59 years and varicella positive prior to initiation of immunosuppression (weak, low)* or being treated with low-dose immunosuppression (weak, very low).*
111. Other live vaccines should *not* be administered to patients with chronic inflammatory diseases on maintenance immunosuppression: LAIV (weak, very low), MMR vaccine in patients receiving low-level (weak, very low) and high-level immunosuppression (weak, very low); and MMRV vaccine in patients receiving low-level (weak, very low) and high-level immunosuppression (strong, very low).
112. Other recommended vaccines, including IIV and HepB vaccine, should *not* be withheld because of concerns about exacerbation of chronic immune-mediated or inflammatory illness (strong, moderate).

RECOMMENDATIONS FOR VACCINATION OF PATIENTS WITH ASPLENIA OR SICKLE CELL DISEASES

XXII. Which Vaccines Should Be Administered to Asplenic Patients and Those With Sickle Cell Diseases?

113. Asplenic patients and those with sickle cell diseases should receive vaccines including PCV13 for children aged <2

years, as recommended routinely for immunocompetent persons based on the CDC annual schedule. No vaccine is contraindicated (strong, moderate) except LAIV (weak, very low).

114. PCV13 should be administered to asplenic patients and patients with sickle cell diseases aged ≥2 years based on the CDC annual schedule for children and in recommendations 27a–c (strong, very low-moderate).

115. PPSV23 should be administered to asplenic patients and patients with a sickle cell disease aged ≥2 years (strong, low) with an interval of ≥8 weeks after PCV13, and a second dose of PPSV23 should be administered 5 years later (strong, low).

116. For PPSV23-naive patients aged ≥2 years for whom a splenectomy is planned, PPSV23 should be administered ≥2 weeks prior to surgery (and following indicated dose(s) of PCV13; strong, moderate) or ≥2 weeks following surgery (weak, low).*

117. One dose of Hib vaccine should be administered to unvaccinated persons aged ≥5 years who are asplenic or have a sickle cell disease (weak, low).

118. Meningococcal vaccine should be administered to patients aged ≥2 months who are asplenic or have a sickle cell disease (strong, low), as in recommendation 29. However, MCV4-D should not be administered in patients aged <2 years because of a reduced antibody response to some pneumococcal serotypes when both MCV4 and PCV are administered simultaneously (strong, low). Revaccination with MCV4 (or MPSV4 for those aged >55 years who have not received MCV4) is recommended every 5 years (strong, low).

RECOMMENDATIONS FOR VACCINATION OF PATIENTS WITH ANATOMIC BARRIER DEFECTS AT RISK FOR INFECTIONS WITH VACCINE-PREVENTABLE PATHOGENS

XXIII. Which Vaccinations Should Be Given to Individuals With Cochlear Implants or Congenital Dysplasias of the Inner Ear or Persistent Cerebrospinal Fluid Communication With the Oropharynx or Nasopharynx?

119. Adults and children with profound deafness scheduled to receive a cochlear implant, congenital dysplasias of the inner ear, or persistent cerebrospinal fluid (CSF) communication with the oropharynx or nasopharynx should receive all vaccines recommended routinely for immunocompetent persons based on the CDC annual schedule. No vaccine is contraindicated (strong, moderate).

120. Patients with a cochlear implant, profound deafness and scheduled to receive a cochlear implant, or persistent communications between the CSF and oropharynx or nasopharynx should receive PCV13 as described in the standard schedule for children and recommendations 27a–c (strong, low-moderate).

121. Patients aged ≥24 months with a cochlear implant, profound deafness and scheduled to receive a cochlear implant, or persistent communications between the CSF and oropharynx or nasopharynx should receive PPSV23, preferably ≥8 weeks after receipt of PCV13 (strong, moderate).

122. PCV13 and PPSV23 should be administered ≥2 weeks prior to cochlear implant surgery, if feasible (strong, low).

INTRODUCTION

Vaccination of immunocompromised patients is important because impaired host defenses predispose patients to an increased risk or severity of vaccine-preventable infection. These patients may also have greater exposure to pathogens due to frequent contact with medical environments [1]; however, vaccination rates are frequently low [2–4]. Undervaccination of immunocompromised patients may occur because clinicians have insufficient or inaccurate information concerning the safety, efficacy, and contraindication to vaccination of such patients. Specialty clinicians may lack the infrastructure needed to administer vaccines to their at-risk patient populations.

Data on safety, immunogenicity, and efficacy/effectiveness of vaccines for immunocompromised populations are limited. Prelicensure studies often exclude immunocompromised persons, and postlicensure studies examine small numbers of immunocompromised patients. These small numbers are problematic when assessing adverse effects [5]. Furthermore, immune defects vary among and within categories of patients with immune deficiencies (eg, degree of immune deficiency, nutritional status, immunosuppressive regimen), which may limit the generalizability of study findings.

The objective of this guideline is to provide primary care and specialty clinicians with evidence-based recommendations for active vaccination of immunocompromised patients and members of their household in order to safely prevent vaccine-preventable infections, with the ultimate goal of decreasing associated morbidity and mortality. Recommended vaccination schedules for immunocompetent adults and children as well as certain groups at high risk for vaccine-preventable infections are updated and published annually by the Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics (AAP), and the American Association of Family Physicians [5]. Additional information on vaccination of immunocompromised patients is also available, for example, guidelines for use of specific vaccines and guidelines for particular populations [6–14], but comprehensive guidelines are not.

SCOPE OF GUIDELINE

This guideline addresses children and adults with primary (congenital) immune deficiencies; patients with secondary

immune deficiencies due to HIV infection, cancers associated with immune deficiency, cancer chemotherapy, stem cell or solid organ transplant (SOT), sickle cell diseases, and surgical asplenia; and patients with chronic inflammatory diseases treated with systemic corticosteroid therapy, immunomodulator medications, and/or biologic agents. Vaccination of immunocompetent patients who have an anatomic host defense abnormality (eg, cerebrospinal fluid [CSF] leak) associated with vaccine-preventable infections and of individuals living in a household with immunocompromised patients is also addressed. Vaccination of neonates (including premature neonates), the elderly, burn patients, and pregnant women is beyond the scope of this guideline.

This guideline addresses vaccines routinely recommended on the basis of patient age, social or occupational history, increased risk of infection related to underlying disease or treatment of disease, and travel. Vaccines for bioterrorism are not addressed. Immunobiological agents administered for active vaccination are addressed; immune globulin preparations and monoclonal antibodies used for passive vaccination are not. This guideline focuses on vaccines available in the United States, which are often relevant to other areas. Informed consent prior to vaccination, including provision of a CDC vaccine information statement, documentation of the vaccination, communication about vaccination to the patient (parent) or to clinicians involved in the patient's care, and discussion of vaccination registries, is beyond the scope of this document. The following 23 clinical questions are answered:

1. Who is responsible for vaccinating immunocompromised patients and members of their household?
2. When should vaccines be administered to immunocompetent patients in whom initiation of immunosuppressive medications is planned?
3. Which vaccines can be safely administered to individuals living in a household with immunocompromised patients, and what precautions should immunocompromised patients observe after vaccination of household members?
4. Which vaccines can be administered to immunocompromised patients contemplating international travel?
5. Should immunocompromised patients or those scheduled to receive immunosuppressive therapy receive varicella vaccine (VAR)?
6. Should immunocompromised patients or those who will undergo immunosuppression receive zoster vaccine (ZOS)?
7. Should immunocompromised patients receive influenza vaccine?
8. Which vaccines should be administered to patients with primary (congenital) complement deficiencies?
9. Which vaccines should be administered to patients with phagocytic cell deficiencies (eg, chronic granulomatous disease [CGD], leukocyte adhesion deficiency, Chediak–Higashi syndrome)?
10. Which vaccines should be administered to patients with innate immune defects that result in defects of cytokine generation/response or cellular activation (eg, defects of the interferon-gamma/interleukin-12 [IFN-γ/IL-12] axis)?
11. Which vaccines should be administered to patients with minor antibody deficiencies?
12. Which vaccines should be administered to patients with major antibody deficiencies who are receiving immunoglobulin therapy?
13. Which vaccines should be administered to patients with combined immunodeficiencies?
14. Which inactivated vaccines should be administered to human immunodeficiency virus (HIV)-infected patients?
15. Should live vaccines be administered to HIV-infected patients?
16. Which vaccines should be given to patients with cancer?
17. Should hematopoietic stem cell transplant (HSCT) donors and patients be vaccinated before transplantation?
18. Which vaccines should be administered to adults and children after HSCT?
19. For adult and child SOT candidates and living donors, which vaccines should be administered during pretransplant evaluation?
20. Which vaccines should be administered to SOT recipients?
21. Which vaccines should be administered to patients with chronic inflammatory diseases maintained on immunosuppressive therapies?
22. Which vaccines should be administered to asplenic patients and those with sickle cell diseases?
23. Which vaccines should be given to individuals with cochlear implants or congenital dysplasias of the inner ear or persistent CSF communication with the oropharynx or nasopharynx?

METHODOLOGY

Practice Guidelines

"Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate healthcare for specific clinical circumstances" [6]. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation [6].

Panel Composition

The Infectious Diseases Society of America (IDSA) Standards and Practice Guidelines Committee (SPGC) collaborated with partner organizations and convened a panel of 12 experts in vaccination of immunocompromised patients with a goal of devising

recommendations for clinical practice. The panel represented diverse geographic areas, pediatric and adult practitioners, and a wide breadth of specialties (gastroenterology, immunology, infectious diseases, hematology and oncology, rheumatology, and stem cell and solid organ transplantation) and organizations (CDC; American College of Rheumatology; North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition; AAP; Pediatric Infectious Diseases Society; and European Group for Blood and Marrow Transplantation).

Process Overview and Consensus Development Based on Evidence

Panel subgroups reviewed the initial literature search, selected references, evaluated evidence, drafted recommendations, and summarized the evidence for each section. Published guidelines [7, 8, 15] formed the basis for recommendations on vaccination of patients with HIV or HSCT, with modifications based on newer references and discussion among panel members. The evidence evaluation process was based on the IDSA Handbook on Clinical Practice Guideline Development, which involves a systematic weighting of the quality of evidence and the grade of recommendation using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Table 1) [9].

Drafts were circulated among panel members for commentary and discussed on 14 occasions by teleconference or in-person meeting. Feedback from 3 external peer reviews and endorsing organizations was obtained and used to modify the document. The guideline was reviewed and endorsed by AAP; American Society of Hematology; American Society of Pediatric Hematology/Oncology; European Group for Blood and Marrow Transplantation; North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition; and Pediatric Infectious Diseases Society. The guideline was reviewed and approved by the IDSA SPGC and board of directors.

Literature Review and Analysis

The expert panel reviewed and analyzed literature published from January 1 1966 plus some more recent publications. Computerized English-language literature searches of the National Library of Medicine PubMed database were performed using the terms "vaccination," "vaccine," "immunization," and names of specific vaccines for each patient population or disorder under consideration. Selected references in selected publications were also reviewed. The literature was limited for many vaccines and patient populations and primarily comprised case series evaluating vaccine immunogenicity and safety in particular populations of immunocompromised patients. There were few comparative or efficacy trials described in the literature.

RESULTS

The results are organized into general sections (vaccine safety, vaccine efficacy, timing of vaccination, vaccination of individuals living in a household with immunocompromised patients, vaccine administration, travel vaccines, varicella and zoster vaccination of immunocompromised patients, influenza vaccination of immunocompromised patients) and sections on vaccines for specific immunocompromising conditions (primary immune deficiency, HIV infection, oncology, HSCT, SOT, patients with chronic inflammatory diseases on immunosuppressive medications, asplenia, and patients with CSF leaks or cochlear implants). Each section on immunocompromising conditions addresses both inactivated and live vaccines. Recommendations for vaccination of patients with immunocompromising conditions are provided in Tables 2–7. Recommendations not addressed by the CDC ACIP or the AAP Committee on Infectious Diseases or that deviate from their recommendations are marked with an asterisk.

General Principles

Definitions of High- and Low-Level Immunosuppression

The degree of immune impairment in patients with primary or secondary immunodeficiency is variable. For this guideline, certain generalizations have been made. Patients with high-level immunosuppression include those:

- with combined primary immunodeficiency disorder (eg, severe combined immunodeficiency),
- receiving cancer chemotherapy,
- within 2 months after solid organ transplantation,
- with HIV infection with a CD4 T-lymphocyte count <200 cells/mm^3 for adults and adolescents and percentage <15 for infants and children,
- receiving daily corticosteroid therapy with a dose ≥20 mg (or >2 mg/kg/day for patients who weigh <10 kg) of prednisone or equivalent for ≥14 days, and
- receiving certain biologic immune modulators, that is, a tumor necrosis factor-alpha (TNF-α) blocker or rituximab [14].

After HSCT, duration of high-level immunosuppression is highly variable and depends on type of transplant (longer for allogeneic than for autologous), type of donor and stem cell source, and posttransplant complications such as graft vs host disease (GVHD) and their treatments.

Patients with low-level immunosuppression include:

- asymptomatic HIV-infected patients with CD4 T-lymphocyte counts of 200–499 cells/mm^3 for adults and adolescents and percentage 15–24 for infants and children,
- those receiving a lower daily dose of systemic corticosteroid than for high-level immunosuppression for ≥14 days or receiving alternate-day corticosteroid therapy, and

Table 2. Vaccination of Persons With HIV Infection

Vaccine	Low-Level or No Immunosuppression[a]		High-Level Immunosuppression[b]	
	Recommendation	Strength, Evidence Quality	Recommendation	Strength, Evidence Quality
Haemophilus influenzae b conjugate	U: age <5 y R: age 5–18 y[c]	Strong, high Strong, low	U: age <5 y R: age 5–18 y[c]	Strong, high Strong, low
Hepatitis A	U	Strong, moderate	U: age 1 y	Strong, moderate
Hepatitis B[d]	R	Strong, moderate	R	Strong, moderate
Diphtheria toxoid, tetanus toxoid, acellular pertussis	U	Strong, moderate	U	Strong, moderate
Tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis	U	Strong, very low	U	Strong, very low
Tetanus toxoid, reduced diphtheria toxoid	U	Strong, low	U	Strong, low
Human papillomavirus (HPV4)[e]	U: 11–26 y	Strong, very low	U: 11–26 y	Strong, very low
Influenza-inactivated (inactivated influenza vaccine)	U	Strong, high	U	Strong, high
Influenza-live attenuated (live attenuated influenza vaccine)	X[f]	Weak, very low	X	Weak, very low
Measles, mumps, and rubella–live	U: age 12 mo–13 y U: age ≥14 y	Strong, moderate Weak, very low	X: age 12 mo–13 y X: age ≥14 y	Strong, moderate Strong, moderate
Measles, mumps, and rubella–varicella–live	X	Strong, very low	X	Strong, very low
Meningococcal conjugate[g]	U: age 11–18 y	Strong, moderate	U: age 11–18 y	Strong, moderate
Pneumococcal conjugate (PCV13)	U: age <5 y R: age 5 y[h] R: age 6–18 y[h] R: age ≥19 y[i]	Strong, moderate Strong, moderate Strong, low Strong, low	U: age <5 y R: age 5 y R: age 6–18 y R: age ≥19 y[i]	Strong, moderate Strong, moderate Strong, low Strong, very low
Pneumococcal polysaccharide (PPSV23)[j]	R: age ≥2 y	Strong, moderate	R: age 2–18 y R: adult (CD4 T lymphocytes <200 cells/mm^3)	Strong, moderate Weak, low
Polio–inactivated (inactivated poliovirus vaccine)	U	Strong, moderate	U	Strong, moderate
Rotavirus–live	U	Strong, low	U	Weak, very low
Varicella–live	U: age 1–8 y U: age ≥9 y	Strong, high Strong, very low	X	Strong, moderate
Zoster–live	X	Strong, low	X	Strong, moderate

Abbreviations: R, recommended—administer if not previously administered or not current; such patients may be at increased risk for this vaccine-preventable infection; U, usual—administer if patient not current with recommendations for dose(s) of vaccine for immunocompetent persons in risk and age categories; X, contraindicated.

[a] Asymptomatic human immunodeficiency virus (HIV) infection with CD4 T-cell lymphocyte counts of 200–499 cells/mm^3 for adults and adolescents and percentages of 15–24 for infants and children.

[b] CD4 T-cell lymphocyte count <200 cells/mm^3 for adults and adolescents and percentage <15 for infants and children.

[c] One dose.

[d] High-dose hepatitis B vaccine (40 μg) should be considered for adults (weak, moderate) and adolescents (weak, low) with HIV infection. The latter recommendation deviates from recommendations of the Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention.

[e] Quadrivalent human papillomavirus vaccine (HPV4) is preferred over HPV2 vaccine because of its activity against genital warts. This recommendation deviates from recommendations of the Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention.

[f] Live attenuated influenza vaccine may be considered in otherwise healthy HIV-infected patients aged 5–17 years on combination antiretroviral therapy regimen for ≥16 weeks with CD4 T-lymphocyte percentage ≥15 and HIV plasma RNA <60 000 copies.

[g] For HIV-infected patients, meningococcal conjugate vaccine, quadrivalent is administered as a 2-dose primary series separated by ≥2 months. A booster dose (third dose) should be administered at age 16 years if the initial series was given at 11–12 years and at age 16–18 years if the initial series was given at age 13–15 years.

[h] For patients not fully vaccinated with PCV13 by previous administration.

[i] For patients aged ≥19 years with HIV who have received PPSV23, PCV13 should be administered after an interval of ≥1 year after the last PPSV23 dose (weak, low).

[j] PPSV23 should be administered 8 weeks or longer after indicated dose(s) of PCV13. A second dose of PPSV23 should be administered 5 years after the initial dose.

Table 3. Vaccination of Patients With Cancer

Vaccine	Prior to or During Chemotherapy		Starting ≥3 mo Postchemotherapy and ≥6 mo Post Anti–B-Cell Antibodies for Inactivated Vaccines; See Each Live Vaccine for Interval	
	Recommendation	Strength, Evidence Quality	Recommendation	Strength, Evidence Quality
Haemophilus influenzae b conjugate	U[a]	Weak, low	U	Strong, moderate
Hepatitis A	U[a]	Weak, low	U	Strong, very low
Hepatitis B	U[a]	Weak, low	U R: adults	Strong, moderate Strong, very low
Diphtheria toxoid, tetanus toxoid, acellular pertussis; tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis	U[a]	Weak, low	U: age 0–18 y R: adults with acute lymphoblastic leukemia or lymphoma	Strong, moderate Weak, very low
Human papillomavirus	U: 11–26 y[a]	Weak, very low	U	Strong, very low
Influenza-inactivated (inactivated influenza vaccine)	U[a]	Strong, low-moderate[a]	U[b]	Strong, moderate
Influenza-live attenuated (live attenuated influenza vaccine)	X	Weak, very low	U	Strong, low
Measles, mumps, and rubella–live	X[c]	Strong, moderate	Starting at 3 mo: U	Strong, low
Measles, mumps, and rubella–varicella–live	X[c]	Strong, moderate	Starting at 3 mo: U	Weak, very low
Meningococcal conjugate	U[a]	Weak, low	U	Strong, low
Pneumococcal conjugate-13 (PCV13)	R: <6 y R: age ≥6 y[d]	Strong, low Strong, very low	U	Strong, low
Pneumococcal polysaccharide (PPSV23)	R: age ≥2 y	Strong, low	U	Strong, low
Polio–inactivated (inactivated poliovirus vaccine)	U[a]	Weak, low	U	Strong, low
Rotavirus–live	X	Strong, very low	Not applicable	
Varicella–live	X[c]	Strong, moderate	Starting at 3 mo: U[e]	Weak, very low
Zoster–live	X[c]	Strong, very low	Starting at 3 mo: U[e]	Weak, very low

Abbreviations: R, recommended—administer if not previously administered or not current; such patients may be at increased risk for this vaccine-preventable infection; U, usual—administer if patient not current with recommendations for dose(s) of vaccine for immunocompetent persons in risk and age categories; X, contraindicated.

[a] Administer inactivated influenza vaccine (IIV) annually to patients with hematological malignancies (strong, moderate) or solid tumor malignancies (strong, low) except those receiving anti–B-cell antibodies such as rituximab or alemtuzumab or intensive chemotherapy such as for induction or consolidation chemotherapy for acute leukemia (weak, low). Administration of inactivated vaccines other than IIV, which are routinely recommended for healthy children in the annually updated CDC recommendations, can be considered for children with malignancies who are receiving maintenance chemotherapy (weak, low). However, vaccines administered while receiving cancer chemotherapy should not be considered valid doses (strong, low). Administration of indicated inactivated vaccines 2 or more weeks prior to chemotherapy is preferred.

[b] IIV can be administered ≤3 months after chemotherapy, but response rate may be low.

[c] These live vaccines should not be administered unless the vaccine is otherwise indicated based on the annually updated Centers for Disease Control and Prevention recommendations AND the patient is not immunosuppressed AND there will be an interval of ≥4 weeks prior to initiation of chemotherapy.

[d] For patients aged ≥19 years with human immunodeficiency virus who have received PPSV23, PCV13 should be administered after an interval of ≥1 year after the last PPSV23 dose (weak, low).

[e] Although measles, mumps, and rubella vaccine has been given safely 3 months after completion of chemotherapy, data on the safety, immunogenicity, and efficacy of varicella or zoster vaccine after completion of chemotherapy are not available.

- those receiving methotrexate (MTX) ≤0.4 mg/kg/week, azathioprine ≤3 mg/kg/day, or 6-mercaptopurine ≤1.5 mg/kg/day [10].

Safety of Vaccination of Immunocompromised Persons

Vaccines are categorized as live or inactivated (ie, nonlive vaccines include toxoids and other purified proteins, purified polysaccharide, protein–polysaccharide conjugate or oligosaccharide, inactivated whole or partially purified viruses, and proteins in virus-like particles). Limited evidence indicates that inactivated vaccines generally have the same safety profile in immunocompromised patients as in immunocompetent individuals [11]. However, the magnitude, breadth, and persistence of the immune response to vaccination may be reduced or absent in immunocompromised persons.

Table 4. Vaccinations Prior to or After Allogeneic or Autologous Hematopoietic Stem Cell Transplant

	Pre-HSCT		Post-HSCT	
Vaccine	Recommendation	Strength, Evidence Quality	Recommendation; Earliest Time Posttransplant; Number of Doses	Strength, Evidence Quality
Haemophilus influenzae b conjugate	U	Strong, moderate	R; 3 mo; 3 doses	Strong, moderate
Hepatitis A	U	Strong, very low	R; 6 mo; 2 doses	Weak, low
Hepatitis B	U	Strong, low	R; 6 mo; 3 doses	Strong, moderate
DTaP, DT, Td, Tdap	U	Strong, low	R; age <7 y: DTaP; 6 mo; 3 doses R; age ≥7 y: DTaP*; 6 mo; 3 doses OR 1 dose Tdap, then 2 doses DT* or Td; 6 mo	Strong, low Weak, very low DTaP: weak, moderate DT, Td: weak, low
Human papillomavirus	U: 11–26 y	Strong, very low	U; 6 mo; 3 doses	Weak, very low
Influenza-inactivated (inactivated influenza vaccine)	U	Strong, low	R; 4 mo	Strong, moderate
Influenza-live attenuated (live attenuated influenza vaccine)	X	Weak, very low	X	Weak, very low
Measles, mumps, and rubella–live	U[a]	Strong, very low	X[b]	Strong, low
Measles, mumps, and rubella–varicella–live	U[a]	Weak, very low	X	Strong, very low
Meningococcal conjugate	U	Strong, very low	R; age 11–18 y; 6 mo; 2 doses	Strong, low
Pneumococcal conjugate (PCV13)	R[c]	Strong, low	R; 3 mo; 3 doses	Strong, low
Pneumococcal polysaccharide (PPSV23)	R[c]	Strong, very low	R; ≥12 mo post if no GVHD	Strong, low
Polio-inactivated (inactivated poliovirus vaccine)	U	Strong, very low	R; 3 mo; 3 doses	Strong, moderate
Rotavirus–live	X	Weak, very low	X	Weak, very low
Varicella–live	U[a]	Strong, low	X[d]	Strong, low
Zoster–live	R[a,e]: age 50–59 y* U[a]: age ≥60 y	Weak, very low Strong, low	X X	Strong, low Strong, low

Abbreviations: DT, diphtheria toxoid, tetanus toxoid, DTaP, diphtheria toxoid, tetanus toxoid, acellular pertussis; GVHD, graft-vs-host disease; HSCT, hematopoietic stem cell transplant; R, recommended—administer if not previously administered or current; such patients may be at increased risk for this vaccine-preventable infection; Td, tetanus toxoid, reduced diphtheria toxoid; Tdap, Tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis; U, usual—administer if patient not current with recommendations for dose(s) of vaccine for immunocompetent persons in risk and age categories; X, contraindicated.

[a] These live vaccines should not be administered unless the vaccine is otherwise indicated based on the annually updated Centers for Disease Control and Prevention recommendations AND the patient is not immunosuppressed AND there will be an interval of ≥4 weeks prior to transplant.

[b] Administer to adolescents and adults (strong, low) and to children (strong, moderate) if measles seronegative, the timing is ≥24 months after transplant, no GVHD is present, and the patient is not receiving immunosuppressive medication. Two doses should be administered.

[c] If not previously administered.

[d] Administer if varicella seronegative, the timing is ≥24 months after transplant, no GVHD is present, and the patient is not receiving immunosuppressive medication. Two doses should be administered (strong, low).

[e] Consider if the patient is not severely immunosuppressed AND the patient is varicella immune as defined by documentation of age-appropriate varicella vaccination, serologic evidence of immunity, documentation of varicella or zoster infection, or birth in the United States before 1980 [45] AND there will be an interval of ≥4 weeks prior to transplant.

*Indicates recommendation for a course of action that deviates from recommendations of the Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention.

Live vaccines are generally contraindicated in immunodeficient patients because attenuation is relative. However, there are important evidence-based exceptions, such as administration of VAR or MMR vaccine to HIV-infected children with mild to moderate immune deficiency (Tables 2–7) [7]. It is important to distinguish between contraindications based on clinical evidence and contraindications based on theoretical considerations. Oral polio vaccine (OPV) is contraindicated for patients with severe combined immune deficiency (SCID) because paralytic poliomyelitis has occurred after vaccination. In contrast, VAR is generally considered contraindicated for children with inflammatory bowel disease (IBD) who are receiving 6-mercaptopurine. Also, live, attenuated, cold-adapted intranasal influenza vaccine is not administered to immunocompromised patients based on insufficient clinical data to support these judgments. The decision to administer or withhold a vaccine should be based on balancing the burden of the vaccine-preventable disease and risk of developing severe or

Table 5. Vaccinations Prior to or After Solid Organ Transplant

Vaccine	Pretransplant		Starting 2–6 mo Posttransplant	
	Recommendation	Strength, Evidence Quality	Recommendation	Strength, Evidence Quality
Haemophilus influenzae b conjugate	U	Strong, moderate	U	Strong, moderate
Hepatitis A	U: age 12–23 mo R: ≥2 y	Strong, moderate Strong, moderate	R, if not completed pretransplant	Strong, moderate
Hepatitis B	U: age 1–18 y R: ≥18 y	Strong, moderate Strong, moderate	R, if not completed pretransplant[a]	Strong, moderate
Diphtheria toxoid, tetanus toxoid, acellular pertussis; tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis	U	Strong, moderate	U, if not completed pretransplant	Strong, moderate
Human papillomavirus	U: females 11–26 y U: males 11–26 y	Strong, moderate Strong, low	U: females 11–26 y U: males 11–26 y	Strong, moderate Strong, low
Influenza-inactivated (inactivated influenza vaccine)	U	Strong, moderate	U[b]	Strong, moderate
Influenza-live attenuated (live attenuated influenza vaccine)	X	Weak, low	X	Weak, low
Measles, mumps, and rubella–live	R[c]: 6–11 mo U[d]: age ≥12 mo	Weak, very low Strong, moderate	X	Strong, low
Measles, mumps, and rubella–varicella–live	U[d]	Strong, moderate	X	Strong, low
Meningococcal conjugate	U	Strong, moderate	U	Strong, moderate
Pneumococcal conjugate (PCV13)	U: age ≤5 y R: age ≥6 y[e]	Strong, moderate Strong, very low	U: Age 2–5 y R: age ≥6 y if not administered pretransplant[e]	Strong, moderate Strong, very low
Pneumococcal polysaccharide (PPSV23)	R: age ≥2 y	Strong, moderate	R: age ≥2 y, if not administered pretransplant	Strong, moderate
Polio-inactivated (inactivated poliovirus vaccine)	U	Strong, moderate	U	Strong, moderate
Rotavirus–live	U[c]	Strong, moderate	X	Strong, low
Varicella–live	R[f]: 6–11 mo U[d]	Weak, very low Strong, low	X[g]	Strong, low
Zoster–live	R[h]: age 50–59 y U[i]: age ≥60 y	Weak, low Strong, moderate	X	Strong, low

Abbreviations: R, recommended—administer if not previously administered or not current; such patients may be at increased risk for this vaccine-preventable infection; U, usual—administer if patient not current with annually updated Centers for Disease Control and Prevention recommendations for immunocompetent persons in risk and age categories; X, contraindicated.

[a] Consider hepatitis B vaccine for hepatitis B-infected liver transplant patients (weak, low).

[b] Inactivated influenza vaccine may be administered to solid organ transplant recipients despite intensive immunosuppression (eg, during the immediate posttransplant period), particularly in an outbreak situation (weak, low).

[c] Administer only if patient is not immunosuppressed and the timing is ≥4 weeks prior to transplant.

[d] Administer only if patient is nonimmune, not severely immunosuppressed, and the timing is ≥4 weeks prior to transplant.

[e] For patients aged ≥19 years who have received PPSV23, PCV13 should be administered after an interval of ≥1 year after the last PPSV23 dose (weak, low).

[f] Administer only if patient is not immunosuppressed and the timing is ≥4 weeks prior to transplant. This recommendation deviates from recommendations of the Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention.

[g] Selected seronegative patients with renal or liver transplant have been safely vaccinated. This recommendation deviates from recommendations of the Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention.

[h] Administer only if patient is not severely immunosuppressed, the timing is ≥4 weeks prior to transplant, and the patient is varicella immune as defined by documentation of age-appropriate varicella vaccination, serologic evidence of immunity, documentation of varicella or zoster infection, or birth in the United States before 1980 [45, 375]. This recommendation deviates from recommendations of the Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention.

[i] Administer only if patient is not severely immunosuppressed and the timing is ≥4 weeks prior to transplant.

Table 6. Vaccination of Persons With Chronic Inflammatory Diseases on Immunosuppressive Medications

	Planned Immunosuppression		Low-level Immunosuppression[a]		High-level Immunosuppression[a]	
Vaccine	Recommendation	Strength, Evidence Quality	Recommendation	Strength, Evidence Quality	Recommendation	Strength, Evidence Quality
Haemophilus influenzae b conjugate	U	Strong, moderate	U	Strong, low	U	Strong, low
Hepatitis A	U	Strong, moderate	U	Strong, low	U	Strong, low
Hepatitis B	U	Strong, moderate	U	Strong, low	U	Strong, low
Diphtheria toxoid, tetanus toxoid, acellular pertussis; tetanus toxoid, reduced diphtheria toxoid; tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis	U	Strong, moderate	U	Strong, low	U	Strong, low
Human papillomavirus	U: 11–26 y	Strong, moderate	U: 11–26 y	Strong, low	U: 11–26 y	Strong, very low
Influenza-inactivated (inactivated influenza vaccine)	U	Strong, moderate	U	Strong, moderate	U	Strong, moderate
Influenza-live attenuated (live attenuated influenza vaccine)	X	Weak, very low	X	Weak, very low	X	Weak, very low
Measles, mumps, and rubella–live	U[b]	Strong, moderate	X	Weak, very low	X	Weak, very low
Measles, mumps, and rubella–varicella–live	U[b]	Strong, low	X	Weak, very low	X	Strong, very low
Meningococcal conjugate	U	Strong, moderate	U	Strong, moderate	U	Strong, low
Pneumococcal conjugate (PCV13)	R[c]	Strong, moderate	U: <6 y R: ≥6 y[c]	Strong, low strong, very low	U: <6 y R: ≥6 y[c]	Strong, low strong, very low
Pneumococcal polysaccharide (PPSV23)	R: age ≥2 y	Strong, low	R: age ≥2 y	Strong, low	R: age ≥2 y	Strong, very low
Polio-inactivated (inactivated poliovirus vaccine)	U	Strong, moderate	U	Strong, moderate	U	Strong, low
Rotavirus–live	U	Strong, moderate	X	Weak, very low	X	Weak, very low
Varicella–live	U[b]	Strong, moderate	X[d]	Weak, very low	X	Strong, moderate
Zoster–live	R: age 50–59 y[e] U: age ≥60 y	Weak, low strong, low	R: age 50–59 y[e] U: age ≥60 y	Weak, very low Strong, very low	X	Weak, very low

Abbreviations: R, recommended—administer if not previously administered or not current; such patients may be at increased risk for this vaccine-preventable infection; U, usual—administer if patient not current with recommendations for dose(s) of vaccine for immunocompetent persons in risk and age categories; X, contraindicated.

[a] Low-level immunosuppression includes treatment with prednisone <2 mg/kg with a maximum of ≤20 mg/day; methotrexate ≤0.4 mg/kg/week; azathioprine ≤3 mg/kg/day; or 6-mercaptopurine ≤1.5 mg/kg/day. High-level immunosuppression regimens include treatment with doses higher than those listed for low-dose immunosuppression and biologic agents such as tumor necrosis factor antagonists or rituximab.

[b] Administer only if patient is nonimmune, not severely immunosuppressed, and the timing is ≥4 weeks prior to initiation of immunosuppressive medications.

[c] For patients aged ≥19 years who have received PPSV23, PCV13 should be administered after an interval of ≥1 year after the last PPSV23 dose (weak, low).

[d] Administration of varicella vaccine can be considered for nonvaricella-immune patients treated for chronic inflammatory disease who are receiving long-term low-dose immunosuppression (weak, very low). This recommendation deviates from recommendations of the Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention.

[e] This recommendation deviates from recommendations of the Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention [10].

Table 7. Vaccination of Persons With Asplenia or a Sickle Cell Disease, Cochlear Implants, or Cerebrospinal Fluid Leak

	Asplenia or a Sickle Cell Disease		Cochlear Implants[a] or Cerebrospinal Fluid Leak	
Vaccine	Recommendation	Strength, Evidence Quality	Recommendation	Strength, Evidence Quality
Haemophilus influenzae b conjugate	U: age <5 y R: age ≥5 y	Strong, moderate weak, low	U	Strong, moderate
Hepatitis A	U	Strong, moderate	U	Strong, moderate
Hepatitis B	U	Strong, moderate	U	Strong, moderate
Diphtheria toxoid, tetanus toxoid, acellular pertussis; tetanus toxoid, reduced diphtheria toxoid; tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis	U	Strong, moderate	U	Strong, moderate
Human papillomavirus	U	Strong, moderate	U	Strong, moderate
Influenza-inactivated (inactivated influenza vaccine)	U	Strong, moderate	U	Strong, moderate
Influenza-live attenuated (live attenuated influenza vaccine)	X	Weak, very low	U	Strong, moderate
Measles, mumps, and rubella–live	U	Strong, moderate	U	Strong, moderate
Measles, mumps, and rubella–varicella–live	U	Strong, moderate	U	Strong, moderate
Meningococcal conjugate	R: age 2–55 y[b]	Strong, low	U	Strong, moderate
Meningococcal polysaccharide	R: age >55 y[b]	Strong, low	U	Strong, moderate
Pneumococcal conjugate (PCV13)	U: age <6 y[c] R: age ≥6 y[d]	Strong, moderate Strong, very low	U: age <6 y[c] R: age ≥6 y[d]	Strong, moderate strong, low
Pneumococcal polysaccharide (PPSV23)	R: age ≥2 y[e]	Strong, low	R: age ≥2 y[e]	Strong, moderate
Polio-inactivated (inactivated poliovirus vaccine)	U	Strong, moderate	U	Strong, moderate
Rotavirus–live	U	Strong, moderate	U	Strong, moderate
Varicella–live	U	Strong, moderate	U	Strong, moderate
Zoster–live	U	Strong, moderate	U	Strong, moderate

Abbreviations: R, recommended—administer if not previously administered or not current; such patients may be at increased risk for this vaccine-preventable infection; U, usual—administer if patient not current with recommendations for dose(s) of vaccine for immunocompetent persons in risk and age categories; X, contraindicated.

[a] Includes patients with profound hearing loss who are scheduled to receive a cochlear implant or have inner ear–cerebrospinal fluid communication.

[b] A 2-dose primary series should be administered with an additional dose every 5 years.

[c] Two doses of PCV13 for children aged 2–5 years who have not received doses of PCV or received <3 doses of PCV7.

[d] If PCV13 has not been administered. For patients aged ≥19 years who have received PPSV23, PCV13 should be administered after an interval of ≥1 year after the last PPSV23 dose (weak, low).

[e] Administer 8 or more weeks after indicated dose(s) of PCV13 with a single revaccination with PPSV23 5 years after the initial dose (strong, moderate).

life-threatening infection with the wild-type pathogen and the risks of adverse effects from vaccination.

Concerns have been expressed that antigenic stimulation of vaccination could trigger a flare or onset of chronic inflammatory disease. The Institute of Medicine recently assessed the relationships between vaccines (MMR, acellular pertussis-containing, DT, tetanus toxoid, influenza, HepB, HepA, and HPV vaccines) and adverse effects [5]. Evidence was inadequate to establish or refute a causal relationship between each vaccine and onset or exacerbation of multiple sclerosis, systemic lupus erythematosus (SLE), vasculitis, rheumatoid arthritis (RA), or juvenile idiopathic arthritis. Overall, the preponderance of clinical evidence indicates that vaccines are not important triggers of disease flares in such patients and should not be withheld for that reason (see "Recommendations for Vaccination of Patients with Chronic Inflammatory Diseases of Immunosuppressive Medications" section).

For SOT patients, concerns have been raised that vaccination might trigger rejection. However, the preponderance of clinical evidence, most relating to trivalent inactivated influenza vaccine (IIV), indicates that vaccines are not important triggers of rejection episodes and should not be withheld for that reason (see "Recommendations for Vaccination of Solid Organ Transplant Recipients" section).

Vaccine Efficacy and Effectiveness

There are few data on vaccine efficacy or effectiveness in immunocompromised patients. In children with sickle cell disease, there was a 93% reduction in the rate of invasive pneumococcal disease caused by vaccine serotypes after routine administration of 7-valent pneumococcal conjugate vaccine (PCV7) [12]; however, herd-type immunity may have contributed to vaccine effectiveness. Other examples are the demonstrated efficacy of IIV in HIV-infected adults [13] and cardiac transplant patients, and the efficacy of VAR against severe varicella in renal and liver transplant recipients [16–18], children with leukemia [19], and children with HIV [20].

The estimate of effectiveness of most vaccines in immunocompromised patients is based on a surrogate marker, typically serum antibodies against the pathogen. However, there are limitations to the use of antibody measurements for determination of the adequacy of preexisting immunity or a response to vaccination. For many pathogens, a serum antibody concentration that correlates with protection (eg, a protective concentration of antibodies to ≥1 proteins of *Bordetella pertussis*) has yet to be established [21, 22]. Asplenic patients may require a higher antibody concentration than immunocompetent persons in order to protect against invasive infection with *Streptococcus pneumoniae* and *Haemophilus influenzae* type b [23, 24]. The correlation of antibody concentration with protection may be imperfect because such assays do not measure antibody functional activity [25]. Assays of functional antibodies [26] or antibody avidity [27] may be more predictive of protection. For prevention of zoster, cell-mediated immunity (CMI) is more closely associated with protection than are serum antibody concentrations [28].

Guideline and Conflict of Interest

All panel members complied with the IDSA's policy on conflict of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. They were provided IDSA's conflict-of-interest disclosure statement and asked to identify ties to companies that develop products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The panel decided on a case-by-case basis whether conflict should limit member participation. Potential conflicts are listed in the Acknowledgments section.

Revision Dates

At annual intervals, the panel chair, SPGC liaison advisor, and SPGC chair will determine the need for guideline revisions by reviewing the current literature. If necessary, the entire panel will be reconvened. When appropriate, the panel will recommend revisions to the IDSA SPGC, board, and other collaborating organizations for review and approval.

RECOMMENDATIONS FOR RESPONSIBILITY FOR VACCINATIONS

I. Who Is Responsible for Vaccinating Immunocompromised Patients and Members of Their Household?

Recommendations

1. Specialists who care for immunocompromised patients share responsibility with the primary care provider for ensuring that appropriate vaccinations are administered to immunocompromised patients (strong, low).*
2. Specialists who care for immunocompromised patients share responsibility with the primary care provider for recommending appropriate vaccinations for members of immunocompromised patients' households (strong, very low).*

Evidence Summary

In many cases, immunocompromised patients visit specialists more frequently than they do their primary care clinician, providing opportunities for vaccination. For example, vaccination rates were higher among pregnant women offered influenza vaccine by their obstetrician or other specialty provider compared with those not offered vaccine (70.8% vs 14.4%) [29]. Therefore, specialists are in a pivotal position to ensure vaccination by administering vaccines or providing specific advice to patients and primary care providers. Specialists should educate patients and members of their household on the importance of vaccination of household members for the protection of the immunocompromised patient.

RECOMMENDATIONS FOR TIMING OF VACCINATION

II. When Should Vaccines Be Administered to Immunocompetent Patients in Whom Initiation of Immunosuppressive Medications is Planned?

Recommendations

3. Vaccines should be administered prior to planned immunosuppression if feasible (strong, moderate).
4. Live vaccines should be administered ≥4 weeks prior to immunosuppression (strong, low) and should be avoided within 2 weeks of initiation of immunosuppression (strong, low).*
5. Inactivated vaccines should be administered ≥2 weeks prior to immunosuppression (strong, moderate).

Evidence Summary

Certain immunocompromised patients have a window of opportunity before initiation of immunosuppressive medications

Table 8. Safety of Administration of Live Vaccines to Contacts of Immunocompromised Persons

Live Vaccine	Shedding of Agent? (site)	Transmissibility from Vaccinated Immunocompetent Person?	Recommendation for Administering Vaccines (When Indicated) to Healthy Immunocompetent Contacts of Immunocompromised Patients
Influenza, live, attenuated nasal	Yes (nasal secretions)	Rare (from 1 vaccinated toddler)	Administer (strong, low); vaccinated persons to avoid close contact with persons with hematopoietic stem cell transplant or severe combined immune deficiency for 7 d (weak, very low)
Measles, mumps, and rubella	Measles: no Mumps: no Rubella: yes (nasopharynx, in low titer; breast milk)	No, except mother-to-infant transmission of rubella vaccine virus via breast milk	Administer (strong, moderate)
Polio, oral	Yes (stool)	Yes, with rare cases of vaccine-associated paralytic poliomyelitis	Do *not* administer (strong, high)
Rotavirus, oral	Yes (stool)	Yes, but no reported cases of symptomatic infection in contacts	Administer (strong, low)
Typhoid, oral	No	No	Administer (strong, low)
Varicella	Yes (skin lesions)	Rare, limited to vaccinees with skin lesions	Administer (strong, moderate); if skin lesions develop, avoid close contact with immunocompromised persons
Yellow fever	No, except possibly shed in breast milk	Yes (at least 3 cases of encephalitis in infants exposed to the vaccine via nursing)	Administer (strong, moderate) except to women who are nursing
Zoster	Yes (rarely recovered from injection site vesicles)	Not reported	Administer to those aged ≥60 y (strong, moderate); if skin lesions develop, avoid close contact with immunocompromised persons

during which indicated vaccines can be administered while the patient is immunocompetent (or more immunocompetent than following initiation of immunosuppression). However, indicated treatment of underlying disease should not be delayed to achieve vaccination goals. Response to vaccination and safety of live vaccines is higher prior to initiation of immunosuppression. After administration of live viral vaccines, the period of viral replication and development of immunologic response is generally <3 weeks, so vaccination ≥4 weeks prior to immunosuppression (2 weeks prior for inactivated vaccines) is likely to be safe [16]. Development of a robust immune response may take longer than these time intervals, however, particularly if the vaccination is for primary vaccination rather than as a booster.

RECOMMENDATIONS FOR VACCINATION OF HOUSEHOLD MEMBERS OF IMMUNOCOMPROMISED PATIENTS

Reduction of exposure to vaccine-preventable infections is important for risk reduction. This can be accomplished by educating immunocompromised patients and members of their household on infection control practices and by vaccinating household members and healthcare contacts to provide a "circle of protection." For example, influenza vaccination of healthcare personnel at a long-term care facility for elderly patients reduced mortality more than vaccination of the patients [30, 31]. All members of the immunocompromised patient's household as well as all healthcare contacts should be vaccinated. Requiring annual influenza vaccination of healthcare personnel can increase vaccination rates [32]. However, data supporting the effectiveness of vaccinating adults to protect young infants from pertussis are limited [33]. Household members should be up-to-date with all routinely recommended vaccinations including annual influenza vaccine [34].

III. Which Vaccines Can Be Safely Administered to Household Members of Immunocompromised Patients, and What Precautions Should Immunocompromised Patients Observe After Vaccination of Household Members?

Recommendations (Table 8)

6. Immunocompetent individuals who live in a household with immunocompromised patients can safely receive inactivated vaccines based on the CDC–ACIP's annually updated recommended vaccination schedules for children and adults (hereafter, CDC annual schedule; strong, high) or for travel (strong, moderate).
7. Individuals who live in a household with immunocompromised patients age ≥6 months should receive influenza vaccine annually (strong, high). They should receive either:

(a) Inactivated influenza vaccine (IIV; strong, high) or
(b) Live attenuated influenza vaccine (LAIV) provided they are healthy, not pregnant, and aged 2–49 years (strong, low). Exceptions include individuals who live in a household with an immunocompromised patient who was a hematopoietic stem cell transplant (HSCT) recipient within 2 months after transplant or with graft vs host disease (GVHD) or is a patient with severe combined immune deficiency (SCID).* In these exceptions, LAIV should not be administered (weak, very low) or, if administered, contact between the immunocompromised patient and household member should be avoided for 7 days (weak, very low).

8. Healthy immunocompetent individuals who live in a household with immunocompromised patients should receive the following live vaccines based on the CDC annual schedule: combined measles, mumps, and rubella (MMR) vaccine (strong, moderate); rotavirus vaccine in infants aged 2–7 months (strong, low); varicella vaccine (VAR; strong, moderate); and zoster vaccine (ZOS; strong, moderate). Also, these individuals can safely receive the following vaccines for travel: yellow fever vaccine (strong, moderate) and oral typhoid vaccine (strong, low).
9. OPV should *not* be administered to individuals who live in a household with immunocompromised patients (strong, moderate).
10. Highly immunocompromised patients should avoid handling diapers of infants who have been vaccinated with rotavirus vaccine for 4 weeks after vaccination (strong, very low).
11. Immunocompromised patients should avoid contact with persons who develop skin lesions after receipt VAR or ZOS until the lesions clear (strong, low).

Evidence Summary

When transmission of live vaccine from a vaccine recipient occurs, illness from an attenuated vaccine strain is likely to be less severe than from wild-type virus or bacteria. Studies of vaccine virus shedding after vaccination with LAIV have demonstrated that 80% of healthy recipients aged 8–36 months shed vaccine virus strains for a mean duration of 7.6 days [35–40]. Among 345 patients aged 5–49 years, 30% had detectable virus in nasal secretions after receiving LAIV. Duration and amount of shedding correlated inversely with age, and maximal shedding occurred within 2 days of vaccination [36, 41]. LAIV virus was transmitted in a day-care center to 1 healthy toddler who remained asymptomatic. Based on this single case, the estimated frequency of transmission is 0.6%–2.9% among toddlers attending a day-care center [40]. Transmission of LAI virus to an immunocompromised person has not been demonstrated despite nonrestrictive recommendations for LAIV administration to household members. Although data are limited, it is considered safe to administer LAIV to individuals who live with immunocompromised persons except for HSCT recipients in protected environments with positive air pressure and hepa-filtered air [41]. HSCT patients within 2 months after transplant or with GVHD and patients with a primary SCID are likely to be severely immunocompromised; therefore, in the opinion of the panel, household members should not receive LAIV.

The only report of transmission of MMR viruses from immunocompetent vaccinees involved transmission to nursing neonates of rubella vaccine virus via breast milk [42]. Yellow fever encephalitis developed in at least 3 nursing infants following yellow fever vaccination of their mothers [43].

Transmission of varicella virus from immunocompetent persons has been limited to vaccinees who developed a rash, and the risk appears to be low [44, 45]. Therefore, susceptible household members should receive VAR to protect immunocompromised persons from potential exposure to wild-type disease. Household members aged ≥60 years who qualify for zoster vaccination should be vaccinated. Individuals with a VAR- or ZOS-associated rash may be contagious and should avoid close contact with immunocompromised persons until the lesions have resolved [45–47].

Children receiving rotavirus vaccines may shed live virus in stool for 2–4 weeks and transmit vaccine virus, but symptomatic disease is rare [48, 49]. In a study of 110 pairs of infant twins in which 1 twin was given a 2-dose monovalent rotavirus vaccine (RV1; Rotarix, GlaxoSmithKline) series and the other placebo, the transmission rate was 18.8% (95% confidence interval [CI], 10.9%–29.0%), but none of the affected infants became symptomatic [50]. The risk of transmission and the theoretical risk of developing rotavirus disease as a result of the contact are lower than the risk of an unimmunized infant developing rotavirus diarrhea with wild-type virus with resultant rotavirus disease in the immunocompromised contact.

Healthcare personnel should receive influenza vaccine annually and receive HepB, VAR, MMR, and Tdap vaccines or provide documentation of immunity to minimize exposure of immunocompromised persons in healthcare facilities. Mandatory annual influenza vaccination, recommended by multiple professional organizations, has been implemented in certain healthcare facilities, resulting in very high influenza vaccine coverage [36, 51–53].

OPV, which is administered internationally, but not in the United States, is associated with a risk of transmission to household members, with a small risk of vaccine-associated paralytic poliomyelitis (VAPP) in those household members. The risk is higher in immunocompromised individuals living with a vaccinee [54, 55].

Vaccine Administration

Most vaccine doses and routes are the same for immunocompromised and immunocompetent persons. An exception is HepB vaccine for adult hemodialysis patients whose regimen is 3 or 4 40-μg doses vs 3 10- or 20-μg doses for immunocompetent adults receiving Recombivax (Merck) or Engerix (GlaxoSmithKline), respectively [56], or for certain HIV-infected patients not responding to standard regimens [57, 58] (see HIV section). Certain immunocompromised patients may have thrombocytopenia that may be a relative contraindication to an intramuscular injection. Clinical experience suggests that intramuscular injections are safe if the platelet count is ≥30 000–50 000 cells/mm^3, a ≤23-gauge needle is used, and constant pressure is maintained at the injection site for 2 minutes [59]. Inactivated poliovirus (IPV) vaccine and pneumococcal polysaccharide vaccine-23 (PPSV23) may be administered subcutaneously. An intradermal IIV is licensed. Multiple indicated vaccines can be administered simultaneously, with the same recommendations as for immunocompetent persons.

VACCINES FOR INTERNATIONAL TRAVEL

IV. Which Vaccines Can Be Administered to Immunocompromised Persons Contemplating International Travel?

Recommendations

12. Clinicians may administer inactivated vaccines indicated for travel based on the CDC annual schedule for immunocompetent adults and children (strong, low).
13. Yellow fever vaccine generally should *not* be administered to immunocompromised persons (strong, moderate). If travel to an endemic area cannot be avoided, vaccination can be considered in the following minimally immunocompromised human immunodeficiency virus (HIV)–infected individuals:
    (a) asymptomatic HIV-infected adults with CD4 T-cell lymphocyte count ≥200 cells/mm^3 (weak, low)
    (b) asymptomatic HIV-infected children aged 9 months–5 years with CD4 T-cell lymphocyte percentages of ≥15 (weak, very low).
14. With certain exceptions (eg, yellow fever vaccine and MMR vaccine in certain HIV-infected patients [see recommendation 13 and HIV section] and in certain HSCT patients [see HSCT section]), live vaccines should *not* be given to immunocompromised persons (strong, low).

Evidence Summary

The immunocompromised person's vaccination status should be assessed and vaccinations updated as needed before travel [60, 61]. Helpful information can be found at the CDC Travelers' Health website and in the "Yellow Book—CDC Information for International Travel" (both at http://wwwnc.cdc.gov/travel).

Immunocompromised persons should avoid travelling to areas where yellow fever is endemic [62]. Data are very limited on yellow fever vaccine in immunocompromised persons. Investigators recently studied the effect of yellow fever vaccine in 70 patients with rheumatic diseases including RA, SLE, and spondyloarthropathies who were treated with immunosuppressive drugs [63]. Mild adverse effects (eg, rash, myalgia, elevated hepatic transaminases) occurred in 22.5% of vaccinees, suggesting a reasonably safety profile. However, sample size was inadequate for detecting rare serious complications, and cases of yellow fever vaccine–associated viscerotropic disease have been reported in this population [62]. Yellow fever vaccine has been safely administered to a limited number of post-HSCT patients [64–66] and to more than 200 HIV-infected adults, the majority of whom had CD4 T-cell lymphocyte counts >200 cells/mm^3 [62, 67, 68]. An increase in relapse of multiple sclerosis was noted in 7 yellow fever vaccine recipients [69].

RECOMMENDATIONS FOR VAR AND ZOS IN IMMUNOCOMPROMISED PATIENTS

VAR

V. Should Immunocompromised Patients or Those Scheduled to Receive Immunosuppressive Therapy Receive VAR?

Recommendations

15. VAR should be given to immunocompetent patients without evidence of varicella immunity (ie, age-appropriate varicella vaccination, serologic evidence of immunity, clinician-diagnosed or -verified history of varicella or zoster, or laboratory-proven varicella or zoster; strong, moderate) if it can be administered ≥4 weeks before initiating immunosuppressive therapy (strong, low).
16. A 2-dose schedule of VAR, separated by >4 weeks for patients aged ≥13 years and by ≥3 months for patients aged 1–12 years, is recommended if there is sufficient time prior to initiating immunosuppressive therapy (strong, low).
17. VAR should *not* be administered to highly immunocompromised patients. However, certain categories of patients (eg, patients with HIV infection without severe immunosuppression or with a primary immune deficiency disorder without defective T-cell–mediated immunity, such as primary complement component deficiency disorder or chronic granulomatous disease [CGD]) should receive VAR, adhering to a 2-dose schedule separated by a 3-month interval (strong, moderate).
18. VAR can be considered for patients without evidence of varicella immunity (defined in recommendation 16) who are

receiving long-term, low-level immunosuppression (weak, very low).*

19. VAR should be administered to eligible immunocompromised patients as the single antigen product, not VAR combined with MMR vaccine (strong, low).

Evidence Summary

Varicella severity and mortality are increased in children and adults for many conditions associated with immune compromise and immunosuppressive therapy [70, 71]. VAR, which contains live-attenuated VZV (Oka strain), is not licensed for use in immunocompromised patients because of its potential to cause severe disease in patients who lack sufficient T-cell–mediated immune responses [72–74].

Varicella vaccination with sufficient time prior to immunosuppression is useful in patients without evidence of varicella immunity (defined in recommendation 16). Immune response is nearly optimal in 2 to 3 weeks, and replicating VZV should be cleared after 3 weeks. Vaccine-related rash, which has occurred up to 42 days after vaccination, is uncommon after 21 days in immunocompetent vaccinees [46, 75]. Vaccine virus given in the week before starting therapy for malignancy was associated with 1 death and has resulted in reactivation of VZV that subsequently became resistant to antiviral drugs [73, 76, 77]. A 2-dose schedule that is separated by ≥28 days for those aged ≥13 years and by ≥3 months for children aged 12 months–12 years is desirable for maximal protection. Most VAR studies of immunocompromised children used a single dose; therefore, the potential for protection is likely greater than what has been reported to date. Some immunocompromised patients had lower immune response to VAR than that observed in immunocompetent persons [78, 79].

Malignancy. Leukemic children on maintenance chemotherapy were vaccinated within a specific window for timing of chemotherapy and lymphocyte concentration threshold. Two doses induced either VZV-specific humoral immunity or CMI, or both, in >90% of vaccinees [19, 80, 81] and resulted in >85% efficacy after household exposure. VAR was safely administered to >50 Japanese children with nonlymphoma tumors with clinical and immunological outcomes similar to those for acute leukemia [82, 83]. The results of >10 other small vaccination studies in approximately 150 children with solid tumors closely replicated the Japanese experience.

Varicella vaccination in children with leukemia was often complicated, however, by systemic reactions (eg, fever and disseminated rash in 40%) that affected the chemotherapy schedule and required treatment with acyclovir [73, 82, 84]. Severe reactions have occurred in children with other malignancies [82]. Additional arguments against the use of VAR in children with malignancies include the following: (1) children who received VAR prior to immunosuppression may retain protective immunity, (2) risk of exposure to varicella has diminished, (3) antiviral agents are available for treatment, (4) chemotherapy regimens change frequently and often are more immunosuppressive than those under which varicella vaccination was studied, and (5) protection will likely be superior if vaccination occurs after significant immune recovery.

The CDC ACIP recommends that patients on chemotherapy or radiation for hematopoietic malignancies receive live virus vaccines when in remission and off therapy for ≥3 months with evidence of substantial CMI recovery [11, 45].

HSCT. Safety and immunogenicity were satisfactory when VAR was administered to a small number of HSCT recipients (allogeneic and autologous) at 12–24 months posttransplantation when they were not immunosuppressed and met criteria similar to those for other immunocompromised children [85]. More than 30 additional allogeneic HSCT recipients safely received 2 doses of VAR 24 months after transplant when they were off therapy, had no GVHD, had a normal phytohemagglutinin or mitogen response, and had a CD4 T-cell lymphocyte count ≥200 cells/mm^3 [86]. At least 85% developed specific antibody, generally in association with VZV-specific CMI. Similarly, VAR was safely administered ≥2 years after HSCT to 46 children who were off immunosuppression, had a CD4 T-cell lymphocyte count ≥200 cells/mm^3, and had responded to ≥1 other vaccine [87]. VAR is commonly safely administered ≥24 months after successful HSCT. The clinical efficacy of VAR in this situation has not been established. The presence or absence of anti-varicella antibody is not likely an accurate predictor of protection, since VZV-specific CMI is essential for recovery from VZV infections. Patients receiving VAR must not be receiving prophylactic anti-herpes viral therapy or immune globulin therapy because these treatments interfere with vaccine effect.

Renal transplant. Varicella vaccination after renal transplantation, within carefully controlled limits of maintenance immunosuppression and immunologic specifications, was well tolerated. At 6–12 months after vaccination, 75%–85% had VZV antibody. Mild varicella occurred 2–4 years after vaccination in 3 of 34 patients [17].

Liver transplant. VAR was administered after liver transplantation to 15 varicella-naive children and to 7 previously vaccinated children who had lost their VZV antibody. These patients were ≥6 months posttransplantation, were on limited dosages of immunosuppressive medications, and had not been treated for rejection episodes during the prior month. No safety issues were identified. Immune responses were good, and 10 varicella exposures occurred without subsequent varicella [16, 18].

HIV infection. Approximately 100 children aged <8 years with HIV safely received VAR without alterations in their CD4 T-cell lymphocyte percentage or count or in their plasma viral load [79, 88]. They had a baseline CD4 T-cell lymphocyte

percentage ≥15 and most were on combination antiretroviral therapy (cART). Two doses administered 3 months apart resulted in good immune responses similar to those in HIV-infected children convalescing from natural varicella, which appeared not to pose risk for repeat infection. Effectiveness of VAR in HIV-infected children is suggested by several long-term follow-up studies with effectiveness in preventing varicella (82%) and zoster (100%) [20, 89]. Optimal timing for vaccination is after ≥3 months of successful cART [79].

Other immunosuppressive conditions. Patients with cellular immune deficiencies, patients receiving immunosuppressive drugs similar in type and dose to those used for the conditions mentioned above, and patients receiving high-dose steroid therapy should not receive VAR [90, 91]. VAR was safe and immunogenic in 25 pediatric patients with rheumatic diseases who were receiving MTX, and no disease flares were associated with vaccination [92, 93]. Six pediatric patients with IBD on immunosuppressive therapy who received VAR tolerated it and had good immune responses; however, 5 of them received their initial dose of VAR prior to immunosuppression [92]. There are no data on VAR in patients receiving biological immunosuppressants, patients receiving drugs that deplete B cells or antagonize costimulatory molecules, or varicella-naive immunocompromised adults. Since adults are less responsive to VZV antigens and more susceptible to varicella complications than children, there is additional uncertainty about vaccination timing for adults who have been severely immunosuppressed. Most advisory groups indicate that adult vaccination should be guided by recommendations for children; however, VAR should be administered only when an immunocompromised adult has substantially recovered from immunosuppression.

MMRV vaccine has not been evaluated in immunocompromised patients and should not be administered to persons with primary or secondary immunodeficiency because it contains ≥7-fold more VZV than monovalent VAR. When administered as a first dose to immunocompetent children aged <4 years, it is significantly more likely to cause fever and febrile seizures than MMR vaccine and VAR administered separately [94, 95].

Herpes Zoster Vaccine

The incidence and severity of herpes zoster (HZ) increase with age and also with degree of immune compromise. ZOS is not licensed for use in highly immunocompromised patients for the same reasons as those against administration of VAR to these patients. Two differences that may be relevant are that ZOS contains 14-fold more (at expiry) live VZV than does VAR and most immunocompromised patients at risk for HZ (except allogeneic HSCT patients) had previously developed primary VZV immunity and should have residual VZV-specific immune memory, even with immunosuppression.

VI. Should Immunocompromised Patients or Those Who Will Undergo Immunosuppression Receive ZOS?

Recommendations

20. ZOS should be given to patients aged ≥60 years if it can be administered ≥4 weeks before beginning highly immunosuppressive therapy (strong, low).
21. ZOS should be considered for varicella-positive patients (ie, persons with a history of varicella or zoster infection or who are varicella–zoster virus [VZV] seropositive with no previous doses of VAR) aged 50–59 years if it can be administered ≥4 weeks before beginning immunosuppressive therapy (weak, low).*
22. ZOS should be administered to patients aged ≥60 years who are receiving therapy considered to induce a low level of immunosuppression (strong, low).
23. ZOS should *not* be administered to highly immunocompromised patients (strong, very low).

Evidence Summary

Persons with varicella immunity that was induced by VAR are at lower risk for HZ than those with a history of varicella disease and should not receive ZOS. In some clinical situations, immunosuppression that results in increased risk for zoster can be delayed for a significant period of time (eg, prior to organ transplantation, chemotherapy, use of biological modifiers); however, urgent treatments should not be delayed. ACIP suggests administering ZOS ≥2 weeks prior to immunosuppression [10]; the panel suggests 4 weeks for all live vaccines. A strong VZV-specific response to ZOS occurs within 2 weeks in immunocompetent persons [96].

ZOS should be considered in varicella-positive patients (ie, persons with a history of varicella or zoster infection or are VZV seropositive with no previous doses of VAR) who will undergo immunosuppressive therapy and are aged 50–59 years. Some vaccine-boosted immunity may persist during immunosuppression and attenuate, if not prevent, subsequent HZ.

ZOS will likely be well tolerated in patients receiving low-dose immunosuppressive therapies defined by the ACIP as "not sufficiently immunosuppressive to cause concerns for vaccine safety" [10], such as low-dose prednisone (<2 mg/kg; maximum ≤20 mg/day), MTX (≤0.4 mg/kg/week), azathioprine (≤3 mg/kg/day), and 6-mercaptopurine (≤1.5 mg/kg/day). ZOS was well tolerated in a cohort of 62 adults with hematological malignancies, including 31 with stem cell transplant (autologous, 26; allogeneic, 5), except for 1 patient who experienced trigeminal zoster 3 weeks after vaccination [97]. Vaccine efficacy in these patient populations is unknown.

Absence of safety and efficacy data precludes ZOS in patients on biological immunosuppressants. However, clinical features of HZ that developed in >100 patients receiving TNF-α modulators

for RA resulted in acceptable severity, suggesting that such patients could tolerate the less-pathogenic VZV in ZOS [98, 99]. Risk of zoster is higher for patients receiving anti–TNF-α antibodies than for those receiving TNF-α-antagonists [98]. Data on zoster vaccination of varicella-immune immunocompromised patients aged <50 years are limited. Preliminary results of zoster vaccination in 286 HIV-infected adults on stable antiretroviral therapy showed safety and immunogenicity.

RECOMMENDATIONS FOR INFLUENZA VACCINE IN THE IMMUNOCOMPROMISED HOST

VII. Should Immunocompromised Patients Receive Influenza Vaccine?

Recommendations

24. Annual vaccination with IIV is recommended for immunocompromised patients aged ≥6 months (strong, moderate) except for patients who are very unlikely to respond (although unlikely to be harmed by IIV), such as those receiving intensive chemotherapy* (strong, low) or those who have received anti–B-cell antibodies within 6 months* (strong, moderate).
25. LAIV should *not* be administered to immunocompromised persons (weak, very low).

Evidence Summary

IIV can be safely administered to and is indicated annually for all immunocompromised patients aged ≥6 months including patients receiving immunosuppressive therapy for chronic inflammatory disease, oncology patients receiving chemotherapy, immunosuppressed transplant patients, HIV patients, and primary immunodeficiency patients (eg, common variable immune deficiency [CVID]) [100–104]. Patients aged <9 years who have never received influenza vaccine or received only 1 dose in the previous season should be vaccinated with 2 doses given 1 month apart [41]. Relatively small observational studies support the immunogenicity of IIV in all these groups except primary immunodeficiency patients. Data summarized elsewhere in this guideline emphasize the safety of IIV in immunocompromised populations. Immune response to IIV is good in most children with IBD or rheumatologic inflammatory illnesses, except those receiving anti–TNF-α antibodies. Immune response is often poor in cancer chemotherapy patients; in adults receiving azathioprine, infliximab, or rituximab; and in SOT recipients receiving mycophenolate. A single study of antibody-deficient patients on immunoglobulin therapy showed poor immunogenicity but no safety issues [105].

LAIV is contraindicated in immunocompromised patients because the risks are unknown in most populations. It has been studied in HIV-infected patients and 28 children with malignancies, among whom no safety issues were identified [38, 39, 106, 107]. LAIV and IIV were compared in 243 pediatric patients with HIV infection aged 5–17 years on a stable cART regimen [39]. Safety and immunogenicity of both vaccines were similar to those reported in immunocompetent children.

RECOMMENDATIONS FOR VACCINATION OF PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISORDERS

Primary immunodeficiency disorders are a heterogeneous group that includes genetic congenital disorders that affect the functioning of either the innate or adaptive immune systems [108]. Defects of the adaptive immune system are divided into defects in antibody production alone or defects in T cells that result in combined (cell- and antibody-mediated) immunodeficiency. Depending on the type of disorder, the impaired immune response may result in vaccine failure or, with live vaccines, vaccine-associated disease. However, vaccination can be safe and effective in many situations. Vaccination of asplenic patients is addressed in question XXII.

VIII. Which Vaccines Should Be Administered to Patients With Primary (Congenital) Complement Deficiencies?

Recommendations

26. Patients with primary complement deficiencies should receive all routine vaccines based on the CDC annual schedule; none are contraindicated (strong, low).
27. Patients with primary complement deficiencies and who are:
    (a) aged 2–5 years should receive 1 dose of pneumococcal conjugate vaccine (PCV)13 if they have received 3 doses of PCV (either 7-valent PCV [PCV7] or PCV13) before age 24 months and 2 doses of PCV13 (8 weeks apart) if they have received an incomplete schedule of ≤2 doses of PCV7 (PCV7 or PCV13) before age 24 months (strong, low).
    (b) aged 6–18 years with a classic pathway (C1, C2, C3, C4), alternate pathway, or severe mannan-binding lectin (MBL) deficiency who have not received PCV13 should receive a single dose of PCV13 (strong, very low).
    (c) aged ≥19 years with a classic pathway (C1, C2, C3, C4), alternate pathway, or severe MBL deficiency who are PCV13 naive should receive a single dose of PCV13 (strong, very low). For those who have received PPSV23, PCV13 should be administered ≥1 year after the last PPSV23 dose (weak, low).
28. Patients aged ≥2 years with an early classic pathway, alternate pathway, or severe MBL deficiency should receive PPSV23 ≥8 weeks after PCV13, and a second dose of PPSV23 should be given 5 years later (strong, low).

29. Patients with primary complement deficiencies should receive conjugate meningococcal vaccine. A 4-dose series of bivalent meningococcal conjugate vaccine and *Haemophilus influenzae* type b conjugate vaccine (HibMenCY; MenHibrix, GlaxoSmithKline) should be administered at age 2, 4, 6, and 12–15 months for children aged 6 weeks–18 months (strong, low) or a 2-dose primary series of meningococcal conjugate vaccine, quadrivalent (MCV4) should be administered to patients with primary complement component deficiency at age 9 months–55 years (MCV4-D [Menactra, Sanofi Pasteur] for those aged 9–23 months; MCV4-D or MCV4-CRM [Menveo, Novartis] for those aged 2–54 years; strong, low). For persons aged >55 years, MPSV4 should be administered if they have not received MCV4 and MCV4 should be administered if they have received MCV4 (strong, low). For patients aged 9–23 months, the doses should be administered 3 months apart; for patients aged ≥2 years, the doses should be administered 2 months apart. MCV4-D should be administered ≥4 weeks after a dose of PCV13 because of a reduced antibody response to some pneumococcal serotypes when MCV4-D and PCV7 are administered simultaneously (strong, low).
30. Patients with a primary complement component deficiency should be revaccinated with MCV4 (or MPSV4 for those aged >55 years who have not received MCV4) every 5 years (strong, low) [109].

Evidence Summary

Immunogenicity of MPSV4 has been demonstrated in patients with complement deficiencies [110–116]. Revaccination is needed to maintain levels of antibody to both MPSV4 [113, 115] and MCV4 [117–119]. Occasional reports of poor or aberrant antibody responses in patients with early classic complement component deficiency [120–123] support the potential (not established) importance of monitoring antibody responses in this subset. CDC's ACIP recommends routine use of PCV13 for immunocompromised persons [109, 124]. MCV4-D can interfere with the response to some serotypes of PCV7 when both are administered simultaneously [481].

Since influenza may predispose to invasive bacterial respiratory infection [125, 126], annual influenza vaccination is important in this group. Influenza vaccine has not been studied in patients with complement deficiencies, but safety is likely similar to that in immunocompetent persons.

IX. Which Vaccines Should Be Administered to Patients With Phagocytic Cell Deficiencies (eg, CGD, Leukocyte Adhesion Deficiency, Chediak–Higashi Syndrome)?

Recommendations

31. Patients with phagocytic cell deficiencies should receive all inactivated vaccines based on the CDC annual schedule (strong, low). Children aged 2–5 years should receive PCV13 as in recommendation 27a (weak, very low).
32. Patients aged ≥6 years with phagocytic cell deficiencies other than CGD (unless patient with CGD is receiving immunosuppressive medication) should receive PCV13 as in recommendations 27b and 27c (weak, very low).
33. Patients aged ≥2 years with phagocytic cell deficiencies other than CGD (unless patient with CGD is receiving immunosuppressive medication) should receive PPSV23 ≥8 weeks after receipt of PCV13, and a second dose of PPSV23 should be given 5 years later (weak, low).
34. Live bacterial vaccines, such as bacillus Calmette–Guérin (BCG) or oral typhoid vaccine, should *not* be administered to patients with a phagocytic cell defect (strong, moderate).
35. Live viral vaccines should be administered to patients with CGD and to those with congenital or cyclical neutropenia (weak, low).
36. Live viral vaccines should *not* be administered to patients with leukocyte adhesion deficiency, defects of cytotoxic granule release such as Chediak–Higashi syndrome (see section on combined immunodeficiencies), or any other undefined phagocytic cell defect (strong, low).

Evidence Summary

For inactivated vaccines, but not for live viral vaccines except in CGD patients, patients with phagocytic cell defects should have normal immune responses and the same adverse effects as immunocompetent individuals. Patients with CGD are not at increased risk for infections with pneumococcus [127, 128], and there is limited data on the risk of invasive pneumococcal infection in patients with other phagocytic cell defects [127, 128]. There are no data on which to base a recommendation for live, oral rotavirus vaccine in CGD patients with IBD. *Staphylococcus aureus* is a major pathogen in individuals with phagocytic defects. Because influenza infection may predispose to respiratory infection with this organism [129], annual influenza vaccination is important.

Live vaccines, especially viruses, should be avoided in patients with leukocyte adhesion deficiency or cytotoxic granule-release defects (eg, Chediak–Higashi syndrome) because the defective cytotoxicity of T and natural killer (NK) cells results in abnormal immune response [130, 131]. Since some defects that affect neutrophil function may also affect lymphocyte function and potentially depress response to live vaccines, individuals with phagocytic defects undefined at a molecular level should not receive live vaccines. Dissemination of BCG can occur in CGD patients [132–135]. There are no reported cases of vaccine-associated disease caused by live oral typhoid vaccine in CGD patients. However, nontyphoidal salmonella infection is the most common cause of bacteremia [127], confirming poor control of this group of organisms. Therefore, live oral typhoid vaccine should be avoided in CGD patients.

X. Which Vaccines Should Be Administered to Patients With Innate Immune Defects Resulting in Defects of Cytokine Generation/Response or Cellular Activation (eg, Defects of the Interferon-gamma/Interleukin-12 Axis)?

Recommendations

37. Patients with innate immune defects that result in defects of cytokine generation/response or cellular activation should receive all inactivated vaccines based on the CDC annual schedule (strong, very low).
38. For patients with innate immune defects that result in defects of cytokine generation/response or cellular activation, PCV13 should be administered as in recommendations 27a–c (weak to strong, very low to low).
39. The advice of a specialist should be sought regarding individual conditions concerning use of live vaccines in patients with innate immune defects that result in defects of cytokine generation/response or cellular activation/inflammation generation (strong, low).
40. Live bacterial vaccines should *not* be administered to patients with defects of the interferon-gamma/interleukin-12 (IFN-γ/IL-12) pathways (strong, moderate).
41. Live viral vaccines should *not* be administered to patients with defects of IFN (alpha or gamma) production (strong, low).

Evidence Summary

There is a group of heterogeneous defects of innate immunity in which cytokine generation or response and resultant cellular activation and inflammation are abnormal. In some cases, functioning of the adaptive immune response may also be affected. Inactivated vaccines often induce adequate immune responses without serious adverse events in patients with defects of cytokine generation/response or cellular activation (eg, defects of the IFN-γ/IL-12 axis). However, given the increasing variety of newly recognized disorders, an immunologist should be consulted. Many have increased susceptibility to mycobacterial infections including disseminated BCG [136–140]. Many molecular defects can result in defects of antiviral immunity [141, 142], contraindicating the use of live viral vaccines.

XI. Which Vaccines Should Be Administered to Patients With Minor Antibody Deficiencies?

Recommendations

42. Patients with immunoglobulin (Ig)A deficiency or specific polysaccharide antibody deficiency (SPAD) should receive all routine vaccinations based on the CDC annual schedule, provided that other components of their immune systems are normal (strong, low).
43. Children with SPAD or ataxia–telangiectasia should receive PCV13 as described in recommendations 27a–c (weak to strong, very low to low). Those aged ≥2 years should receive PPSV23 ≥8 weeks after indicated doses of PCV13, and a second dose should be given 5 years later (strong, low).
44. Monitoring of vaccine responses can be useful for assessing the degree of immunodeficiency of patients with minor antibody deficiencies and level of protection (weak, moderate).
45. OPV should *not* be administered to IgA-deficient patients (strong, low).

Evidence Summary

Patients with minor antibody deficiencies are likely to be able to mount at least partial antibody responses to vaccines, which may aid in the assessment of the degree of immunodeficiency. In some instances, apparently minor antibody deficiencies are associated with a CMI defect (eg, DiGeorge syndrome [143, 144]), which is an important consideration before giving live vaccines. In SPAD [145], protein–polysaccharide conjugate vaccines will, to some extent, overcome the defect and produce some antibody response [146].

In ataxia–telangiectasia, response to PPSV23 is, for the most part, poor. In small studies, PCV7 was immunogenic in most patients, although not comparable to immunocompetent controls [147–149]. OPV should not be administered to IgA-deficient patients [150–152].

XII. Which Vaccines Should Be Administered to Patients With Major Antibody Deficiencies Receiving Immunoglobulin Therapy?

Recommendations

46. Inactivated vaccines other than IIV are *not* routinely administered to patients with major antibody deficiencies during immunoglobulin therapy (strong, low).
    (a) For patients with suspected major antibody deficiencies, all inactivated vaccines can be administered as part of immune response assessment prior to immunoglobulin therapy (strong, low).
47. IIV can be administered to patients with major antibody deficiencies and some residual antibody production (weak, low).
48. Live OPV should *not* be administered to patients with major antibody deficiencies (strong, moderate).
49. Live vaccines (other than OPV) should *not* be administered to patients with major antibody deficiencies (weak, low).*

Evidence Summary

Most patients with major antibody deficiency disorders will be on immunoglobulin replacement therapy in order to receive continual passive immunity. Vaccination with live or

inactivated vaccines is rarely undertaken in patients receiving immunoglobulin for complete agammaglobulinemia. These patients will not have antibody response, although a T-cell response that aids recovery from some viral infections is possible.

IIV can be useful in patients with an incomplete deficiency of antibody production who are receiving immunoglobulin replacement therapy. In these patients, it is possible that the immunoglobulin does not contain antibodies against circulating strains of influenza, and T-cell–mediated responses are likely to contribute to protection from severe disease. Some patients with CVID responded to polysaccharide and protein vaccine antigens; the magnitude of response may have correlated with clinical severity of the immunodeficiency [153–155]. Adults with major humoral immunodeficiencies, mainly on immunoglobulin therapy, had very poor responses to IIV, particularly those with CVID, but had some response to the A (H1N1) component [105].

VAPP is a recognized complication of major antibody deficiency syndromes [156–158], but the absence of chronic OPV secretors among 2 sizeable cohorts of antibody-deficient patients suggests that the condition is rare [159, 160]. There is no published evidence of harm from inactivated vaccines unique to this patient population.

Live virus vaccines should be avoided since the risk is unknown and they are unlikely to lead to protection because of preexisting neutralizing antibody from administered immunoglobulin.

XIII. Which Vaccines Should Be Administered to Patients With Combined Immunodeficiencies?

Recommendations

50. For patients with suspected combined immunodeficiencies, all inactivated vaccines can be administered as part immune response assessment prior to commencement of immunoglobulin therapy (strong, low).
    (a) For patients with combined immunodeficiencies who are receiving immunoglobulin therapy, inactivated vaccines should *not* be routinely administered (strong, low).
51. For patients with combined immunodeficiencies and residual antibody production potential, IIV can be administered (weak, very low).
52. Children with partial DiGeorge syndrome (pDGS) should undergo immune system assessment with evaluation of lymphocyte subsets and mitogen responsiveness in order to determine whether they should be given live viral vaccines. Those with ≥500 CD3 T cells/mm^3, ≥200 CD8 T cells/mm^3, *and* normal mitogen response should receive MMR vaccine and VAR (weak, low).*
53. Patients with SCID, DGS with a CD3 T-cell lymphocyte count <500 cells/mm^3, other combined immunodeficiencies with similar CD3 T-cell lymphocyte counts, Wiskott–Aldrich syndrome, or X-linked lymphoproliferative disease and familial disorders that predispose them to hemophagocytic lymphohistiocytosis should *avoid* all live vaccines (strong, moderate).

Evidence Summary

Vaccines are often administered before diagnosis of combined immune deficiency. Inactivated vaccines do not cause significant adverse effects, whereas live vaccines (eg, rotavirus) may produce chronic infection in patients with combined immune deficiency [161–163]. Immunity in DGS patients varies from normal to complete athymia. With a CD3 T-cell lymphocyte count >500 cells/mm^3 and normal mitogen response, MMR and VZV vaccines are safe and produce high seroconversion rates [164–166]; however, antibody levels may fall significantly after 1 year [167] (a finding of unclear clinical significance). There are no published data on live virus vaccination in other partial T-cell defects. Extrapolation from HIV-infected persons suggests that a CD4 T-cell lymphocyte count ≥200 cells/mm^3 (adults) or percentage ≥15 (children) is a reasonable criterion but is of uncertain validity.

T-cell–deficient children receiving live viral vaccines have developed VAPP [168], disseminated measles infection including pneumonitis [169–171], and chronic rotavirus infection [161–163, 172] after receiving the relevant vaccines. In disorders that predispose to hemophagocytic lymphohistiocytosis (eg, perforin deficiency), immune response to viruses is abnormal because of defective cytotoxicity of T and NK cells. Therefore, live vaccines should be avoided [173]. Disseminated BCG may be the presenting feature of SCID or it may develop during stem cell transplantation [174].

RECOMMENDATIONS FOR VACCINATION OF HIV-INFECTED ADULTS, ADOLESCENTS, AND CHILDREN

XIV. Which Inactivated Vaccines Should Be Administered to HIV-Infected Patients?

Recommendations (Table 2)

54. HIV-infected patients should be vaccinated according to the CDC annual schedule for the following inactivated vaccines: IIV (strong, high); PCV13 in patients aged <2 years (strong, moderate); *H. influenzae* type b conjugate (Hib) vaccine (strong, high); diphtheria toxoid, tetanus toxoid, acellular pertussis (DTaP) vaccine (strong, moderate); tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis (Tdap) vaccine (strong, very low); tetanus toxoid, reduced diphtheria toxoid (Td) vaccine (strong, low); hepatitis B (HepB) vaccine (strong, moderate); hepatitis A

(HepA) vaccine (strong, moderate); inactivated poliovirus (IPV) vaccine (strong, moderate); and quadrivalent human papillomavirus (HPV4) vaccine* in females and males aged 11–26 years (strong, very low) with additions noted below.

55. PCV13 should be administered to HIV-infected patients aged ≥2 years as in recommendations 27a–c (Table 2; strong, low to moderate).
56. PPSV23 should be administered to HIV-infected children aged ≥2 years who have received indicated doses of PCV (strong, moderate), HIV-infected adults with CD4 T-lymphocyte counts of ≥200 cells/mm^3 (strong, moderate), and HIV-infected adults with CD4 T-lymphocyte counts of <200 cells/mm^3 (weak, low). PPSV23 should be given ≥8 weeks after indicated dose(s) of PCV13, and a second dose of PPSV23 should be given 5 years later (strong, low).
57. HIV-infected children who are aged >59 months and have not received Hib vaccine should receive 1 dose of Hib vaccine (strong, low). Hib vaccine is *not* recommended for HIV-infected adults (weak, low).
58. HIV-infected children aged 11–18 years should receive a 2-dose primary series of MCV4 2 months apart (strong, moderate). A single booster dose (third dose) should be given at age 16 years if the primary series was given at age 11 or 12 years and at age 16–18 years if the primary series was given at age 13–15 years (strong, low). If MCV4 is administered to HIV-infected children aged 2–10 years because of risk factors for meningococcal disease, a 2-dose primary series of MCV4 should be administered with a 2-month interval between doses, and a booster dose should be given 5 years later (strong, very low).
59. HIV-infected patients should receive the HepB vaccine series (strong, moderate), with consideration of high-dose HepB vaccine (40 μg/dose) for adults (weak, moderate) and adolescents* (weak, low). One to 2 months after completion, patients should be tested for anti-HBs (antibodies to HepB surface antigen; strong, low). If a postvaccination anti-HB concentration of ≥10 mIU/mL is not attained, a second 3-dose series of HepB vaccine (strong, low; alternative: 1 dose of HepB vaccine after which anti-HBs is tested*), using standard dose (strong, moderate) or high dose (40 μg*; weak, low) for children and high dose for adolescents* and adults (strong, low), should be administered.
60. HepB vaccine containing 20 μg of HepB surface antigen (HBsAg) combined with HepA vaccine (HepA–HepB; Twinrix), 3-dose series, can be used for primary vaccination of HIV-infected patients aged ≥12 years (strong, moderate).*
61. Internationally adopted HIV-infected children who have received doses of OPV should receive a total of 4 doses of a combination of OPV and IPV vaccine (strong, low).
62. HPV4 vaccine is recommended over bivalent human papillomavirus (HPV2) vaccine because HPV4 vaccine prevents genital warts (strong, low),* although there are no data on differences between the vaccines for preventing cervical dysplasia in HIV-infected women.

Evidence Summary

Administration of inactivated vaccines to HIV-infected persons appears safe as no increases in adverse effects or HIV-specific adverse effects have been recognized. However, data are not sufficient to comment on rare adverse effects. Concern about accelerating progression of the HIV infection is unfounded. A transient increase in plasma HIV viral load may occur after vaccination in children not receiving cART but this resolves in 2 to 6 weeks [102, 175, 176]. Patients receiving cART do not experience significant changes in viral load or T-cell concentrations after administration of either live or inactivated vaccines [79, 177–181]. In general, live vaccines are contraindicated in HIV-infected persons with low CD4 T-cell lymphocyte counts or percentages.

Vaccination guidelines for HIV-infected adolescents and adults have been published by the CDC, National Institutes of Health (NIH), and HIV Medical Association (HIVMA) of IDSA [8]; guidelines for HIV-infected children have been published by CDC, NIH, HIVMA of IDSA, Pediatric Infectious Diseases Society, and AAP [7].

HIV-infected children often have lower antibody and CMI responses to vaccines than immunocompetent persons, although these responses may still be protective [79, 88, 177–180, 182]. The vaccine-induced responses correlate with the adequacy of the CD4+ T-cell pool and plasma HIV load at the time of vaccination, each of which is an independent predictor of the magnitude of the immune response [79, 177, 178, 180, 183]. In some, but not all, studies, the CD4+ T-cell lymphocyte percentage at the time of vaccination in children on a stable cART regimen is a better predictor of response than is the nadir percentage count prior to starting cART [79, 177–179]. Antibody levels from prior vaccination may increase after cART even in the absence of a vaccine boost. Responses to vaccines are significantly better in patients who have been on cART ≥3 months, specifically after improvement in the CD4+ T-cell lymphocyte percentage (optimally ≥15) and reduction in plasma HIV viral load (optimally to <1000 copies/mL), suggesting that vaccinations should be delayed until cART has been undertaken [184].

Influenza Vaccination With IIV

Antibody responses to IIV are blunted in patients who have untreated HIV [185–187] and are improved in patients who do not have progressive HIV disease and/or are receiving cART [188]. Efficacy of IIV in HIV-infected adults was established in 5 controlled trials; efficacy and clinical effectiveness ranged from 27% to 78% [13, 189]. In HIV-infected adults, IIV was not associated with increased or unusual adverse effects, although rare adverse effects may not have been detected [41]. In contrast

with previous reports [190, 191], subsequent prospective trials found no significant long-term difference in HIV RNA levels between influenza-vaccinated and unvaccinated HIV-positive patients [192, 193]. The monovalent 2009 pandemic A (H1N1) vaccine was immunogenic in HIV-infected children but less immunogenic in HIV-infected adults than in HIV-uninfected adults [194]. No safety issues were identified [181, 195], although the presence of the adjuvant "Adjuvant System 03" (ASO_3) was associated with a small increase in plasma HIV RNA in 1 study [176].

Pneumococcal Vaccination

PCV is safe and efficacious [196–199] in HIV-infected children and is more immunogenic than PPSV23 [200–202]. However, the antibody produces decays more rapidly than in uninfected children, has lower functional activity, and the anamnestic response is blunted [203]. Two doses of PCV7 were safely administered to HIV-infected children aged <18 years on cART, followed by 1 dose of PPSV23 [178]. The antibody response was excellent and persistence was similar to that observed in uninfected children. Although PCV13 has not been studied in HIV-infected children, PCV13 has replaced PCV7 in the vaccination schedule [124, 204]. A randomized, controlled trial of PCV7 in HIV-infected adults in Malawi, the majority of whom were not on antiretroviral therapy, showed that the vaccine was safe and had an efficacy of 75% in preventing recurrent invasive pneumococcal infection [205]. CDC's ACIP recommends routine use of a single dose of PCV13 for immunocompromised adults [109].

PPSV23 efficacy has been studied primarily in adults/adolescents with CD4 T-lymphocyte counts ≥200 cells/mm^3. Most studies have shown that PPSV23 reduces pneumococcal bacteremia and decreases mortality in HIV-infected adults [206–208]. However, 1 study performed in Uganda found an increase in pneumococcal disease in vaccine recipients [209]. Although efficacy is uncertain for individuals with CD4 counts <200 cells/mm^3, PPSV23 should be offered to such patients with consideration of revaccination once antiretroviral therapy has resulted in a CD4 count ≥200 cells/mm^3.

Haemophilus influenzae Type b Vaccination

HIV-infected children not on cART are less likely to respond to Hib vaccine, and their antibody responses often fall below levels associated with long-term protection (≥0.15 μg/mL) within 1 year [210]. Nevertheless, Hib vaccination was highly effective over a 2-year period in HIV-infected children in South Africa [182, 211] and Malawi [212].

Meningococcal Vaccination

As in immunocompetent persons, MCV4 is preferred over MPSV4 for HIV patients aged 9 months–54 years and can be given to immunocompetent adults without concern for hyporesponsiveness if the recipient has received MPSV [213, 214]. If MCV4 is administered to HIV-infected children aged ≥2 years, a 2-dose primary series of MCV4 should have a 2-month interval between doses [215, 216]. A single dose of MCV4 was safely administered to 320 HIV-infected children aged >11 years on cART with a CD4 T-cell lymphocyte percentage ≥15 [215] and to children aged 2–11 years with a CD4 T-cell lymphocyte percentage ≥25. Antibody against ≥1 serotype showed a 4-fold increase to 1 or more antigens in 88% of vaccinees and in 50%–70% of individual serotypes. Although antibody levels were significantly lower than in HIV-uninfected children, protective titers were present in 55%–90% (depending on serotype) after vaccination. Antibody levels fell approximately 50% in the 6 months after vaccination. A 2-dose regimen of MCV4 was administered to 59 HIV-infected children aged 2–10 years with a good safety profile and generally good immunogenicity that varied with serogroup [216]. Response after a single MCV4 dose was high to serogroup A (92%) and W-135 (98%); responses improved after a second dose for serogroup C (from 43% to 80%; $P < .0001$) and serogroup Y (from 76% to 84%; P = .38).

Diphtheria, Tetanus, Pertussis Vaccination

Children with HIV often have low to undetectable levels of antibody against pertussis, diphtheria, and tetanus [179, 217–221] after receiving 3 or 4 doses of Diphtheria toxoid, whole cell pertussis, tetanus toxoid vaccine (DPT) or diphtheria toxoid, tetanus toxoid, acellular pertussis (DTaP) vaccine. Booster vaccination of HIV-infected children with DTaP is safe and does not significantly affect the CD4 T-lymphocyte cell count or HIV RNA levels [179, 221]. Although the booster dose of DTaP vaccine significantly increases anti-pertussis [179] and anti-tetanus [218] antibody levels, they remain significantly lower than those induced in uninfected children after a primary series or a booster dose at 4 to 6 years. The efficacy of primary or booster DTaP vaccination in HIV-infected children is unknown. Tdap vaccination has not been studied in HIV-infected children or adults.

Hepatitis B Vaccination

HepB infection is commonly acquired by infants born to mothers dually infected with HepB virus (HBV) and HIV. The efficacy of infant prophylaxis against HBV, HepB, and HepB immune globulin (HBIG) within 12 hours of birth in the presence of HIV infection is unknown. However, prophylaxis is likely to minimize, but not entirely prevent, mother-to-child transmission [222]. Children born to HIV-infected mothers should receive their first dose of HepB vaccine before hospital discharge [223].

HepB vaccine is indicated and can be safely given to HIV-infected patients, but immunogenicity is lower than in HIV-negative adults. Only 18%–72% of HIV-positive persons

develop protective concentrations of antibodies to HepB surface antigen (HBsAg), which are generally lower in magnitude and wane more quickly than in adults without HIV infection [56, 224–226]. Low CD4 count and ongoing HIV viremia are associated with poor vaccine responses [57, 225–228]. In patients not receiving cART, only 30%–50% develop a protective antibody response (anti-HBs concentration of ≥10 mIU/mL in immunocompetent persons) [229]. However, protective levels are reached in 60%–70% of vaccinees receiving cART, with responsiveness proportional to the percentage of CD4+ T lymphocytes and the extent of virus suppression [230–234].

The frequent failure of the primary vaccine series is the rationale for testing for anti-HBs after the third dose of vaccine. When antibody was absent after the standard primary series, a subsequent single booster dose significantly increased the number of vaccinees with protective antibody levels in 2 studies [230, 235] but led to only a small increase in another study [229]. Repeating a 3-dose series induced protective antibody levels in >75% of patients who failed an initial series [236]. However, this response also declined quickly after boosting, even when vaccines containing a higher content of HBsAg were used [230, 233, 236]. Doubling the HepB vaccine dosage from 20 μg to 40 μg significantly increased seroconversion rates [57, 58]. In the pre-cART era, the dose of HBsAg was successfully doubled for HIV-infected children [237]. All strategies are more successful in patients who are on cART. In HIV-infected patients aged 12–20 years who received primary vaccination with a 3-dose series of high-dose HepB vaccine (40 μg of HBsAg; given as Engerix-B, as is done for dialysis patients) or a combined HepA–HepB vaccine (Twinrix), the response rate (73%–75% seroresponse) was superior to that with standard HepB vaccine containing 20 μg of HBsAg (Engerix-B; 60% seroresponse) [233, 238]. A similar outcome occurred with a 3-dose series of high-dose HepB vaccine among 267 adult HIV-infected patients with CD4 T-lymphocyte counts >200 cells/mm^3, the majority of whom were receiving antiretroviral therapy [58]. Seroreversion is also common. Approximately 30% of HIV-infected children who were vaccinated while receiving cART did not have seroprotective antibody levels 3 years after vaccination, but 82% had an anamnestic response to a single additional dose of HepB vaccine [239]. The importance of persistent anti-HBs is unclear. There is no evidence in HIV-uninfected children that loss of antibody after successful vaccination results in subsequent clinically significant infection or chronic infection [240].

For HIV-infected patients who are negative for HBsAg and anti-HBs but are anti-HBc (antibodies to HepB core antigen) positive, there is a possibility of recrudescence of past, occult HBV infection and vaccination recommendations vary. Some data suggest that these patients are not HBV immune and should receive a complete vaccine series [241, 242], while others suggest a single dose of vaccine followed by anti-HBs testing 2 weeks later. Current guidelines from the CDC, NIH, and the HIV Medicine Association of the IDSA for the prevention and treatment of opportunistic infections in HIV-infected adolescents and adults recommend giving the complete series in patients with a positive isolated HBV core antibody and a negative test for HBV DNA [8].

Hepatitis A Vaccination

HepA is immunogenic in HIV-infected patients, and no safety issues were identified in more than 300 vaccinees [177, 243, 244]. Almost 100% of HIV-infected children on cART with a CD4 T-cell lymphocyte percentage ≥20–25 seroconverted [245]. Younger HIV-infected children have antibody responses similar to those of uninfected vaccinees, but responses are 10- to 50-fold lower in older children with a longer duration of HIV infection. HIV-infected persons should be vaccinated against HepA prior to a decline in CD4 counts to improve the likelihood of an adequate response. Although responses are better in patients who respond to cART, vaccination should not be delayed in at-risk patients. Seroreversion occurs in 10% of HIV-infected vaccinees within 2 years, but a third dose of HepA vaccine is safe and generates high antibody titers that are similar in magnitude to those achieved with 2 doses in uninfected persons. Eighty-five percent of HIV-infected adults maintained seropositive antibodies 6 to 10 years after 2 doses of vaccine [246].

Polio Vaccination

Anti-polio antibody concentrations after IPV vaccination are lower in HIV-infected children who are not receiving cART than in uninfected children [247]. Also, booster responses in untreated HIV-infected adults are significantly blunted [248].

HPV Vaccination

HPV4 vaccine was safe and immunogenic when administered to 126 HIV-infected children aged 7–11 years with CD4 T-lymphocyte percentages ≥15 [180]. However, there are no data regarding safety and efficacy of either vaccine in HIV-positive adolescents. HPV4 vaccine was safe and immunogenic in 109 HIV-infected adult males [249]. For HIV-infected patients, HPV4 vaccine is preferred over HPV2 vaccine because of the protection afforded by HPV4 vaccine against genital warts, which are more prevalent and more subject to relapse in HIV-infected patients than in HIV-uninfected persons [250].

XV. Should Live Vaccines Be Administered to HIV-Infected Patients?

Recommendation (Table 2)

63. HIV-exposed or -infected infants should receive rotavirus vaccine according to the schedule for uninfected infants (strong, low).

64. HIV-infected patients should *not* receive LAIV (weak, very low).
65. MMR vaccine should be administered to clinically stable HIV-infected children aged 1–13 years without severe immunosuppression (strong, moderate) and HIV-infected patients aged ≥14 years without measles immunity and with a CD4 T-cell lymphocyte count ≥200/mm^3 (weak, very low).
66. HIV-infected children with a CD4 T-cell percentage <15 (strong, moderate) or patients aged ≥14 years with a CD4 T-cell lymphocyte count <200 cells/mm^3 should *not* receive MMR vaccine (strong, moderate).
67. HIV-infected patients should *not* receive quadrivalent MMR-varicella (MMRV) vaccine (strong, very low).
68. Varicella-nonimmune, clinically stable HIV-infected patients aged 1–8 years with ≥15% CD4 T-lymphocyte percentage (strong, high), aged 9–13 years with ≥15% CD4 T-lymphocyte percentage (strong, very low), and aged ≥14 years with CD4 T-lymphocyte counts ≥200 cells/mm^3 should receive VAR (strong, very low). The 2 doses should be separated by ≥3 months (strong, moderate).

Evidence Summary

Rotavirus Vaccination

HIV infection is neither a contraindication nor a precaution for the 2 licensed live-attenuated rotavirus vaccines for HIV-infected or HIV-exposed infants [251]. To date, rotavirus vaccine trials in resource-poor countries, which invariably involved administration to HIV-infected infants, have not uncovered unusual or severe adverse events. Monovalent live rotavirus vaccine (RV1; Rotarix; GlaxoSmithKline) was safe and immunogenic in 178 HIV-infected infants including 13 with CD4 T-lymphocyte percentages <25 [252, 253]. Pentavalent live rotavirus vaccine (RV5; RotaTeq; Merck) has been associated with persistent, severe diarrhea in infants with SCID [162]. There are no data on the efficacy of rotavirus vaccines in HIV-infected children.

LAI Vaccination

LAIV is not licensed for administration to immunocompromised patients and is not recommended by the CDC for immunocompromised patients. LAIV was safely administered to 188 HIV-infected children and adults who fulfilled certain clinical and immunologic criteria [38, 39, 106]. The immune response to LAIV in HIV-infected patients was comparable to that in uninfected individuals [38, 39, 106].

MMR Vaccination

The prevalence and titer of measles antibody is low in measles-vaccinated HIV-infected children, even if they are receiving cART [218, 254–257]. Rubella antibody titers are also reduced in HIV-infected children with significant immune suppression [258, 259]. MMR vaccine was safely administered to HIV-infected children with ≥15% CD4 T lymphocytes in >1200 patients [260, 261]. However, some severe complications occurred in children with lower CD4 T-cell lymphocyte percentages or counts [262]. Titers of MMR antibodies increased after cART in previously vaccinated patients, but ≥50% remained seronegative. Administration of an additional dose of MMR vaccine to children on cART who had ≥15% CD4 T lymphocytes induced detectable measles antibody in 75%–90% [218, 257, 260], rubella antibody in >90%, and mumps antibody in >60% [260]. No significant adverse effects have been associated with vaccine administration in adults with CD4 counts >200 cells/mm^3 [263].

Varicella Vaccination

ACIP recommends varicella vaccination for HIV-positive children with mild to moderate immune suppression based on safety data [45, 79, 256]. No data exist regarding vaccine safety or efficacy in HIV-infected adults (see Varicella section).

Zoster Vaccination

Preliminary data on zoster vaccination in HIV-infected adults on stable antiretroviral therapy showed safety in 286 patients and immunogenicity (see Zoster vaccine section).

RECOMMENDATIONS FOR VACCINATION IN PATIENTS WITH CANCER

XVI. Which Vaccines Should Be Given to Patients With Cancer?

Recommendations (Table 3)

69. Patients aged ≥6 months with hematological malignancies (strong, moderate) or solid tumor malignancies (strong, low) *except* those receiving anti–B-cell antibodies* (strong, moderate) or intensive chemotherapy, such as for induction or consolidation chemotherapy for acute leukemia (weak, low), should receive IIV annually.*
70. PCV13 should be administered to newly diagnosed adults with hematological (strong, very low) or solid malignancies (strong, very low) and children with malignancies (strong, very low) as described in recommendations 27a-c. PPSV23 should be administered to adults and children aged ≥2 years (strong, low) at least 8 weeks after the indicated dose(s) of PCV13.
71. Inactivated vaccines (other than IIV) recommended for immunocompetent children in the CDC annual schedule can be considered for children who are receiving maintenance chemotherapy (weak, low). However, vaccines administered during cancer chemotherapy should *not* be

considered valid doses (strong, low) unless there is documentation of a protective antibody level (strong, moderate).

72. Live viral vaccines should *not* be administered during chemotherapy (strong, very low to moderate).
73. Three months after cancer chemotherapy, patients should be vaccinated with inactivated vaccines (strong, very low to moderate) and the live vaccines for varicella (weak, very low); measles, mumps, and rubella (strong, low); and measles, mumps, and rubella–varicella (weak, very low) according to the CDC annual schedule that is routinely indicated for immunocompetent persons. In regimens that included anti–B-cell antibodies, vaccinations should be delayed at least 6 months (strong, moderate).

Evidence Summary

Therapy for cancer has become increasingly intensive and has included immunosuppressive monoclonal antibodies. Since many vaccination studies were conducted during an era in which weaker immunosuppressive therapies were used, the results of such studies might not accurately represent the current risks and benefits of vaccinations in oncology patients today.

Inactivated vaccines in children. Children with cancer can safely receive inactivated vaccines. In general, the vaccines should not be administered during induction or consolidation therapy because of poor response rates during these periods [264]. While vaccines administered during less-intensive phases of chemotherapy are less immunogenic compared with those administered off chemotherapy [265], they are not harmful and appear to provide seroprotection for some pathogens for some patients [266–269]. Many children have protective serum antibodies against certain vaccine-preventable diseases ≥6 months after cessation of chemotherapy [270]. The routine childhood vaccination schedule should be reinitiated 3 months after completion of chemotherapy, when cellular and humoral immunity has recovered [271–274]. Routine revaccination with a single dose of each vaccine antigen can be considered [270, 275], but it is uncertain if this is necessary. Another management plan that can be considered for patients who have received intense chemotherapy is serologic testing for vaccine-preventable diseases with a recognized serologic correlate of protection (eg, diphtheria toxoid, Hib, HepA, HepB, IPV, rubella, influenza, measles, tetanus toxoid, varicella vaccines) and vaccination of those with inadequate serum antibody concentrations.

Influenza vaccine. Influenza vaccination with IIV is recommended for immunocompromised patients [41, 276]. Patients with colorectal cancer who received influenza vaccine had fewer chemotherapy interruptions and higher 1-year survival rates [277]. Study results in patients with hematological malignancies have been variable and are probably related to the type of malignancy and treatment received. In patients with multiple myeloma, the immune response to 1 dose of vaccine was only 19% [278]. Similar results have been seen in patients with lymphoma [279–281], although a more recent study showed a higher seroprotection [282]. A 2-dose schedule is a possible strategy but was not more immunogenic in some studies [308] and has not been recommended by ACIP. Adults with lymphoma who received a 2-dose schedule showed responses of approximately 30% after 1 dose and approximately 45% after 2 doses of vaccine [337]. Two doses of pandemic 2009 A (H1N1) vaccine in patients with chronic myeloid leukemia and B-cell malignancies resulted in a higher seroconversion than 1 dose; however, seroconversion was still lower than after a single dose in immunocompetent controls [328]. No patient who received maintenance rituximab responded to vaccination. Similarly, none of 67 lymphoma patients responded to adjuvanted 2009 A (H1N1) vaccine within the first 6 months after rituximab therapy [284]. The response to IIV was impaired in lymphoma patients who completed a rituximab-containing regimen ≥6 months earlier [285].

Patients receiving intensive chemotherapy are likely to be less responsive to influenza vaccination; however, the seasonal nature of influenza may warrant timely administration of IIV to induce immunity. The effectiveness is likely to be low in those at highest risk for severe disease. Most influenza virus infections in acute leukemia patients undergoing chemotherapy were nosocomially acquired; therefore, influenza vaccination of family members and hospital staff should be strongly encouraged or required [286].

Data on IIV efficacy in adult patients with solid tumors are limited. In lung cancer patients, the vaccination response was similar to that seen in immunocompetent controls [287]. Similarly, the humoral response was adequate in a group of women with breast cancer [288, 289]. In a study of patients with various solid tumors, the response to vaccination was better than in patients with lymphoma [290]. Breast cancer patients with ongoing chemotherapy had poorer responses [291]. Influenza vaccination was cost effective in working-age patients with cancer [292].

Pneumococcal vaccine. Antibody responses to PPSV23 are often impaired in patients with hematological malignancies, including patients with multiple myeloma [278] or treated Hodgkin lymphoma [293, 294]. In contrast, a good response can be obtained before antitumor therapy is initiated [295, 296]. Antibody responses can be elicited in splenectomized patients with non-Hodgkin and Hodgkin lymphomas [297]. Repeated vaccinations with PPSV23, before and after splenectomy, induced repeated antibody responses and were not associated with serious adverse effects during administration of approximately 600 doses to 380 patients [298, 299]. A single dose of a PCV7 gave suboptimal responses in patients who had been treated for Hodgkin lymphoma [300] or chronic lymphocytic leukemia [301]. Priming with

PCV7 improved the response to the PPSV23 in patients with previously treated Hodgkin lymphoma, including splenectomized patients [302, 303]. No data regarding the safety or immunogenicity of PCV13 in these patients are available [124, 204], but CDC's ACIP recommends routine use of PCV13 for immunocompromised persons [109, 124]. Patients with mixed solid tumors were reported to respond well to vaccination with PPSV23 [290].

Diphtheria–tetanus–pertussis vaccine. Hammarström et al showed that 41% of acute leukemia patients were not seroprotected against tetanus [304]. In contrast, Nordoy et al reported that treatment of low-grade non-Hodgkin lymphoma patients with radio immunotherapy did not influence immunity to tetanus [280]. Responses to DT vaccinations in adult patients with hematological malignancies have not been systematically studied. Six or more months after completing chemotherapy for leukemia, all of 59 children had protective antibody titers against tetanus and all responded to a single dose of booster vaccination [270].

HepB vaccine. Patients with hematological malignancies, particularly B-cell lymphomas treated with anti-CD20 monoclonal antibody therapy, are prone to reactivation of HepB infection during therapy [305]. The response rate to HepB vaccination is poor in patients who were receiving therapy for hematological malignancies [306, 307]. Although there are no data, it may be reasonable to vaccinate unvaccinated patients with HepB vaccine either prior to or after discontinuation of therapy against their malignancy.

Preliminary data suggest that immune responses for patients who received monoclonal antibodies for lymphoma are poor for at least the first 6 months after completion of treatment [308]. A recent study suggests that responses to recall antigens are better than primary responses against antigens not previously encountered [309]. Patients who received autologous HSCT and thereafter rituximab responded well to vaccination with Hib and tetanus vaccines but not to PPSV23 given 6 and 9 months after the last rituximab infusion [310].

Contraindication to live viral vaccines. Live viral vaccines are contraindicated during chemotherapy because of the risk of disseminated disease. Administration after 3–6 months appears to be safe [266, 269]. Although VAR has been administered to children with acute lymphoblastic leukemia receiving maintenance chemotherapy, it is generally not administered during these therapies [81, 83].

RECOMMENDATIONS FOR VACCINATION OF HEMATOPOIETIC STEM CELL TRANSPLANT PATIENTS

XVII. Should HSCT Donors and Patients Be Vaccinated Before Transplantation?

Recommendations (Table 4)

74. The HSCT donor should be current with routinely recommended vaccines based on age, vaccination history, and exposure history according to the CDC annual schedule (strong, high). However, administration of MMR, MMRV, VAR, and ZOS vaccines should be avoided within 4 weeks of stem cell harvest (weak, very low). Vaccination of the donor for the benefit of the recipient is *not* recommended (weak, moderate).
75. Prior to HSCT, candidates should receive vaccines indicated for immunocompetent persons based on age, vaccination history, and exposure history according to the CDC annual schedule if they are not already immunosuppressed (strong, very low to moderate) and when the interval to start of the conditioning regimen is ≥4 weeks for live vaccines (strong, low) and 2 weeks for inactivated vaccines (strong, moderate).
76. Nonimmune HSCT candidates aged ≥12 months should receive VAR (as a 2-dose regimen if there is sufficient time) if they are not immunosuppressed and when the interval to start the conditioning regimen is ≥4 weeks (strong, low).

Evidence Summary

Donor immunity can be transferred to the HSCT recipient [311–318], and vaccination of the donor has been shown to improve posttransplant immunity [315, 319–321]. However, there are logistical problems to vaccinating donors and ethical considerations if a vaccine is administered solely for the benefit of the HSCT recipient. Only vaccines that are indicated and recommended based on the donor's age, vaccination history, and exposure history should be administered. It is not known if vaccination of donors with MMR, MMRV, VAR, or ZOS vaccines within 4 weeks of stem cell harvesting causes safety issues for the HSCT recipient.

In most HSCT patients, antigen-specific antibody titers progressively decrease with time after HSCT, and patients may become susceptible to infections such as tetanus [314, 322], poliovirus [323–325], and measles [326, 327]. The clinical relevance of decreased antibodies to vaccine-preventable diseases among recipients is difficult to assess because, with the exception of infections caused by pneumococci and influenza, a limited number of cases of vaccine-preventable diseases have been reported among HSCT recipients [328]. In general, post-HSCT patients should be viewed as "never vaccinated" patients regardless of the pre-HSCT vaccination history of the patient or the donor.

The guidelines for vaccination of HSCT candidates and recipients have been adapted from the Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplant Recipients: A Global Perspective that was prepared in collaboration with several international organizations [15]. Based

on available data, there are no differences in recommendations for autologous and allogeneic HSCT patients.

It has been shown that existing recipient immunity frequently is retained for several months after HSCT [316, 326]. Patients respond poorly to vaccination early after HSCT. By vaccinating the seronegative patient before HSCT, it is likely that some protection will persist. No data exist regarding the interval needed between varicella vaccination and start of conditioning; however, a 4-week interval is likely to be safe. In patients with cancer who are undergoing chemotherapy and in children with acute leukemia that is in remission, a rash has been noted up to 60 days after vaccination [329, 330]. The strategy of pretransplant vaccination of seronegative patients has not been tested in a clinical study. However, this strategy is likely to be safe because children with acute leukemia who received VAR subsequently underwent allogeneic HSCT without developing clinical manifestations of varicella [331].

XVIII. Which Vaccines Should Be Administered to Adults and Children After HSCT?

Recommendations (Table 4)

77. One dose of IIV should be administered annually (strong, moderate) to persons aged ≥6 months starting 6 months after HSCT (strong, moderate) and starting 4 months after if there is a community outbreak of influenza as defined by the local health department (strong, very low). For children aged 6 months–8 years who are receiving influenza vaccine for the first time, 2 doses should be administered (strong, low).
78. Three doses of PCV13 should be administered to adults and children starting at age 3–6 months after HSCT (strong, low). At 12 months after HSCT, 1 dose of PPSV23 should be given provided the patient does not have chronic GVHD (strong, low). For patients with chronic GVHD, a fourth dose of PCV13 can be given at 12 months after HSCT (weak, very low).*
79. Three doses of Hib vaccine should be administered 6–12 months after HSCT (strong, moderate).
80. Two doses of MCV4 should be administered 6–12 months after HSCT to persons aged 11–18 years, with a booster dose given at age 16–18 years for those who received the initial post-HSCT dose of vaccine at age 11–15 years (strong, low).
81. Three doses of tetanus/diphtheria–containing vaccine should be administered 6 months after HSCT (strong, low). For children aged <7 years, 3 doses of DTaP should be administered (strong, low). For patients aged ≥7 years, administration of 3 doses of DTaP should be considered (weak, very low).* Alternatively, a dose of Tdap vaccine should be administered followed by either 2 doses of DT vaccine (weak, moderate)* or 2 doses of Td vaccine (weak, low).
82. Three doses of HepB vaccine should be administered 6–12 months after HSCT (strong, moderate). If a postvaccination anti-HBs concentration of ≥10 mIU/mL is not attained, a second 3-dose series of HepB vaccine (strong, low; alternative: 1 dose of HepB vaccine after which anti-HBs is tested*), using standard dose (strong, moderate) or high dose (40 μg*; weak, low) for children and high dose for adolescents* and adults (strong, low), should be administered.
83. Three doses of IPV vaccine should be administered 6–12 months after HSCT (strong, moderate).
84. Consider administration of 3 doses of HPV vaccine 6–12 months after HSCT for female patients aged 11–26 years and HPV4 vaccine for males aged 11–26 years (weak, very low).
85. Do *not* administer live vaccines to HSCT patients with active GVHD or ongoing immunosuppression (strong, low).
86. A 2-dose series of MMR vaccine should be administered to measles-seronegative adolescents and adults (strong, low) and to measles-seronegative children (strong, moderate) 24 months after HSCT in patients with neither chronic GVHD nor ongoing immunosuppression and 8–11 months (or earlier if there is a measles outbreak) after the last dose of immune globulin intravenous (IGIV).
87. A 2-dose series of VAR should be administered 24 months after HSCT to varicella-seronegative patients with neither GVHD nor ongoing immunosuppression and 8–11 months after the last dose of IGIV (strong, low).

Evidence Summary

Influenza vaccine. Influenza, which is often a severe illness after HSCT, is associated with mortality of 10%–15% in individuals not treated with antiviral medication [332]. Patients infected with the 2009 pandemic influenza A (H1N1) virus were at increased risk for pneumonia and for mechanical ventilation and had significant mortality despite oseltamivir therapy [333, 334]. Fatal influenza illness can occur several years after HSCT [332]. Lifelong annual vaccination with IIV is therefore recommended for all HSCT recipients. The time when vaccination should be initiated after HSCT depends, in part, on anticipation of influenza in the patient's community but is more likely to be effective when the time interval after HSCT is longer, preferably ≥6 months [335–337]. Even in cases where there is no serological response, T-cell responses that prevent serious disease may be elicited [338, 339]. During community outbreaks, HSCT recipients should be vaccinated against influenza immediately if it is >4 months after HSCT. Children aged <9 years who are receiving influenza vaccine for the first time require 2 doses administered ≥4 weeks apart. For IIV, data regarding the effectiveness of a second dose in older children and adults are conflicting. However, studies showed improved response rates to vaccines against 2009 pandemic A (H1N1) [335, 337, 340]. LAIV should

not be used because the safety and efficacy of this vaccine in HSCT patients are unknown and an IIV alternative exists.

Pneumococcal vaccine. HSCT recipients are at a significantly higher risk for invasive pneumococcal infection than the general population [341–344]. However, PPSV23 is usually ineffective when given during the first year after transplantation, particularly in patients with chronic GVHD [345–349]. In 3 prospective trials, PCV7 given after HSCT was more immunogenic than historical controls given PPSV23 [350–352]. In a comparative trial of PCV7 and PPSV23 in adult HSCT recipients, PCV7 given to donors and recipients was more immunogenic than PPSV23 given to donors and recipients [353]. In 1 of these trials there were similar and substantial antibody responses to vaccination with a 3-dose PCV7 series whether started at 3 months (early) or 9 months (late) posttransplant [350]. Thus, early vaccination may be preferred. However, early vaccination may result in a shorter duration of protective concentrations of antibody, and a fourth booster dose may be indicated if vaccination is given early after HSCT [350]. It is likely beneficial to administer PPSV23 for the fourth dose of vaccine starting 12 months after HSCT to provide immunity to additional serotypes [350, 354]. However, a fourth dose of PCV13 might be preferable in patients with chronic GVHD who are unlikely to respond to PPSV23 [346, 349, 355]. CDC's ACIP recommends routine use of PCV13 for immunocompromised persons [109, 124].

Hib conjugate vaccine. Vaccination with Hib can elicit protective immune responses after allogeneic HSCT [347, 348, 356]. The timing after HSCT is important since the immune response to Hib vaccine early after HSCT, that is, <6 months, resulted in poor responses in children who received transplants [357].

Diphtheria–tetanus–pertussis vaccine. There are 2 categories of diphtheria and tetanus vaccines: those containing a "full" dose of diphtheria toxoid in combination with tetanus toxoid (DT) and those containing a reduced quantity of diphtheria toxoid (Td). In the United States, DT vaccine is not approved for persons aged >6 years due to adverse effects. However, experience with adult HSCT recipients indicates a lower risk for adverse effects than in previously vaccinated immunocompetent adults [358], suggesting that the adverse effect profile of DT vaccine may be acceptable in this population. It has not yet been determined whether the immune response to Td is equivalent to the response to DT vaccine.

HSCT recipients may be vulnerable to complications from pertussis, although there are very limited published data [359, 360]. For immunocompetent individuals, acellular pertussis vaccine that is administered as DTaP is recommended in young children, and a single booster dose of a vaccine containing Tdap is recommended in children starting at age 10 years and for adolescents and adults (to replace a dose of adult Td booster). Ideally, posttransplant patients are viewed as "never vaccinated" and, consequently, they should receive full doses of toxoids, DT, and DTaP. However, DTaP is indicated only for children aged <7 years. Tdap is less likely than DTaP vaccine to cause local side effects in immunocompetent adults. Preliminary data in autologous HSCT recipients [361, 362] show that the response to pertussis (and tetanus) antigens in Tdap is poor, irrespective of the timing of vaccination post-HSCT [361], suggesting that this vaccine should be used as a booster rather than as part of the primary series. A 3-dose series of a vaccine with high tetanus and pertussis content, that is, DTaP, may be more immunogenic in HSCT recipients and thus should be considered for the initial vaccination regardless of patient age.

HepB vaccine. There are limited data regarding the efficacy of HepB vaccination in HSCT recipients. In a study of autologous HSCT recipients, 69% seroconverted after a vaccine series [363]. Similarly, in a study of allogeneic HSCT recipients, 64% seroconverted; this rate was lower than that in age-matched controls [364]. Thus, a determination of postvaccine anti-HBs concentration is indicated in order to determine if additional doses of vaccine are needed.

MMR vaccine. Most HSCT patients become seronegative to measles during an extended follow-up [326, 327]. There have been reports of severe and fatal measles in HSCT recipients [365, 366]. Administration of MMR vaccine can be considered 2 years after transplantation in allogeneic HSCT patients without chronic GVHD or ongoing immunosuppression. In Brazil, 34 patients who were not receiving immunosuppressive drugs were safely vaccinated 1–2 years after HSCT [367]. Since adults who experience natural measles infection prior to transplantation usually retain immunity for several years after HSCT, it is recommended that a measles serology be performed, with vaccination of only seronegative patients. The responses to measles vaccine varied, with a higher response rate observed in adults than in children [367–370]. In order to achieve protective and long-lasting immunity, a second dose is recommended for children who have undergone HSCT. Rubella vaccination is indicated in women with the potential to become pregnant. The presence of measles antibodies from IGIV or other blood products may interfere with the response to measles vaccine and possibly certain other live vaccines, for example, varicella. Therefore, it is appropriate to delay administration of these vaccines for 8 months (after an IGIV dose of 400 mg/kg body mass) or 11 months (after an IGIV dose of 2 gm/kg body mass). However, if risk of exposure to measles is high, MMR vaccine can be given sooner, but the dose should be repeated after the interval noted above [223].

Varicella vaccine. VAR can be considered for seronegative HSCT recipients who meet the criteria for live virus vaccination delineated above for measles vaccine. One center required a

CD4 T-lymphocyte count ≥200 cell/mm^3 and documentation of a response to ≥1 other vaccine as prerequisites for VAR administration [85, 87, 371]. ZOS should not be administered as there are no data on safety or effectiveness.

Other vaccines. There are no data regarding vaccination of HSCT recipients with HPV vaccines. The use of BCG vaccine is contraindicated because it is a live bacterial vaccine with a potential risk of serious adverse effects. The same is true for live rotavirus vaccines that are licensed by the US Food and Drug Administration only for young infants.

Patients with chronic GVHD can mount responses to protein-based vaccines. The risk for exacerbation of GVHD is low based on experience in several hundred patients [325, 348, 350, 358]. However, vaccination with polysaccharide-based vaccines is often ineffective, and PCV13 is preferred over PPSV23 in patients with GVHD [349, 355]. Although there are no data, it might be reasonable to delay vaccination of patients treated with high doses of corticosteroids or recent therapy with immunosuppressive monoclonal antibodies such as rituximab or alemtuzumab because the antibody response may be low. Live vaccines are not recommended because their safety is not assured given the immunosuppression of GVHD and its therapy.

RECOMMENDATIONS FOR VACCINATION OF SOLID ORGAN TRANSPLANT RECIPIENTS

XIX. For Adult and Child Solid Organ Transplant Candidates and Living Donors, Which Vaccines Should Be Administered During Pretransplant Evaluation?

Recommendations (Table 5)

88. Living donors should be current with vaccines based on age, vaccination history, and exposure history according to the CDC annual schedule (strong, high); MMR, MMRV, VAR, and ZOS vaccine administration should be avoided within 4 weeks of organ donation (weak, very low). Vaccination of donors solely for the recipient's benefit is generally not recommended (weak, low).
89. Adults and children with chronic or end-stage kidney, liver, heart, or lung disease, including solid organ transplant (SOT) candidates, should receive all age-, exposure history-, and immune status-appropriate vaccines based on the CDC annual schedule for immunocompetent persons (strong, moderate).
91. Adult SOT candidates; adults with end-stage kidney disease; and pediatric patients who are SOT candidates; are aged <6 years and have end-stage kidney, heart, or lung disease; or are aged 6–18 years and have end-stage kidney disease should receive PCV13 as in recommendations 27a-c (strong, very low).
92. Adults and children aged ≥2 years who are SOT candidates or have end-stage kidney disease should receive PPSV23 if they have not received a dose within 5 years and have not received 2 lifetime doses (strong, moderate). Patients with end-stage kidney disease should receive 2 lifetime doses 5 years apart (strong, low). Adults and children aged ≥2 years with end-stage heart or lung disease as well as adults with chronic liver disease, including cirrhosis, should receive a dose of PPSV23 if they have never received a dose (strong, low). When both PCV13 and PPSV23 are indicated, PCV13 should be completed 8 weeks prior to PPSV23 (strong, moderate).

Anti-HBs–negative SOT candidates should receive the HepB vaccine series (strong, moderate) and, if on hemodialysis and aged ≥20 years, they should receive the high-dose (40 μg) HepB vaccine series (strong, moderate). If a postvaccination anti-HBs concentration of ≥10 mIU/mL is not attained, a second 3-dose series of HepB vaccine (strong, low; alternative: 1 dose of HepB vaccine after which anti-HBs is tested*) should be administered, using standard dose (strong, moderate) or high dose* for children (weak, low) and high dose for adolescents* and adults (strong, low). HepA-unvaccinated, -undervaccinated, or -seronegative SOT candidates (particularly liver transplant candidates) aged 12–23 months (strong, moderate) and ≥2 years (strong, moderate) should receive a HepA vaccine series.

93. Combined HepA–HepB vaccine can be used for SOT candidates aged ≥12 years of age* in whom both vaccines are indicated (strong, moderate).
94. The HPV vaccine series should be administered to SOT candidates aged 11–26 years (strong, low-moderate).
95. SOT candidates aged 6–11 months can receive MMR vaccine if they are not receiving immunosuppression and if transplantation is not anticipated within 4 weeks (weak, very low). If transplantation is delayed (and the child is not receiving immunosuppression), the MMR vaccine should be repeated at 12 months (strong, moderate).
96. The VAR should be administered to SOT candidates without evidence of varicella immunity (as defined in recommendation 16) if they are not receiving immunosuppression and if transplantation is not anticipated within 4 weeks (strong, moderate). The VAR can be administered to varicella-naive SOT candidates aged 6–11 months who are not immunosuppressed provided the timing is ≥4 weeks prior to transplant (weak, very low).* Optimally, 2 doses should be administered ≥3 months apart (strong, low).
97. SOT candidates aged ≥60 years (strong, moderate) and varicella-positive candidates (as defined in recommendation 22) aged 50–59 years (weak, low)* who are not severely immunocompromised should receive ZOS if transplantation is *not* anticipated within 4 weeks.

Evidence Summary

SOT candidates should receive indicated vaccinations prior to transplantation, preferably early in their disease [372–374]. Live vaccines are generally not administered just prior to or post-transplant. Vaccination guidelines for SOT candidates and recipients have been published [373, 374], including information on travel-related vaccines [375] and the 2009 pandemic influenza A (H1N1) vaccine [376].

A standard vaccine series should be given to pediatric SOT candidates with the aim of completing the primary series and booster doses prior to transplantation [1, 377]. Vaccinated children with chronic renal failure had serum antibodies against measles, mumps, rubella, varicella, HepB, *H. influenzae* type b, and *S. pneumoniae* in 1 study [378]. In another study [379], early MMR vaccination led to protective titers in 88% of infants with chronic renal failure. Practices for monitoring specific antibody titers vary [380]. It may be reasonable to monitor titers to some vaccine-preventable pathogens (eg, HepB) [381, 382]. However, except for annual monitoring of anti-HBs titers in hemodialysis patients and kidney recipients, there is no consensus on the interpretation of results or the implications for revaccination.

Because influenza can be severe in patients with end-stage organ disease, annual vaccination with IIV is recommended for all transplantation candidates or recipients aged ≥6 months [373, 376, 383].

Patients awaiting transplant are at increased risk for invasive pneumococcal disease. CDC's ACIP recommends routine use of PCV13 for immunocompromised persons, including those who have had a SOT [109, 124]. Protective titers can be attained after pneumococcal polysaccharide vaccination in most patients [384, 385], although these titers can wane within 2 years [386]. Because most adults have protective titers to Hib, pretransplant Hib vaccination of adults is unnecessary. In addition, adult patients who require splenectomy should receive MCV4.

Fewer than 50% of patients with chronic kidney disease have protective titers against tetanus [387]. Five years after Td booster vaccination of a cohort of hemodialysis patients, 71% had protective antibody levels to tetanus, but only 32% had protective titers to diphtheria [387]. Tdap vaccination has not been studied in this population.

HepB can be transmitted via HBsAg-positive or HBsAg-negative/anti-HBc–positive donors [388, 389], blood transfusions, and, rarely, nosocomial outbreaks. HepB vaccination is less effective in patients on hemodialysis than in patients at an earlier stage of renal disease [390, 391]. Hemodialysis guidelines [56] recommend high-dose vaccine (ie, 40 μg), testing anti-HBs levels 1 to 2 months after the last dose of the vaccine series and also annually, as well as revaccination if anti-HBs levels are <10 mIU/mL.

HepB vaccination is also less effective in patients with end-stage liver disease [372, 392, 393]. Vaccination strategies include enhanced-potency vaccine, accelerated schedules (if transplant is imminent), and adjuvants [394, 395]. Seroconversion was better after repeated high-dose (80 μg) vaccine administration in nonresponders in 1 study [396]. Despite a report of immunity transfer from vaccinated living liver donors [397], HepB vaccination of these donors is not recommended.

Vaccination of SOT candidates with HepA vaccine is important because this vaccine can cause fulminant hepatitis in patients with underlying liver disease, particularly HepC. Patients with chronic liver disease respond to HepA vaccine, although at lower rates than do immunocompetent individuals [398, 399]. Vaccination before liver disease becomes advanced is likely to be more effective [400]. Combined HepA–HepB vaccine is useful in pretransplant vaccination.

Transplant patients are at higher risk for HPV-related genital warts, cervical cancer, and other anogenital malignancies. Data are awaited on efficacy of pretransplant vaccination in prevention of posttransplant HPV infection.

Live vaccines. The risk of posttransplant disease from pretransplant administration of live vaccines such as VAR, MMR, or ZOS vaccines has not been completely defined. A waiting period of 4 weeks was chosen based, in part, on the outer range of risk for developing skin lesions postvaccination for most patients. Many patients receive posttransplant chemoprophylaxis for herpes simplex and cytomegalovirus infections that is active against VZV, which helps prevent infection but also reduces vaccine efficacy. Most transplant centers will not administer live vaccines to candidates scheduled for transplant within 3 to 4 weeks; however, more data are needed to determine the optimal timing of vaccination.

Rotavirus vaccines should be administered to pretransplant infants starting at age 2 months (6 weeks is acceptable) with completion of the series by age 8 months. Although viral shedding can occur for ≥15 days after administration, it is unknown whether adverse consequences will result if transplantation occurs shortly after vaccination (Table 5).

VAR should be considered in SOT candidates because of disease severity after transplantation [71]. Fewer than 5% of adult renal transplant candidates were varicella-seronegative [401]. Children with nephrotic syndrome in remission who were not significantly immunosuppressed were safely vaccinated [82], but long-term efficacy remains unknown. VAR was safely administered to uremic children, including those awaiting transplantation [17, 402–404], and to 11 adults awaiting renal transplantation [401]. Almost all pediatric vaccinees seroconverted after 2 doses, and VZV antibody persisted in 75%–100% for ≥2 years after transplantation. The incidence of varicella in vaccinees was reduced by approximately 75% after transplantation compared with the incidence in unvaccinated renal transplant recipients; the severity of illness was generally milder in vaccinees who developed varicella. VAR was safe and

effective in 704 pediatric renal transplant candidates [17, 402], with 42% retaining VZV antibodies >10 years posttransplant [402]. Vaccinated patients had a lower risk for varicella posttransplant, less severe disease, and less HZ than unvaccinated patients [402]. Pediatric liver transplantation candidates had a seroconversion rate of 95% in 1 study [16], but only 3 of 11 seroconverted in another study [405]. Varicella vaccination of 29 children with chronic liver disease who were not receiving immunosuppressive medication resulted in seroconversion, although antibody levels were lower than in immunocompetent children [406]. Some authors recommend monitoring varicella titers and administering a third dose pretransplant if titers wane [407], However, commercially available assays exhibit poor sensitivity for detection of VAR-induced antibodies.

ZOS should be administered to pretransplant candidates who meet ACIP-defined criteria (aged ≥60 years and not severely immunosuppressed) or are aged 50–59 years, are varicella-positive (defined in recommendation 22), and not severely immunocompromised if transplantation is not expected within 4 weeks [10]. This recommendation is based on posttransplant morbidity of zoster rather than evidence of ZOS efficacy in this setting.

XX. Which Vaccines Should Be Administered to SOT Recipients?

Recommendations

98. Vaccination should be withheld from SOT recipients during intensified immunosuppression, including the first 2-month posttransplant period, because of the likelihood of inadequate response (strong, low). However, IIV can be administered ≥1 month after transplant during a community influenza outbreak (weak, very low).
99. Standard age-appropriate inactivated vaccine series should be administered 2 to 6 months after SOT based on the CDC annual schedule (strong, low to moderate), including IIV (strong, moderate; Table 5).
100. PCV13 should be administered 2 to 6 months after SOT if not administered before SOT, with the timing based on the patient's degree of immunosuppression, as described in recommendations 27a–c (strong, very low to moderate; Table 5).
101. For SOT patients aged ≥2 years, 1 dose of PPSV23 should be administered 2 to 6 months after SOT, with the timing based on the patient's degree of immunosuppression, and ≥8 weeks after indicated doses of PCV13, if not given within 5 years and if the patient has received no more than 1 previous lifetime dose (strong, moderate).
102. HepB vaccine should be considered for chronic HepB-infected recipients 2 to 6 months after liver transplant in an attempt to eliminate the lifelong requirement for HepB immune globulin (HBIG; weak, low).*
103. MMR vaccine and VAR should generally *not* be administered to SOT recipients because of insufficient safety and effectiveness data (strong, low), except for varicella in children without evidence of immunity (as defined in recommendation 15) who are renal or liver transplant recipients, are receiving minimal or no immunosuppression, and have no recent graft rejection (weak, moderate).*
104. Vaccination should *not* be withheld because of concern about transplant organ rejection (strong, moderate).

Evidence Summary

The optimal time to begin vaccination after transplant is not defined, but many centers wait ≥2 months to avoid high doses of antirejection medications that would impede seroconversion. The degree of immunosuppression varies by patient, and some patients may not mount adequate vaccine responses at 2 months posttransplant. An exception may be administration of IIV 1 month after SOT during a community outbreak of influenza based on expert opinion [376].

Influenza can cause severe illness in SOT patients [276, 383]. Seroconversion has varied by vaccine and among transplant types [103, 104, 408–419]. Efficacy and effectiveness have varied by epidemic strain and between influenza A and B virus types and influenza A subtypes [103, 104], as well as by immunosuppressive regimen (eg, mycophenolate mofetil) or recent rejection [409, 416, 419, 420]. Some studies have noted increased responses with repeat doses of influenza vaccine [410]. Effectiveness of influenza vaccine was demonstrated against influenza-like illness in 29% and 33% of heart recipients who received 1 of 2 influenza vaccines compared with 63% of control unvaccinated heart transplant recipients [413]. In 2 studies, cellular immune responses to influenza vaccine were impaired [415, 421]. In a recent study of 51 730 adult renal transplant recipients, influenza vaccination in the first posttransplant year was associated with lower risks of allograft loss and death [422]. A recent randomized controlled trial of high-dose intradermal (15 μg) vs standard-dose intramuscular influenza vaccine in organ transplant recipients found no significant differences in response, suggesting that the intradermal vaccine may be an acceptable alternative [423].

ACIP recommends PCV13 for adults and children with a SOT and PPSV23 for adults and children aged ≥2 years with a SOT [109, 124]. Pneumococcal vaccination with PPSV23 is associated with seroconversion rates as high as 94% in some, but not all, studies [411, 424–427]. In adult renal transplant patients, antibody levels and persistence after PCV7 were not superior compared with the levels and persistence in those receiving PPSV23 [427, 428]. Adult liver recipients did not have an enhanced response to PPSV23 after a prior dose of PCV7 ("prime-boost" strategy), and the authors concluded that 1 PPSV23 dose remains the standard for posttransplant recipients [429].

Two doses of PCV7 raised serotype-specific antibody after the first dose of PCV7 in pediatric SOT recipients, although at lower titers than in controls; antibody levels did not rise further after the second PCV7 dose or when a subsequent dose of PPSV23 was administered [430]. Barton et al studied the administration of 3 doses of PCV7 followed by PPSV23 in pediatric SOT recipients [431]. Mean concentrations increased 2-fold in all organ groups after 2 doses of PCV7; however, heart and lung recipients appeared to benefit from the third PCV7 dose. PPSV23 resulted in significantly higher antibody titers to some PCV7 serotypes [431]. Booster vaccination with Td produced good responses in pediatric renal transplant recipients [432].

HepB vaccination in pediatric liver recipients showed a 70% seroconversion rate, with another 50% of nonresponders converting after additional booster and double doses [433]. Responses were superior in children receiving monotherapy rather than combination therapy for immunosuppression [433]. To eliminate the requirement for long-term therapy with costly HBIG after liver transplantation for HepB, some centers have vaccinated these recipients. However, seroconversions occurred in a small proportion of patients using standard or high-dose HepB vaccine [434, 435]. Some anti-HBs–positive liver recipients transplanted for diseases other than HepB infection lost their protective titers posttransplant [394].

Some liver recipients who were seropositive for HepA pretransplant became seronegative posttransplant [436]. Vaccination with a 2-dose HepA vaccine series was well tolerated in 37 liver transplant recipients, but only 26% of the recipients were seropositive at 7 months postvaccination [399]. In another study, satisfactory seroconversion rates in renal and liver recipients were followed by a rapid decline in HepA antibody titers [437].

There are no published data on the immunogenicity of HPV vaccine in SOT recipients. SOT recipients have significant morbidity from HPV warts [438]; therefore, HPV4 vaccine is preferred over HPV2 vaccine in this population.

Varicella-related safety after transplant was shown in a small series of pediatric liver, renal, and intestine transplant recipients [16–18, 439]. In contrast, significant disease was reported after inadvertent administration of VAR to transplant recipients [74, 440]. In a recent report of vaccination of 36 pediatric liver recipients with VAR in which the vaccine was administered a median of 3.0 years posttransplant, vaccination was found to be safe and seroprotective [441]. No data exist on the safety of rotavirus vaccine posttransplant.

Case reports and small series have raised the question of whether vaccines trigger allograft rejection [417]; virtually all larger studies found no excess rejection or clinically significant allograft dysfunction after vaccinations [408, 409, 411–413, 418, 442–444, 407]. One study of 3601 heart transplant recipients at multiple centers found no vaccine-related differences in the incidence or seasonality of rejection [444, 407]. Kimball et al found that influenza vaccination did not lead to anti-HLA alloantibodies nor increased frequency of rejection in heart recipients [443]. A recent study involving 17 kidney and lung transplant recipients demonstrated augmentation of cellular alloimmunity after influenza vaccination. However, the clinical implications are unclear [445]. A study of >50 000 adult renal transplant recipients showed no deleterious effect with vaccination. Importantly, influenza vaccination during the first year after transplantation was associated with decreased risks of allograft loss and death [422].

RECOMMENDATIONS FOR VACCINATION OF PATIENTS WITH CHRONIC INFLAMMATORY DISEASES ON IMMUNOSUPPRESSIVE MEDICATIONS

Patients with chronic inflammatory diseases (including immune-mediated and autoimmune diseases) are often treated with immunosuppressive drugs, as single agents or in combination, for long periods of time. Initiation of immunosuppression should *not* be delayed to facilitate vaccination if immediate treatment is needed.

XXI. Which Vaccines Should Be Administered to Patients With Chronic Inflammatory Diseases Maintained on Immunosuppressive Therapies?

Recommendation (Table 6)

105. Inactivated vaccines, including IIV, should be administered to patients with chronic inflammatory illness treated (strong, low-moderate) or about to be treated (strong, moderate) with immunosuppressive agents as for immunocompetent persons based on the CDC annual schedule.
106. PCV13 should be administered to adults and children with a chronic inflammatory illness that is being treated with immunosuppression as described in the standard schedule for children and in recommendations 27a–c (strong, very low-moderate; Table 6).
107. PPSV23 should be administered to patients aged ≥2 years with chronic inflammatory illnesses with planned initiation of immunosuppression (strong, low), low-level immunosuppression (strong, low), and high-level immunosuppression (strong, very low). Patients should receive PPSV23 ≥8 weeks after PCV13, and a second dose of PPSV23 should be given 5 years later (strong, low).
108. VAR should be administered to patients with chronic inflammatory diseases without evidence of varicella immunity (defined in recommendation 15; strong, moderate) ≥4 weeks prior to initiation of immunosuppression (strong, low) if treatment initiation can be safely delayed.

109. VAR should be considered for patients without evidence of varicella immunity (defined in recommendation 15) being treated for chronic inflammatory diseases with long-term, low-level immunosuppression (weak, very low).*
110. ZOS should be administered to patients with chronic inflammatory disorders who are aged ≥60 years prior to initiation of immunosuppression (strong, low) or being treated with low-dose immunosuppression (strong, very low) and those who are aged 50–59 years and varicella positive prior to initiation of immunosuppression (weak, low)* or being treated with low-dose immunosuppression (weak, very low).*
111. Other live vaccines should *not* be administered to patients with chronic inflammatory diseases on maintenance immunosuppression: LAIV (weak, very low), MMR vaccine in patients receiving low-level (weak, very low) and high-level immunosuppression (weak, very low); and MMRV vaccine in patients receiving low-level (weak, very low) and high-level immunosuppression (strong, very low).
112. Other recommended vaccines, including IIV and HepB vaccine, should *not* be withheld because of concerns about exacerbation of chronic immune-mediated or inflammatory illness (strong, moderate).

Evidence Summary

Findings from 2 prospective trials of IIV in children with IBD [446, 447] suggest that IIV is safe and effective, although immunogenicity may be decreased in patients treated with TNF-α antibodies. In both studies, children receiving 6-mercaptopurine or azathioprine had seroprotection rates comparable to those of immunocompetent controls and nonimmunosuppressed IBD patients for all 3 strains in the vaccine. Children treated with TNF-α antibodies, however, had normal seroprotection rates to both type A vaccine strains but lower seroprotection and seroconversion rates to the type B vaccine strain. Vaccination was not associated with disease exacerbation. In 1 study, the overall coverage with inactivated vaccines, including IIV, in patients with IBD was low, indicating the need for more outreach and education for patients and medical providers [4].

Uncontrolled studies of patients with rheumatic inflammatory chronic illnesses receiving disease-modifying drugs suggested an adequate immune response to IIV. In children with rheumatologic conditions receiving disease-modifying antirheumatic drugs, seroprotection rates to influenza vaccine ranged from 80% to 98% [448]. In adults with RA or SLE, IIV was safe and induced protective antibody concentrations in most patients. However, immunogenicity was reduced in patients receiving azathioprine, infliximab, or rituximab in some studies [100, 101, 449–452]. In addition, antibody response to vaccine was reduced in patients with RA who received rituximab compared to the response in immunocompetent persons or RA patients receiving MTX [453]. Immunogenicity to inactivated H1N1 influenza vaccine was reduced in patients with rheumatic diseases on various immunosuppressive regimens compared with immunogenicity in immunocompetent controls. Patients receiving tocilizumab, an anti–interleukin-6 receptor antibody, for treatment of RA or juvenile idiopathic arthritis had antibody responses to IIV that were similar to those of the comparator groups [454, 455]. Patients tolerated IIV without serious adverse effects or disease flare [456–458].

There are few studies of inactivated vaccines other than IIV in chronic inflammatory disease populations treated with immunosuppression. In adults, responses to PPSV23 were similar among patients with RA treated with TNF-α blockers and immunocompetent controls [459]. However, patients with RA and psoriatic arthritis treated with MTX had reduced responses regardless of anti–TNF-α treatment [459–461], and patients receiving rituximab had reduced responses [462]. RA patients treated with rituximab and MTX had decreased antibody response to PPSV23 compared with RA patients on MTX alone; however, both groups had similar responses to tetanus toxoid [462]. Antibody response to PPSV23 in 190 adults with RA was not adversely affected by treatment with tocilizumab [463]. Antibody response to some PCV7 serotypes was decreased in 31 pediatric patients with juvenile rheumatic diseases on anti–TNF-α therapy compared with the response in immunocompetent controls [464]. CDC's ACIP recommends routine use of PCV13 for immunocompromised persons including those receiving immunosuppressive medications [109, 124]. Immune responses to MCV4 were good irrespective of degree of immunosuppression in 234 children and young adults with juvenile idiopathic arthritis in a multicenter open-label study [465]. HepB vaccine was safe and induced an immune response in most of 44 RA patients in a prospective study [466].

Protection against varicella is important because of the potential severity of varicella infection. Unfortunately, published data on varicella vaccination in this population are limited [93] (see Varicella section).

Although no studies have been published on zoster vaccination in patients receiving immunosuppression, ACIP has concluded that vaccination is safe in adults receiving ≤20 mg per day of prednisone or other low-level immunosuppression [10]. An expert panel of the American College of Rheumatology endorsed these recommendations [467] and stated "until more research becomes available it may be advisable to avoid zoster in patients actively receiving TNFα inhibitors." Zoster vaccination could be considered prior to initiation of immunosuppression for patients aged 13–49 years with a chronic immune-mediated or inflammatory disorder who have a history of varicella or who are seropositive despite no previous varicella vaccination; however, safety and effectiveness data are lacking. MMR revaccination of patients with juvenile idiopathic arthritis resulted in a good immune response to all 3 viruses without serious

adverse effects despite continued therapy with MTX or recent therapy with etanercept or anakinra [468, 469]. However, data are lacking on the safety of primary MMR vaccination and vaccination with other live vaccines in this population.

Exacerbations of autoimmune disease temporally related to influenza vaccination have been reported, yet prospective controlled trials do not support a cause-and-effect relationship (see "Safety of Vaccination of Immunocompromised Patients"). Specifically, influenza vaccination did not increase disease activity in patients with SLE or RA [100, 101, 451, 453, 470–472]. HepB vaccination had no effect on disease activity in patients with SLE or RA [466, 473]. Similarly, pneumococcal vaccination was not associated with worsening of clinical disease activity or laboratory measures of disease activity in patients with RA or SLE [474]. MMR vaccination did not affect disease activity in patients with juvenile idiopathic arthritis [469]. An increase in disease relapses was observed in 7 patients with multiple sclerosis vaccinated with yellow fever vaccine [69].

RECOMMENDATIONS FOR VACCINATION OF PATIENTS WITH ASPLENIA OR SICKLE CELL DISEASES

XXII. Which Vaccines Should Be Administered to Asplenic Patients and Those With Sickle Cell Diseases?

Recommendations (Table 7)

113. Asplenic patients and those with sickle cell diseases should receive vaccines including PCV13 for children aged <2 years, as recommended routinely for immunocompetent persons based on the CDC annual schedule. No vaccine is contraindicated (strong, moderate) except LAIV (weak, very low).
114. PCV13 should be administered to asplenic patients and patients with sickle cell diseases aged ≥2 years based on the CDC annual schedule for children and in recommendations 27a–c (strong, very low-moderate).
115. PPSV23 should be administered to asplenic patients and patients with a sickle cell disease aged ≥2 years (strong, low) with an interval of ≥8 weeks after PCV13, and a second dose of PPSV23 should be administered 5 years later (strong, low).
116. For PPSV23-naive patients aged ≥2 years for whom a splenectomy is planned, PPSV23 should be administered ≥2 weeks prior to surgery (and following indicated dose(s) of PCV13; strong, moderate) or ≥2 weeks following surgery (weak, low).*
117. One dose of Hib vaccine should be administered to unvaccinated persons aged ≥5 years who are asplenic or have a sickle cell disease (weak, low).
118. Meningococcal vaccine should be administered to patients aged ≥2 months who are asplenic or have a sickle cell disease (strong, low), as in recommendation 29. However, MCV4-D should not be administered in patients aged <2 years because of a reduced antibody response to some pneumococcal serotypes when both MCV4 and PCV are administered simultaneously (strong, low). Revaccination with MCV4 (or MPSV4 for those aged >55 years who have not received MCV4) is recommended every 5 years (strong, low).

Evidence Summary

The rate of invasive pneumococcal disease caused by vaccine serotypes in children aged <5 years with sickle cell diseases fell by 93% after implementation of vaccination with PCV7 [12]; however, some of this reduction may have been due to herd-type immunity. In children aged >2 years with sickle cell disease who were given 2 doses of PCV7 followed by a single dose of PPSV23, antibody levels to all serotypes in PCV7 were greater than in children given PPSV23 alone [475]. CDC's ACIP recommends routine use of PCV13 for asplenic patients [109, 124].

The optimal timing of PPSV23 vaccination is ≥2 weeks prior to splenectomy. If vaccination cannot be completed by this time, it should be performed ≥2 weeks following splenectomy because this timing results in higher antibody concentrations or opsonophagocytic titers compared with vaccination at a shorter interval before or after surgery [476–478]. There are no similar data on the effect of timing of Hib, MCV4, or MPSV4 vaccination on serologic responses in patients undergoing splenectomy.

A study in children aged <5 years with sickle cell disease vaccinated with Hib vaccine demonstrated a safety and immunogenicity profile that was similar to that of controls [479]. In a study of 23 patients aged 9–23 years who were splenectomized for Hodgkin disease, antibody response was less than in the control group, but most patients responded to vaccination [480].

A lower antibody response to certain PCV13 serotypes was observed when infants were simultaneously vaccinated with PCV13 and MCV4-D. Therefore, MCV4-D should be administered ≥4 weeks after PCV13 [481, 482]. This was not observed when infants were simultaneously vaccinated with PCV7 and Hib-MenCY [117].

RECOMMENDATIONS FOR VACCINATION OF PATIENTS WITH ANATOMIC BARRIER DEFECTS AT RISK FOR INFECTIONS WITH VACCINE-PREVENTABLE PATHOGENS

XXIII. Which Vaccinations Should Be Given to Individuals With Cochlear Implants or Congenital Dysplasias of the Inner Ear or Persistent CSF Communication With the Oropharynx or Nasopharynx?

Recommendations (Table 7)

119. Adults and children with profound deafness scheduled to receive a cochlear implant, congenital dysplasias of the

inner ear, or persistent cerebrospinal fluid (CSF) communication with the oropharynx or nasopharynx should receive all vaccines recommended routinely for immunocompetent persons based on the CDC annual schedule. No vaccine is contraindicated (strong, moderate; Table 7).

120. Patients with a cochlear implant, profound deafness and scheduled to receive a cochlear implant, or persistent communications between the CSF and oropharynx or nasopharynx should receive PCV13 as described in the standard schedule for children and recommendations 27a–c (strong, low-moderate).

121. Patients aged ≥24 months with a cochlear implant, profound deafness and scheduled to receive a cochlear implant, or persistent communications between the CSF and oropharynx or nasopharynx should receive PPSV23, preferably ≥8 weeks after receipt of PCV13 (strong, moderate).

122. PCV13 and PPSV23 should be administered ≥2 weeks prior to cochlear implant surgery, if feasible (strong, low).

Evidence Summary

The AAP policy statement includes recommendations for pneumococcal, Hib, and influenza vaccinations for children with cochlear implants [483]. CDC guidelines stress the importance of vaccination against *S. pneumoniae* for these patients. CDC's ACIP recommends routine use of PCV13 for adults and children with a cochlear implant [109, 124]. PCV13 has replaced PCV7, and no data are available regarding immunogenicity and safety of PCV13 in these patients. A second dose of PPSV23 can be considered for patients with a cochlear implant, profound deafness who are scheduled to receive a cochlear implant, or persistent CSF communication with the oropharynx or nasopharynx 5 years after the initial dose, although this is not recommended by the ACIP or AAP. The immunogenicity of PCV7 compared with PPSV23 was evaluated in a prospective study of 174 patients with cochlear implants [484]. For children aged 2–5 years, PCV7 was more immunogenic than PPSV23. A review of invasive pneumococcal disease in children aged 24–59 months at high risk of pneumococcal disease revealed 31 cases. Four (13%) were caused by serotypes covered in PPSV23 but not in PCV13, indicating the importance of PPSV23 in this patient population; however, 44% were caused by serotypes not covered by either vaccine [124].

FUTURE DIRECTIONS AND GAPS IN KNOWLEDGE IN VACCINATION OF IMMUNOCOMPROMISED PATIENTS

Listed below are areas that warrant future investigation.

General

a) Understanding the basic aspects of vaccines in various categories of immunocompromised patients, including the epidemiology of vaccine-preventable infections, mediators of vaccine protection and adverse effects of vaccines, and effects of vaccines that contain new adjuvants on vaccine protection and adverse effects of vaccines.

b) Establishment of a registry of immunocompromised vaccine recipients, particularly those receiving live vaccines, to provide additional safety data.

c) Uptake of IIV and other vaccines offered by subspecialists compared with primary care providers and other strategies to increase vaccine uptake in immunocompromised patients.

d) Transmission of LAIV and rotavirus vaccine to immunocompromised patients.

e) Efficacy and safety of zoster vaccination in:

1. Patients aged ≥60 years and <60 years with planned immunosuppression that increases the risk for zoster,
2. Patients receiving low-level immunosuppression,
3. Patients with HIV infection,
4. Patients with chronic inflammatory disorders who are receiving severe immunosuppression (eg, tocilizumab anti–IL-6 receptor antibody) or cyclophosphamide,
5. Immunocompromised populations whose varicella immunity was induced by varicella rather than infection from wild-type virus, and
6. Efficacy of pretransplant zoster vaccination in order to prevent posttransplant zoster in SOT candidates.

HIV

f) Optimal time to initiate vaccination after starting cART for HIV infection.

g) HepB vaccination of HIV-infected persons who are anti-HBs negative but anti-HBc positive (eg, no vaccination or 3-dose series or single dose followed by anti-HBs testing 2 weeks later).

h) Indications for and effect of revaccination of patients vaccinated prior to initiating cART.

Malignancy

i) Safety, immunogenicity, and efficacy of vaccines in patients with malignancy treated with contemporary regimens (eg, immunogenicity and safety of acellular pertussis vaccines with low [ap] or high [aP] antigen content); safety, immunogenicity, and effectiveness of IIV including vaccines with adjuvants during intensive chemotherapy and initial months afterward; need for a routine booster dose after completing chemotherapy; optimal timing of inactivated and live vaccines after completing chemotherapy; and duration of impaired response to vaccines after regimens that include anti–B-cell antibodies).

HSCT/SOT

j) Safety and immunogenicity of single and multiple doses of DTaP or Tdap following HSCT.

k) Safety and immunogenicity of PCV13 in SOT candidates and recipients.

l) Administration of HepB vaccine to chronic hepatitis B–infected liver recipients posttransplant to eliminate the lifelong requirement for HBIG, including optimal dose, number of doses, and role of adjuvants.

m) Immunogenicity and safety of vaccines at various levels of immunosuppression, and efficacy of vaccines in preventing clinical disease in SOT patients.

n) Optimal interval between live vaccination and transplantation, and optimal timing of vaccination after transplantation.

Inflammatory Diseases

o) Efficacy and safety of varicella vaccination in patients with chronic inflammatory diseases being treated with therapies that induce mild immunosuppression.

p) Immunogenicity and safety of adjuvanted influenza vaccine in patients with chronic inflammatory diseases being treated with biologic agents such as anti-TNF antibodies.

Notes

Acknowledgments. The Expert Panel expresses its gratitude to external reviewers Drs Mary Healy, Gregory Poland, and Jane Seward. The panel also thanks Vita Washington, Cindy Hamilton PharmD, ELS, and Genet Demisashi for their continued support throughout the guideline development process.

Financial support. The Infectious Diseases Society of America provided support for this guideline.

Potential conflicts of interest. The following list is a reflection of what has been reported to the IDSA. In order to provide thorough transparency, the IDSA requires full disclosure of all relationships, regardless of relevancy to the guideline topic. Evaluation of such relationships as potential conflicts of interest is determined by a review process that includes assessment by the SPGC chair, the SPGC liaison to the development panel, the Board of Directors liaison to the SPGC, and, if necessary, the Conflict of Interest Task Force of the board. This assessment of disclosed relationships for possible conflict of interest is based on the relative weight of the financial relationship (ie, monetary amount) and the relevance of the relationship (ie, the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. R. A. has served as a subinvestigator on clinical trials funded by ViroPharma, Roche, and the CDC. A. B. has served as a subinvestigator on clinical trials funded by Abbott, UCB, and Merck; served as a consultant to Dyax, Cubist, and Nutricia; received speaking fees from Merck; and received a writing honorarium from Up-To-Date, Inc. E. G. D. has served as a consultant with GlaxoSmithKline and received a grant from Pfizer. I. K. has received research funding from Amino Up Chemical. H. K. has received funding from Pfizer for a clinical trial. M. L. has served as a consultant for Merck, MedImmune, and GlaxoSmithKline; has received honoraria and patent license from Merck; is on an adjudication committee for GlaxoSmithKline; and participates in research studies with Sanofi Pasteur, GlaxoSmithKline, and Merck. P. L. has served as a consultant to ViroPharma, Vical, Clinigen, Astellas Pharma, and Pfizer; served as an investigator for ViroPharma, Astellas Pharma, Pfizer, and Merck; and chaired a Data and Safety Monitoring Board for AiCuris. No conflicts: G. A., L. R., S. D., M. T., L. S., and E. W. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Abbreviations

AAP, American Academy of Pediatrics
BCG, bacillus Calmette–Guérin
cART, combination antiretroviral therapy
CDC, Centers for Disease Control and Prevention
CGD, chronic granulomatous disease
CI, confidence interval
CMI, cell-mediated immunity
CSF, cerebrospinal fluid
CVID, common variable immune deficiency
DGS, DiGeorge syndrome
DPT, diphtheria toxoid, whole cell pertussis vaccine, tetanus toxoid
DT, diphtheria toxoid in combination with tetanus toxoid
DTaP, diphtheria toxoid, tetanus toxoid, acellular pertussis vaccine
GVHD, graft vs host disease
anti-HBs, antibodies to HepB surface antigen
HBIG, hepatitis B immune globulin
HBsAg, hepatitis B surface antigen
HBV, hepatitis B virus
HepA, hepatitis A vaccine
HepB, hepatitis B vaccine
Hib, *Haemophlius influenzae* type b vaccine
HIV, human immunodeficiency virus
HPV4, quadrivalent human papillomavirus vaccine

HSCT, hematopoietic stem cell transplant
HZ, herpes zoster
IBD, inflammatory bowel disease
BIDSA, Infectious Diseases Society of America
IFN-γ/IL-12, interferon-gamma/interleukin-12
IGIV, immune globulin intravenous
IIV, inactivated influenza vaccine
IPV, inactivated poliovirus vaccine
LAIV, live attenuated influenza vaccine
MBL, mannan-binding lectin
MCV4, meningococcal conjugate vaccine, quadrivalent
MMR, measles, mumps, and rubella vaccine
MMRV, MMR-varicella vaccine
MTX, methotrexate
NK, natural killer
OPV, oral polio vaccine
PCV, pneumococcal conjugate vaccine
pDGS, partial DiGeorge syndrome
PPSV, pneumococcal polysaccharide vaccine
RA, rheumatoid arthritis
SCID, severe combined immune deficiency
SLE, systemic lupus erythematosus
SOT, solid organ transplant
SPAD, specific polysaccharide antibody deficiency
SPGC, Standards and Practice Guidelines Committee
Td, tetanus toxoid, reduced diphtheria toxoid vaccine
Tdap, tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis vaccine
TNF, tumor necrosis factor
TT, tetanus toxoid
VAPP, vaccine-associated paralytic poliomyelitis
VAR, varicella vaccine
VZV, varicella-zoster virus
ZOS, zoster vaccine