

# 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.

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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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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,

**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  $\geq 4$  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  $\geq 2$  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  $\geq 6$  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  $\geq 200$  cells/mm<sup>3</sup> (weak, low)
  - (b) asymptomatic HIV-infected children aged 9 months–5 years with CD4 T-cell lymphocyte percentages of  $\geq 15$  (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  $\geq 4$  weeks before initiating immunosuppressive therapy (strong, low).

16. A 2-dose schedule of VAR, separated by >4 weeks for patients aged  $\geq 13$  years and by  $\geq 3$  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  $\geq 60$  years if it can be administered  $\geq 4$  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  $\geq 4$  weeks before beginning immunosuppressive therapy (weak, low).\*
22. ZOS should be administered to patients aged  $\geq 60$  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  $\geq 6$  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  $\leq 2$  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  $\geq 19$  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  $\geq 1$  year after the last PPSV23 dose (weak, low)
28. Patients aged  $\geq 2$  years with an early classic pathway, alternate pathway, or severe MBL deficiency should receive PPSV23  $\geq 8$  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<sub>197</sub> 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  $\geq 2$  years, the doses should be administered 2 months apart. MCV4-D should be administered  $\geq 4$



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  $\geq 6$  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  $\geq 2$  years with phagocytic cell deficiencies other than CGD (unless patient with CGD is receiving immunosuppressive medication) should receive PPSV23  $\geq 8$  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- $\gamma$ /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  $\geq 2$  years should receive PPSV23  $\geq 8$  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 of 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  $\geq 500$  CD3 T cells/mm<sup>3</sup>,  $\geq 200$  CD8 T cells/mm<sup>3</sup>, 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<sup>3</sup>, 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  $\geq 2$  years as in recommendations 27a–c (strong, low to moderate).
56. PPSV23 should be administered to HIV-infected children aged  $\geq 2$  years of age who have received indicated doses of PCV (strong, moderate), HIV-infected adults with CD4 T-lymphocyte counts of  $\geq 200$  cells/mm<sup>3</sup> (strong, moderate), and HIV-infected adults with CD4 T-lymphocyte counts of  $< 200$  cells/mm<sup>3</sup> (weak, low). PPSV23 should be given  $\geq 8$  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  $\mu$ g/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  $\geq 10$  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  $\mu$ g\*; weak, low) for children and high dose for adolescents\* and adults (strong, low), should be administered.
60. HepB vaccine containing 20  $\mu$ g 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  $\geq 12$  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  $\geq 14$  years without measles immunity and with a CD4 T-cell lymphocyte count  $\geq 200/\text{mm}^3$  (weak, very low).

66. HIV-infected children with a CD4 T-cell percentage  $< 15$  (strong, moderate) or patients aged  $\geq 14$  years with a CD4 T-cell lymphocyte count  $< 200$  cells/ $\text{mm}^3$  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  $\geq 15\%$  CD4 T-lymphocyte percentage (strong, high), aged 9–13 years with  $\geq 15\%$  CD4 T-lymphocyte percentage (strong, very low), and aged  $\geq 14$  years with CD4 T-lymphocyte counts  $\geq 200$  cells/ $\text{mm}^3$  should receive VAR (strong, very low). The 2 doses should be separated by  $\geq 3$  months (strong, moderate).

## RECOMMENDATIONS FOR VACCINATION IN PATIENTS WITH CANCER

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

69. Patients aged  $\geq 6$  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  $\geq 2$  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  $\geq 4$  weeks for live vaccines (strong, low) and  $\geq 2$  weeks for inactivated vaccines (strong, moderate).
76. Nonimmune HSCT candidates aged  $\geq 12$  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  $\geq 4$  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  $\geq 6$  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  $\geq 7$  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  $\geq 10$  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 ( $40 \mu\text{g}^*$ ; 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  $\geq 2$  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  $\geq 2$  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  $\geq 20$  years, they should receive the high-dose ( $40 \mu\text{g}$ ) HepB vaccine series (strong, moderate). If a postvaccination anti-HBs concentration of  $\geq 10$  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  $\geq 2$  years (strong, moderate) should receive a HepA vaccine series.
93. Combined HepA–HepB vaccine can be used for SOT candidates aged  $\geq 12$  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-naïve SOT candidates aged 6–11 months who are not immunosuppressed provided the timing is  $\geq 4$  weeks prior to transplant (weak, very low)\*. Optimally, 2 doses should be administered  $\geq 3$  months apart (strong, low).
97. SOT candidates aged  $\geq 60$  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  $\geq 1$  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  $\geq 2$  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  $\geq 8$  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  $\geq 2$  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  $\geq 8$  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)  $\geq 4$  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  $\geq 60$  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  $\geq 2$  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  $\geq 2$  years (strong, low) with an interval of  $\geq 8$  weeks after PCV13, and a second dose of PPSV23 should be administered 5 years later (strong, low).

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

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

118. Meningococcal vaccine should be administered to patients aged  $\geq 2$  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  $\geq 24$  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  $\geq 8$  weeks after receipt of PCV13 (strong, moderate).

122. PCV13 and PPSV23 should be administered  $\geq 2$  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- $\gamma$ /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 comment 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<sup>3</sup> for adults and adolescents and percentage  $<15$  for infants and children,
- receiving daily corticosteroid therapy with a dose  $\geq 20$  mg (or  $>2$  mg/kg/day for patients who weigh  $<10$  kg) of prednisone or equivalent for  $\geq 14$  days, and
- receiving certain biologic immune modulators, that is, a tumor necrosis factor-alpha (TNF- $\alpha$ ) 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<sup>3</sup> 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  $\geq 14$  days or receiving alternate-day corticosteroid therapy, and



**Table 2. Vaccination of Persons With HIV Infection**

Vaccine	Low-Level or No Immunosuppression <sup>a</sup>		High-Level Immunosuppression <sup>b</sup>	
	Recommendation	Strength, Evidence Quality	Recommendation	Strength, Evidence Quality
<i>Haemophilus influenzae</i> b conjugate	U: age <5 y R: age 5–18 y <sup>c</sup>	Strong, high Strong, low	U: age <5 y R: age 5–18 y <sup>c</sup>	Strong, high Strong, low
Hepatitis A	U	Strong, moderate	U: age 1 y	Strong, moderate
Hepatitis B <sup>d</sup>	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) <sup>e</sup>	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 <sup>f</sup>	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 <sup>g</sup>	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 <sup>h</sup> R: age 6–18 y <sup>h</sup> R: age ≥19 y <sup>i</sup>	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 <sup>i</sup>	Strong, moderate Strong, moderate Strong, low Strong, very low
Pneumococcal polysaccharide (PPSV23) <sup>j</sup>	R: age ≥2 y	Strong, moderate	R: age 2–18 y R: adult (CD4 T lymphocytes <200 cells/mm <sup>3</sup> )	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.

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

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

<sup>c</sup> One dose.

<sup>d</sup> 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.

<sup>e</sup> 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.

<sup>f</sup> 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.

<sup>g</sup> 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.

<sup>h</sup> For patients not fully vaccinated with PCV13 by previous administration.

<sup>i</sup> 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).

<sup>j</sup> 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 $\geq 3$ mo Postchemotherapy and $\geq 6$ mo Post Anti-B-Cell Antibodies for Inactivated Vaccines; See Each Live Vaccine for Interval	
	Recommendation	Strength, Evidence Quality	Recommendation	Strength, Evidence Quality
<i>Haemophilus influenzae</i> b conjugate	U <sup>a</sup>	Weak, low	U	Strong, moderate
Hepatitis A	U <sup>a</sup>	Weak, low	U	Strong, very low
Hepatitis B	U <sup>a</sup>	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 <sup>a</sup>	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 <sup>a</sup>	Weak, very low	U	Strong, very low
Influenza-inactivated (inactivated influenza vaccine)	U <sup>a</sup>	Strong, low-moderate <sup>a</sup>	U <sup>b</sup>	Strong, moderate
Influenza-live attenuated (live attenuated influenza vaccine)	X	Weak, very low	U	Strong, low
Measles, mumps, and rubella–live	X <sup>c</sup>	Strong, moderate	Starting at 3 mo: U	Strong, low
Measles, mumps, and rubella–varicella–live	X <sup>c</sup>	Strong, moderate	Starting at 3 mo: U	Weak, very low
Meningococcal conjugate	U <sup>a</sup>	Weak, low	U	Strong, low
Pneumococcal conjugate-13 (PCV13)	R: <6 y R: age $\geq 6$ y <sup>d</sup>	Strong, low Strong, very low	U	Strong, low
Pneumococcal polysaccharide (PPSV23)	R: age $\geq 2$ y	Strong, low	U	Strong, low
Polio–inactivated (inactivated poliovirus vaccine)	U <sup>a</sup>	Weak, low	U	Strong, low
Rotavirus–live	X	Strong, very low	Not applicable	
Varicella–live	X <sup>c</sup>	Strong, moderate	Starting at 3 mo: U <sup>e</sup>	Weak, very low
Zoster–live	X <sup>c</sup>	Strong, very low	Starting at 3 mo: U <sup>e</sup>	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.

<sup>a</sup> 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.

<sup>b</sup> IIV can be administered  $\leq 3$  months after chemotherapy, but response rate may be low.

<sup>c</sup> 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  $\geq 4$  weeks prior to initiation of chemotherapy.

<sup>d</sup> For patients aged  $\geq 19$  years with human immunodeficiency virus who have received PPSV23, PCV13 should be administered after an interval of  $\geq 1$  year after the last PPSV23 dose (weak, low).

<sup>e</sup> 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)  $\leq 0.4$  mg/kg/week, azathioprine  $\leq 3$  mg/kg/day, or 6-mercaptopurine  $\leq 1.5$  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**

Vaccine	Pre-HSCT		Post-HSCT	
	Recommendation	Strength, Evidence Quality	Recommendation; Earliest Time Posttransplant; Number of Doses	Strength, Evidence Quality
<i>Haemophilus influenzae</i> 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 <sup>a</sup>	Strong, very low	X <sup>b</sup>	Strong, low
Measles, mumps, and rubella–varicella–live	U <sup>a</sup>	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 <sup>c</sup>	Strong, low	R; 3 mo; 3 doses	Strong, low
Pneumococcal polysaccharide (PPSV23)	R <sup>c</sup>	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 <sup>a</sup>	Strong, low	X <sup>d</sup>	Strong, low
Zoster–live	R <sup>a,e</sup> : age 50–59 y* U <sup>a</sup> : 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.

<sup>a</sup> 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.

<sup>b</sup> 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.

<sup>c</sup> If not previously administered.

<sup>d</sup> 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).

<sup>e</sup> 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
<i>Haemophilus influenzae</i> 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 <sup>a</sup>	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 <sup>b</sup>	Strong, moderate
Influenza-live attenuated (live attenuated influenza vaccine)	X	Weak, low	X	Weak, low
Measles, mumps, and rubella–live	R <sup>c</sup> : 6–11 mo U <sup>d</sup> : age ≥12 mo	Weak, very low Strong, moderate	X	Strong, low
Measles, mumps, and rubella–varicella–live	U <sup>d</sup>	Strong, moderate	X	Strong, low
Meningococcal conjugate	U	Strong, moderate	U	Strong, moderate
Pneumococcal conjugate (PCV13)	U: age ≤5 y R: age ≥6 y <sup>e</sup>	Strong, moderate Strong, very low	U: Age 2–5 y R: age ≥6 y if not administered pretransplant <sup>e</sup>	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 <sup>c</sup>	Strong, moderate	X	Strong, low
Varicella–live	R <sup>f</sup> : 6–11 mo U <sup>d</sup>	Weak, very low Strong, low	X <sup>g</sup>	Strong, low
Zoster–live	R <sup>h</sup> : age 50–59 y U <sup>i</sup> : 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.

<sup>a</sup> Consider hepatitis B vaccine for hepatitis B-infected liver transplant patients (weak, low).

<sup>b</sup> 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).

<sup>c</sup> Administer only if patient is not immunosuppressed and the timing is ≥4 weeks prior to transplant.

<sup>d</sup> Administer only if patient is nonimmune, not severely immunosuppressed, and the timing is ≥4 weeks prior to transplant.

<sup>e</sup> 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).

<sup>f</sup> 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.

<sup>g</sup> 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.

<sup>h</sup> 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.

<sup>i</sup> 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**

Vaccine	Planned Immunosuppression		Low-level Immunosuppression <sup>a</sup>		High-level Immunosuppression <sup>a</sup>	
	Recommendation	Strength, Evidence Quality	Recommendation	Strength, Evidence Quality	Recommendation	Strength, Evidence Quality
<i>Haemophilus influenzae</i> 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 <sup>b</sup>	Strong, moderate	X	Weak, very low	X	Weak, very low
Measles, mumps, and rubella–varicella–live	U <sup>b</sup>	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 <sup>c</sup>	Strong, moderate	U: <6 y R: ≥6 y <sup>c</sup>	Strong, low strong, very low	U: <6 y R: ≥6 y <sup>c</sup>	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 <sup>b</sup>	Strong, moderate	X <sup>d</sup>	Weak, very low	X	Strong, moderate
Zoster–live	R: age 50–59 y <sup>e</sup> U: age ≥60 y	Weak, low strong, low	R: age 50–59 y <sup>e</sup> 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.

<sup>a</sup> 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.

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

<sup>c</sup> 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).

<sup>d</sup> 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.

<sup>e</sup> 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**

Vaccine	Asplenia or a Sickle Cell Disease		Cochlear Implants <sup>a</sup> or Cerebrospinal Fluid Leak	
	Recommendation	Strength, Evidence Quality	Recommendation	Strength, Evidence Quality
<i>Haemophilus influenzae</i> 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 <sup>b</sup>	Strong, low	U	Strong, moderate
Meningococcal polysaccharide	R: age >55 y <sup>b</sup>	Strong, low	U	Strong, moderate
Pneumococcal conjugate (PCV13)	U: age <6 y <sup>c</sup> R: age ≥6 y <sup>d</sup>	Strong, moderate Strong, very low	U: age <6 y <sup>c</sup> R: age ≥6 y <sup>d</sup>	Strong, moderate strong, low
Pneumococcal polysaccharide (PPSV23)	R: age ≥2 y <sup>e</sup>	Strong, low	R: age ≥2 y <sup>e</sup>	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.

<sup>a</sup> Includes patients with profound hearing loss who are scheduled to receive a cochlear implant or have inner ear–cerebrospinal fluid communication.

<sup>b</sup> A 2-dose primary series should be administered with an additional dose every 5 years.

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

<sup>d</sup> 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).

<sup>e</sup> 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  $\geq 1$  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  $\geq 4$  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  $\geq 2$  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 <i>not</i> 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 $\geq 60$ 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  $\geq 4$  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  $\geq 6$  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).<sup>\*</sup> 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 LAIV 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- $\mu$ g doses vs 3 10- or 20- $\mu$ g 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  $\geq 30\,000$ – $50\,000$  cells/mm<sup>3</sup>, a  $\leq 23$ -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  $\geq 200$  cells/mm<sup>3</sup> (weak, low)
  - (b) asymptomatic HIV-infected children aged 9 months–5 years with CD4 T-cell lymphocyte percentages of  $\geq 15$  (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<sup>3</sup> [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  $\geq 4$  weeks before initiating immunosuppressive therapy (strong, low).
16. A 2-dose schedule of VAR, separated by  $>4$  weeks for patients aged  $\geq 13$  years and by  $\geq 3$  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  $\geq 28$  days for those aged  $\geq 13$  years and by  $\geq 3$  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  $\geq 3$  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  $\geq 200$  cells/mm<sup>3</sup> [86]. At least 85% developed specific antibody, generally in association with VZV-specific CMI. Similarly, VAR was safely administered  $\geq 2$  years after HSCT to 46 children who were off immunosuppression, had a CD4 T-cell lymphocyte count  $\geq 200$  cells/mm<sup>3</sup>, and had responded to  $\geq 1$  other vaccine [87]. VAR is commonly safely administered  $\geq 24$  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-naïve children and to 7 previously vaccinated children who had lost their VZV antibody. These patients were  $\geq 6$  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  $\geq 15$  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  $\geq 3$  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  $\geq 7$ -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  $\geq 60$  years if it can be administered  $\geq 4$  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  $\geq 4$  weeks before beginning immunosuppressive therapy (weak, low).\*
22. ZOS should be administered to patients aged  $\geq 60$  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  $\geq 2$  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-boostered 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  $\leq 20$  mg/day), MTX ( $\leq 0.4$  mg/kg/week), azathioprine ( $\leq 3$  mg/kg/day), and 6-mercaptopurine ( $\leq 1.5$  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- $\alpha$  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- $\alpha$  antibodies than for those receiving TNF- $\alpha$ -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  $\geq 6$  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  $\geq 6$  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- $\alpha$  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  $\leq 2$  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  $\geq 19$  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  $\geq 1$  year after the last PPSV23 dose (weak, low).
28. Patients aged  $\geq 2$  years with an early classic pathway, alternate pathway, or severe MBL deficiency should receive PPSV23  $\geq 8$  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- $\gamma$ /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- $\gamma$ /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  $\geq 2$  years should receive PPSV23  $\geq 8$  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  $\geq 500$  CD3 T cells/mm<sup>3</sup>,  $\geq 200$  CD8 T cells/mm<sup>3</sup>, 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<sup>3</sup>, 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<sup>3</sup> 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  $\geq 200$  cells/mm<sup>3</sup> (adults) or percentage  $\geq 15$  (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  $\geq 2$  years as in recommendations 27a–c (Table 2; strong, low to moderate).
  56. PPSV23 should be administered to HIV-infected children aged  $\geq 2$  years who have received indicated doses of PCV (strong, moderate), HIV-infected adults with CD4 T-lymphocyte counts of  $\geq 200$  cells/mm<sup>3</sup> (strong, moderate), and HIV-infected adults with CD4 T-lymphocyte counts of  $< 200$  cells/mm<sup>3</sup> (weak, low). PPSV23 should be given  $\geq 8$  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  $\mu$ g/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  $\geq 10$  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  $\mu$ g\*; weak, low) for children and high dose for adolescents\* and adults (strong, low), should be administered.
  60. HepB vaccine containing 20  $\mu$ g 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  $\geq 12$  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  $\geq 3$  months, specifically after improvement in the CD4+ T-cell lymphocyte percentage (optimally  $\geq 15$ ) 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<sub>3</sub>) 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  $\geq 200$  cells/mm<sup>3</sup>. 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<sup>3</sup>, PPSV23 should be offered to such patients with consideration of revaccination once antiretroviral therapy has resulted in a CD4 count  $\geq 200$  cells/mm<sup>3</sup>.

### ***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 ( $\geq 0.15$   $\mu\text{g/mL}$ ) 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  $\geq 2$  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  $\geq 15$  [215] and to children aged 2–11 years with a CD4 T-cell lymphocyte percentage  $\geq 25$ . Antibody against  $\geq 1$  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  $\geq 10$  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  $\mu$ g to 40  $\mu$ g 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  $\mu$ g 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  $\mu$ g 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<sup>3</sup>, 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  $\geq 20$ –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  $\geq 15$  [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  $\geq 14$  years without measles immunity and with a CD4 T-cell lymphocyte count  $\geq 200/\text{mm}^3$  (weak, very low).
66. HIV-infected children with a CD4 T-cell percentage  $< 15$  (strong, moderate) or patients aged  $\geq 14$  years with a CD4 T-cell lymphocyte count  $< 200$  cells/ $\text{mm}^3$  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  $\geq 15\%$  CD4 T-lymphocyte percentage (strong, high), aged 9–13 years with  $\geq 15\%$  CD4 T-lymphocyte percentage (strong, very low), and aged  $\geq 14$  years with CD4 T-lymphocyte counts  $\geq 200$  cells/ $\text{mm}^3$  should receive VAR (strong, very low). The 2 doses should be separated by  $\geq 3$  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.

#### LAIV 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  $\geq 15\%$  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  $\geq 50\%$  remained seronegative. Administration of an additional dose of MMR vaccine to children on cART who had  $\geq 15\%$  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/ $\text{mm}^3$  [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  $\geq 6$  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  $\geq 2$  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  $\geq 6$  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  $\geq 6$  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  $\geq 4$  weeks for live vaccines (strong, low) and 2 weeks for inactivated vaccines (strong, moderate).
76. Nonimmune HSCT candidates aged  $\geq 12$  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  $\geq 4$  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  $\geq 6$  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  $\geq 7$  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  $\geq 10$  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  $\mu\text{g}^*$ ; 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  $\geq 6$  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  $\geq 4$  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  $\geq 200$  cell/mm<sup>3</sup> and documentation of a response to  $\geq 1$  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  $\geq 2$  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  $\geq 2$  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  $\geq 20$  years, they should receive the high-dose (40  $\mu$ g) HepB vaccine series (strong, moderate). If a postvaccination anti-HBs concentration of  $\geq 10$  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  $\geq 2$  years (strong, moderate) should receive a HepA vaccine series.

93. Combined HepA–HepB vaccine can be used for SOT candidates aged  $\geq 12$  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  $\geq 4$  weeks prior to transplant (weak, very low)\*. Optimally, 2 doses should be administered  $\geq 3$  months apart (strong, low).

97. SOT candidates aged  $\geq 60$  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 re-vaccination.

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  $\geq 6$  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  $\mu\text{g}$ ), 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  $\mu\text{g}$ ) 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  $\geq 15$  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  $\geq 2$  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 post-transplant, 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  $\geq 60$  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  $\geq 1$  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  $\geq 2$  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  $\geq 8$  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  $\geq 2$  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  $\mu\text{g}$ ) 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  $\geq 2$  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  $\geq 2$  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  $\geq 8$  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)  $\geq 4$  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  $\geq 60$  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- $\alpha$  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- $\alpha$  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 anti-rheumatic 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- $\alpha$  blockers and immunocompetent controls [459]. However, patients with RA and psoriatic arthritis treated with MTX had reduced responses regardless of anti-TNF- $\alpha$  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- $\alpha$  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  $\leq 20$  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 TNF $\alpha$  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  $\geq 2$  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  $\geq 2$  years (strong, low) with an interval of  $\geq 8$  weeks after PCV13, and a second dose of PPSV23 should be administered 5 years later (strong, low).
116. For PPSV23-naïve patients aged  $\geq 2$  years for whom a splenectomy is planned, PPSV23 should be administered  $\geq 2$  weeks prior to surgery (and following indicated dose(s) of PCV13; strong, moderate) or  $\geq 2$  weeks following surgery (weak, low)\*.
117. One dose of Hib vaccine should be administered to unvaccinated persons aged  $\geq 5$  years who are asplenic or have a sickle cell disease (weak, low).
118. Meningococcal vaccine should be administered to patients aged  $\geq 2$  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  $\geq 2$  weeks prior to splenectomy. If vaccination cannot be completed by this time, it should be performed  $\geq 2$  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  $\geq 4$  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  $\geq 24$  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  $\geq 8$  weeks after receipt of PCV13 (strong, moderate).

122. PCV13 and PPSV23 should be administered  $\geq 2$  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  $\geq 60$  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 life-long 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.

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#### References

1. Burroughs M, Moscona A. Immunization of pediatric solid organ transplant candidates and recipients. *Clin Infect Dis* **2000**; 30:857–69.
2. Davies K, Woo P. Immunization in rheumatic diseases of childhood: an audit of the clinical practice of British Paediatric Rheumatology Group members and a review of the evidence. *Rheumatology (Oxford)* **2002**; 41:937–41.
3. Bridges MJ, Coady D, Kelly CA, Hamilton J, Heycock C. Factors influencing uptake of influenza vaccination in patients with rheumatoid arthritis. *Ann Rheum Dis* **2003**; 62:685.
4. Melmed GY, Ippoliti AF, Papadakis KA, et al. Patients with inflammatory bowel disease are at risk for vaccine-preventable illnesses. *Am J Gastroenterol* **2006**; 101:1834–40.
5. Stratton K, Andrew F, Rusch E, Clayton E. Adverse effects of vaccines: evidence and causality. Washington, DC: The National Academies Press, **2012**.
6. Field MJ, Lohr KN. Institute of Medicine committee to advise the Public Health Service on clinical practice guidelines (1990). Clinical practice guidelines: directions for a new program. Washington, DC: National Academy Press, **1990**:52–77.
7. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children. <http://aidsinfo.nih.gov/guidelines/html/5/pediatric-oi-prevention-and-treatment-guidelines/0>. Accessed 8 November 2013.
8. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep* **2009**; 58:229–35.
9. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* **2008**; 336:924–6.
10. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* **2008**; 57:1–30. ; quiz CE2–4.
11. No authors listed. General recommendations on immunization—recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* **2011**; 60:1–64.
12. Halasa NB, Shankar SM, Talbot TR, et al. Incidence of invasive pneumococcal disease among individuals with sickle cell disease before and after the introduction of the pneumococcal conjugate vaccine. *Clin Infect Dis* **2007**; 44:1428–33.
13. Atashili J, Kalilani L, Adimora AA. Efficacy and clinical effectiveness of influenza vaccines in HIV-infected individuals: a meta-analysis. *BMC Infect Dis* **2006**; 6:138.
14. Heijstek MW, Ott de Bruin LM, Bijl M, et al. EULAR recommendations for vaccination in paediatric patients with rheumatic diseases. *Ann Rheum Dis* **2011**; 70:1704–12.
15. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant* **2009**; 15:1143–238.
16. Kano H, Mizuta K, Sakakihara Y, et al. Efficacy and safety of immunization for pre- and post-liver transplant children. *Transplantation* **2002**; 74:543–50.
17. Zamora I, Simon JM, Da Silva ME, Piqueras AI. Attenuated varicella virus vaccine in children with renal transplants. *Pediatr Nephrol* **1994**; 8:190–2.
18. Weinberg A, Horslen SP, Kaufman SS, et al. Safety and immunogenicity of varicella-zoster virus vaccine in pediatric liver and intestine transplant recipients. *Am J Transplant* **2006**; 6:565–8.
19. Gershon AA, Steinberg SP, Gelb L, et al. Live attenuated varicella vaccine. Efficacy for children with leukemia in remission. *JAMA* **1984**; 252:355–62.



20. Son M, Shapiro ED, LaRussa P, et al. Effectiveness of varicella vaccine in children infected with HIV. *J Infect Dis* **2010**; 201:1806–10.
21. Olin P, Hallander HO, Gustafsson L, Reizenstein E, Storsaeter J. How to make sense of pertussis immunogenicity data. *Clin Infect Dis* **2001**; 33 (Suppl 4):S288–91.
22. Cherry JD, Gornbein J, Heininger U, Stehr K. A search for serologic correlates of immunity to *Bordetella pertussis* cough illnesses. *Vaccine* **1998**; 16:1901–6.
23. Rubin LG. Anticapsular antibody requirements for protection against experimental *Haemophilus influenzae* type b bacteremia after splenectomy. *Infect Immun* **1988**; 56:984–6.
24. Hosea SW, Brown EJ, Hamburger MI, Frank MM. Opsonic requirements for intravascular clearance after splenectomy. *N Engl J Med* **1981**; 304:245–50.
25. Ohmit SE, Petrie JG, Cross RT, Johnson E, Monto AS. Influenza hemagglutination-inhibition antibody titer as a correlate of vaccine-induced protection. *J Infect Dis* **2011**; 204:1879–85.
26. Henckaerts I, Durant N, De Grave D, Schuerman L, Poolman J. Validation of a routine opsonophagocytosis assay to predict invasive pneumococcal disease efficacy of conjugate vaccine in children. *Vaccine* **2007**; 25:2518–27.
27. Usinger WR, Lucas AH. Avidity as a determinant of the protective efficacy of human antibodies to pneumococcal capsular polysaccharides. *Infect Immun* **1999**; 67:2366–70.
28. Arvin AM. Immune responses to varicella-zoster virus. *Infect Dis Clin North Am* **1996**; 10:529–70.
29. No authors listed. Influenza vaccination coverage among pregnant women—United States, 2010–11 influenza season. *MMWR Morb Mortal Wkly Rep* **2011**; 60:1078–82.
30. Potter J, Stott DJ, Roberts MA, et al. Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. *J Infect Dis* **1997**; 175:1–6.
31. Carman WF, Elder AG, Wallace LA, et al. Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. *Lancet* **2000**; 355:93–7.
32. No authors listed. Influenza vaccination coverage among health-care personnel—United States, 2010–11 influenza season. *MMWR Morb Mortal Wkly Rep* **2011**; 60:1073–7.
33. Castagnini LA, Healy CM, Rench MA, Wootton SH, Munoz FM, Baker CJ. Impact of maternal postpartum tetanus and diphtheria toxoids and acellular pertussis immunization on infant pertussis infection. *Clin Infect Dis* **2012**; 54:78–84.
34. No authors listed. Recommended immunization schedules for persons aged 0 through 18 Years—United States, 2012. *MMWR Morb Mortal Wkly Rep* **2012**; 61:1–4.
35. Block SL, Yogev R, Hayden FG, Ambrose CS, Zeng W, Walker RE. Shedding and immunogenicity of live attenuated influenza vaccine virus in subjects 5–49 years of age. *Vaccine* **2008**; 26:4940–6.
36. Talbot TR, Crocker DD, Peters J, et al. Duration of virus shedding after trivalent intranasal live attenuated influenza vaccination in adults. *Infect Control Hosp Epidemiol* **2005**; 26:494–500.
37. Ali T, Scott N, Kallas W, et al. Detection of influenza antigen with rapid antibody-based tests after intranasal influenza vaccination (FluMist). *Clin Infect Dis* **2004**; 38:760–2.
38. King JC Jr., Treanor J, Fast PE, et al. Comparison of the safety, vaccine virus shedding, and immunogenicity of influenza virus vaccine, trivalent, types A and B, live cold-adapted, administered to human immunodeficiency virus (HIV)-infected and non-HIV-infected adults. *J Infect Dis* **2000**; 181:725–8.
39. King JC Jr., Fast PE, Zangwill KM, et al. Safety, vaccine virus shedding and immunogenicity of trivalent, cold-adapted, live attenuated influenza vaccine administered to human immunodeficiency virus-infected and noninfected children. *Pediatr Infect Dis J* **2001**; 20:1124–31.
40. Vesikari T, Karvonen A, Korhonen T, et al. A randomized, double-blind study of the safety, transmissibility and phenotypic and genotypic stability of cold-adapted influenza virus vaccine. *Pediatr Infect Dis J* **2006**; 25:590–5.
41. Fiore AE, Uyeki TM, Broder K, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep* **2010**; 59:1–62.
42. Losonsky GA, Fishaut JM, Strussenberg J, Ogra PL. Effect of immunization against rubella on lactation products. II. Maternal-neonatal interactions. *J Infect Dis* **1982**; 145:661–6.
43. Traiber C, Coelho-Amaral P, Ritter VR, Winge A. Infant meningococcal cephalitis caused by yellow fever vaccine virus transmitted via breastmilk. *J Pediatr (Rio J)* **2011**; 87:269–72.
44. Diaz PS, Au D, Smith S, Amylon M, Link M, Arvin AM. Lack of transmission of the live attenuated varicella vaccine virus to immunocompromised children after immunization of their siblings. *Pediatrics* **1991**; 87:166–70.
45. Marin M, Guris D, Chaves SS, Schmid S, Seward JF. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* **2007**; 56:1–40.
46. Sharrar RG, LaRussa P, Galea SA, et al. The postmarketing safety profile of varicella vaccine. *Vaccine* **2000**; 19:916–23.
47. Grossberg R, Harpaz R, Rubtcova E, Loparev V, Seward JF, Schmid DS. Secondary transmission of varicella vaccine virus in a chronic care facility for children. *J Pediatr* **2006**; 148:842–4.
48. Anderson EJ. Rotavirus vaccines: viral shedding and risk of transmission. *Lancet Infect Dis* **2008**; 8:642–9.
49. Payne D, Edwards K, Bowen M. Sibling transmission of vaccine-derived rotavirus (RotaTeq) associated with rotavirus gastroenteritis (case report). *Pediatrics* **2010**; 125:e438–e41.
50. Rivera L, Pena LM, Stainier I, et al. Horizontal transmission of a human rotavirus vaccine strain—a randomized, placebo-controlled study in twins. *Vaccine* **2011**; 29:9508–13.
51. Bernstein HH, Starke JR. Policy statement—recommendation for mandatory influenza immunization of all health care personnel. *Pediatrics* **2010**; 126:809–15.
52. Babcock HM, Gemeinhart N, Jones M, Dunagan WC, Woeltje KF. Mandatory influenza vaccination of health care workers: translating policy to practice. *Clin Infect Dis* **2010**; 50:459–64.
53. Pearson ML, Bridges CB, Harper SA. Influenza vaccination of health-care personnel: recommendations of the Healthcare Infection Control Practices Advisory Committee (HICPAC) and the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* **2006**; 55:1–16.
54. No authors listed. Paralytic poliomyelitis—United States, 1980–1994. *MMWR Morb Mortal Wkly Rep* **1997**; 46:79–83.
55. DeVries AS, Harper J, Murray A, et al. Vaccine-derived poliomyelitis 12 years after infection in Minnesota. *N Engl J Med* **2011**; 364:2316–23.
56. Mast EE, Weinbaum CM, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. *MMWR Recomm Rep* **2006**; 55:1–33; quiz CE1–4.
57. Fonseca MO, Pang LW, de Paula Cavalheiro N, Barone AA, Heloisa Lopes M. Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. *Vaccine* **2005**; 23:2902–8.
58. Launay O, van der Vliet D, Rosenberg AR, et al. Safety and immunogenicity of 4 intramuscular double doses and 4 intradermal low doses vs standard hepatitis B vaccine regimen in adults with HIV-1: a randomized controlled trial. *JAMA* **2011**; 305:1432–40.
59. Atkinson WL, Kroger A, Pickering LK. Section 1: General aspects of vaccination, Part 7: General immunization practices. *Vaccine* **2008**; 26:723.
60. Jong E, Freedman D. *The immunocompromised traveler*. 2010. New York, NY: Oxford University Press.

61. Brunette G, Kozarsky P, Magil I A, Shlim D. CDC health information for international travel 2010. Yellow Book, **2010**, New York, NY: Oxford University Press.
62. Staples JE, Gershman M, Fischer M. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* **2010**; 59:1–27.
63. Mota LM, Oliveira AC, Lima RA, Santos-Neto LL, Taulil PL. Vaccination against yellow fever among patients on immunosuppressors with diagnoses of rheumatic diseases. *Rev Soc Bras Med Trop* **2009**; 42:23–7.
64. Rio B. Vaccination for yellow fever after bone marrow transplantation. *Bone Marrow Transplant*, **1996**; 17(1 Suppl):95.
65. Gowda R, Cartwright K, Bremner JA, Green ST. Yellow fever vaccine: a successful vaccination of an immunocompromised patient. *Eur J Haematol* **2004**; 72:299–301.
66. Yax JA, Farnon EC, Cary Engleberg N. Successful immunization of an allogeneic bone marrow transplant recipient with live, attenuated yellow fever vaccine. *J Travel Med* **2009**; 16:365–7.
67. Veit O, Niedrig M, Chapuis-Taillard C, et al. Immunogenicity and safety of yellow fever vaccination for 102 HIV-infected patients. *Clin Infect Dis* **2009**; 48:659–66.
68. Sidibe M, Yactayo S, Kalle A, et al. Immunogenicity and safety of yellow fever vaccine among 115 HIV-infected patients at a preventive immunisation campaign in Mali. *Trans R Soc Trop Med Hyg* **2012**; 106:437–44.
69. Farez MF, Correale J. Yellow fever vaccination and increased relapse rate in travelers with multiple sclerosis. *Arch Neurol* **2011**; 68:1267–71.
70. Feldman S, Hughes WT, Daniel CB. Varicella in children with cancer: Seventy-seven cases. *Pediatrics* **1975**; 56:388–97.
71. Lynfield R, Herrin JT, Rubin RH. Varicella in pediatric renal transplant recipients. *Pediatrics* **1992**; 90:216–20.
72. Hambleton S. Chickenpox. *Curr Opin Infect Dis* **2005**; 18:235–40.
73. Schrauder A, Henke-Gendo C, Seidemann K, et al. Varicella vaccination in a child with acute lymphoblastic leukaemia. *Lancet* **2007**; 369:1232.
74. Kraft JN, Shaw JC. Varicella infection caused by Oka strain vaccine in a heart transplant recipient. *Arch Dermatol* **2006**; 142:943–5.
75. Ngai AL, Staehle BO, Kuter BJ, et al. Safety and immunogenicity of one vs. two injections of Oka/Merck varicella vaccine in healthy children. *Pediatr Infect Dis J* **1996**; 15:49–54.
76. Bryan CJ, Prichard MN, Daily S, et al. Acyclovir-resistant chronic varicella vaccine strain in a patient with neuroblastoma. *Pediatr Infect Dis J* **2008**; 27:946–8.
77. Levin MJ, Dahl KM, Weinberg A, Giller R, Patel A, Krause PR. Development of resistance to acyclovir during chronic infection with the Oka vaccine strain of varicella-zoster virus in an immunosuppressed child. *J Infect Dis* **2003**; 188:954–9.
78. Gershon AA, LaRussa P, Steinberg S. The varicella vaccine. Clinical trials in immunocompromised individuals. *Infect Dis Clin North Am* **1996**; 10:583–94.
79. Levin MJ, Gershon AA, Weinberg A, Song LY, Fentin T, Nowak B. Administration of live varicella vaccine to HIV-infected children with current or past significant depression of CD4(+) T cells. *J Infect Dis* **2006**; 194:247–55.
80. Gershon AA, Steinberg SP, Gelb L. Live attenuated varicella vaccine use in immunocompromised children and adults. *Pediatrics* **1986**; 78:757–62.
81. Gershon AA, Steinberg SP. Persistence of immunity to varicella in children with leukemia immunized with live attenuated varicella vaccine. *N Engl J Med* **1989**; 320:892–7.
82. Takahashi M, Kamiya H, Baba K, Asano Y, Ozaki T, Horiuchi K. Clinical experience with Oka live varicella vaccine in Japan. *Postgrad Med J* **1985**; 61 (Suppl 4):61–7.
83. Takahashi M. Clinical overview of varicella vaccine: development and early studies. *Pediatrics* **1986**; 78:736–41.
84. Levin MJ. Varicella vaccination of immunocompromised children. *J Infect Dis* **2008**; 197 (Suppl 2):S200–6.
85. Sauerbrei A, Prager J, Hengst U, Zintl F, Wutzler P. Varicella vaccination in children after bone marrow transplantation. *Bone Marrow Transplant* **1997**; 20:381–3.
86. Small TN, Robinson WH, Miklos DB. B cells and transplantation: an educational resource. *Biol Blood Marrow Transplant* **2009**; 15:104–13.
87. Chou JF, Kernan NA, Prockop S, et al. Safety and immunogenicity of the live attenuated varicella vaccine following T replete or T cell-depleted related and unrelated allogeneic hematopoietic cell transplantation (alloHCT). *Biol Blood Marrow Transplant* **2011**; 17:1708–13.
88. Levin MJ, Gershon AA, Weinberg A, et al. Immunization of HIV-infected children with varicella vaccine. *J Pediatr* **2001**; 139:305–10.
89. Wood SM, Shah SS, Steenhoff AP, Rutstein RM. Primary varicella and herpes zoster among HIV-infected children from 1989 to 2006. *Pediatrics* **2008**; 121:e150–6.
90. Dowell SF, Bresee JS. Severe varicella associated with steroid use. *Pediatrics* **1993**; 92:223–8.
91. Lydick E, Kuter BJ, Zajac BA, Guess HA. Association of steroid therapy with vaccine-associated rashes in children with acute lymphocytic leukaemia who received Oka/Merck varicella vaccine. NIAID Varicella Vaccine Collaborative Study Group. *Vaccine* **1989**; 7:549–53.
92. Lu Y, Bousvaros A. Varicella vaccination in children with inflammatory bowel disease receiving immunosuppressive therapy. *J Pediatr Gastroenterol Nutr* **2010**; 50:562–5.
93. Pileggi GS, de Souza CB, Ferriani VP. Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. *Arthritis Care Res (Hoboken)* **2010**; 62:1034–9.
94. Klein NP, Fireman B, Yih WK, et al. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. *Pediatrics* **2010**; 126:e1–8.
95. Jacobsen SJ, Ackerson BK, Sy LS, et al. Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. *Vaccine* **2009**; 27:4656–61.
96. Schlienger K, Lange J, Tyring S. Immunogenicity, kinetics of VZV-specific CD4 T-cell g-IFN production and safety of a live attenuated Oka/Merck zoster vaccine in healthy adults ≥60 years of age. *Clin Vaccine Immunol* **2009**; 16: 1381–1382.
97. Naidus E, Damon L, Schwartz BS, Breed C, Liu C. Experience with use of Zostavax (®) in patients with hematologic malignancy and hematopoietic cell transplant recipients. *Am J Hematol* **2012**; 87:123–5.
98. Strangfeld A, Listing J, Herzer P, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. *JAMA* **2009**; 301:737–44.
99. Wendling D, Streit G, Toussiroit E, Prati C. Herpes zoster in patients taking TNFalpha antagonists for chronic inflammatory joint disease. *Joint Bone Spine* **2008**; 75:540–3.
100. Del Porto F, Lagana B, Biselli R, et al. Influenza vaccine administration in patients with systemic lupus erythematosus and rheumatoid arthritis. Safety and immunogenicity. *Vaccine* **2006**; 24:3217–23.
101. Oren S, Mandelboim M, Braun-Moscovici Y, et al. Vaccination against influenza in patients with rheumatoid arthritis: the effect of rituximab on the humoral response. *Ann Rheum Dis* **2008**; 67:937–41.
102. Fowke KR, D'Amico R, Chernoff DN, et al. Immunologic and virologic evaluation after influenza vaccination of HIV-1-infected patients. *AIDS* **1997**; 11:1013–21.
103. Edvardsson VO, Flynn JT, Deforest A, et al. Effective immunization against influenza in pediatric renal transplant recipients. *Clin Transplant* **1996**; 10:556–60.
104. Duchini A, Hendry RM, Nyberg LM, Viernes ME, Pockros PJ. Immune response to influenza vaccine in adult liver transplant recipients. *Liver Transpl* **2001**; 7:311–3.
105. van Assen S, Holvast A, Telgt DS, et al. Patients with humoral primary immunodeficiency do not develop protective anti-influenza antibody titers after vaccination with trivalent subunit influenza vaccine. *Clin Immunol* **2010**; 136:228–35.

106. Levin MJ, Song LY, Fenton T, et al. Shedding of live vaccine virus, comparative safety, and influenza-specific antibody responses after administration of live attenuated and inactivated trivalent influenza vaccines to HIV-infected children. *Vaccine* **2008**; 26:4210–7.
107. Carr S, Allison KJ, Van De Velde LA, et al. Safety and immunogenicity of live attenuated and inactivated influenza vaccines in children with cancer. *J Infect Dis* **2011**; 204:1475–82.
108. Notarangelo LD. Primary immunodeficiencies. *J Allergy Clin Immunol* **2010**; 125:S182–94.
109. No authors listed. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* **2012**; 61:816–9.
110. Andreoni J, Kayhty H, Densen P. Vaccination and the role of capsular polysaccharide antibody in prevention of recurrent meningococcal disease in late complement component-deficient individuals. *J Infect Dis* **1993**; 168:227–31.
111. Biselli R, Casapolo I, D'Amelio R, Salvato S, Matricardi PM, Brai M. Antibody response to meningococcal polysaccharides A and C in patients with complement defects. *Scand J Immunol* **1993**; 37:644–50.
112. Drogari-Apiranthitou M, Fijen CA, Van De Beek D, Hensen EF, Dankert J, Kuijper EJ. Development of antibodies against tetravalent meningococcal polysaccharides in revaccinated complement-deficient patients. *Clin Exp Immunol* **2000**; 119:311–6.
113. Fijen CA, Kuijper EJ, Drogari-Apiranthitou M, Van Leeuwen Y, Daha MR, Dankert J. Protection against meningococcal serogroup ACYW disease in complement-deficient individuals vaccinated with the tetravalent meningococcal capsular polysaccharide vaccine. *Clin Exp Immunol* **1998**; 114:362–9.
114. Platonov AE, Beloborodov VB, Pavlova LI, Vershinina IV, Kayhty H. Vaccination of patients deficient in a late complement component with tetravalent meningococcal capsular polysaccharide vaccine. *Clin Exp Immunol* **1995**; 100:32–9.
115. Platonov AE, Vershinina IV, Kuijper EJ, Borrow R, Kayhty H. Long term effects of vaccination of patients deficient in a late complement component with a tetravalent meningococcal polysaccharide vaccine. *Vaccine* **2003**; 21:4437–47.
116. Soderstrom C, Braconier JH, Kayhty H, Sjöholm AG, Thureson B. Immune response to tetravalent meningococcal vaccine: opsonic and bactericidal functions of normal and properdin deficient sera. *Eur J Clin Microbiol Infect Dis* **1989**; 8:220–4.
117. No authors listed. Infant meningococcal vaccination: Advisory Committee on Immunization Practices (ACIP) recommendations and rationale. *MMWR Morb Mortal Wkly Rep* **2013**; 62:52–4.
118. Vu DM, Welsch JA, Zuno-Mitchell P, Dela Cruz JV, Granoff DM. Antibody persistence 3 years after immunization of adolescents with quadrivalent meningococcal conjugate vaccine. *J Infect Dis* **2006**; 193:821–8.
119. Gill CJ, Baxter R, Anemona A, Ciavarrò G, Dull P. Persistence of immune responses after a single dose of Novartis meningococcal serogroup A, C, W-135 and Y CRM-197 conjugate vaccine (Menveo<sup>®</sup>) or Menactra<sup>®</sup> among healthy adolescents. *Hum Vaccin* **2010**; 6:881–7.
120. Attwood JT, Williams Y, Feighery C. Impaired IgG responses in a child with homozygous C2 deficiency and recurrent pneumococcal septicaemia. *Acta Paediatr* **2001**; 90:99–101.
121. Berkel AI. Studies of immune response in a patient with selective complete C1q deficiency. *Turk J Pediatr* **1993**; 35:221–6.
122. Hohler T, Stradmann-Bellinghausen B, Starke R, et al. C4A deficiency and nonresponse to hepatitis B vaccination. *J Hepatol* **2002**; 37:387–92.
123. Jackson CG, Ochs HD, Wedgwood RJ. Immune response of a patient with deficiency of the fourth component of complement and systemic lupus erythematosus. *N Engl J Med* **1979**; 300:1124–9.
124. No authors listed. Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children—Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Morb Mortal Wkly Rep* **2010**; 59:258–61.
125. Walter ND, Taylor TH, Shay DK, et al. Influenza circulation and the burden of invasive pneumococcal pneumonia during a non-pandemic period in the United States. *Clin Infect Dis* **2010**; 50:175–83.
126. Jansen AG, Sanders EA, Van Der Ende A, Van Loon AM, Hoes AW, Hak E. Invasive pneumococcal and meningococcal disease: association with influenza virus and respiratory syncytial virus activity? *Epidemiol Infect* **2008**; 136:1448–54.
127. Winkelstein JA, Marino MC, Johnston RB Jr., et al. Chronic granulomatous disease. Report on a national registry of 368 patients. *Medicine (Baltimore)* **2000**; 79:155–69.
128. Van den Berg JM, van Koppen E, Ahlin A, et al. Chronic granulomatous disease: the European experience. *PLoS One* **2009**; 4:e5234.
129. Finelli L, Fiore A, Dhara R, et al. Influenza-associated pediatric mortality in the United States: increase of *Staphylococcus aureus* coinfection. *Pediatrics* **2008**; 122:805–11.
130. Voss LM, Abraham RT, Rhodes KH, Schoon RA, Leibson PJ. Defective T-lymphocyte signal transduction and function in leukocyte adhesion deficiency. *J Clin Immunol* **1991**; 11:175–83.
131. Baetz K, Isaaz S, Griffiths GM. Loss of cytotoxic T lymphocyte function in Chediak-Higashi syndrome arises from a secretory defect that prevents lytic granule exocytosis. *J Immunol* **1995**; 154:6122–31.
132. Kobayashi Y, Komazawa Y, Kobayashi M, et al. Presumed BCG infection in a boy with chronic granulomatous disease. A report of a case and a review of the literature. *Clin Pediatr (Phila)* **1984**; 23:586–9.
133. Smith PA, Wittenberg DF. Disseminated BCG infection in a child with chronic granulomatous disease. A case report. *S Afr Med J* **1984**; 65:821–2.
134. Kawashima H, Hasegawa D, Nakamura M, et al. Hazards of early BCG vaccination: BCGitis in a patient with chronic granulomatous disease. *Pediatr Int* **2007**; 49:418–9.
135. Kusahara K, Ohga S, Hoshina T, et al. Disseminated bacillus Calmette-Guerin lymphadenitis in a patient with gp91phox-chronic granulomatous disease 25 years after vaccination. *Eur J Pediatr* **2009**; 168:745–7.
136. Mansouri D, Adimi P, Mirsaedi M, et al. Inherited disorders of the IL-12-IFN-gamma axis in patients with disseminated BCG infection. *Eur J Pediatr* **2005**; 164:753–7.
137. Dai YS, Liang MG, Gellis SE, et al. Characteristics of mycobacterial infection in patients with immunodeficiency and nuclear factor-kappaB essential modulator mutation, with or without ectodermal dysplasia. *J Am Acad Dermatol* **2004**; 51:718–22.
138. Orange JS, Jain A, Ballas ZK, Schneider LC, Geha RS, Bonilla FA. The presentation and natural history of immunodeficiency caused by nuclear factor kappaB essential modulator mutation. *J Allergy Clin Immunol* **2004**; 113:725–33.
139. Pasic S, Lalic D, Pejnovic N, Vojvodic D, Simic R, Abinun M. Disseminated bacillus Calmette-Guerin infection in a girl with hyperimmunoglobulin E syndrome. *Acta Paediatr* **1998**; 87:702–4.
140. Pasic S. Local bacillus Calmette-Guerin infection in hyperimmunoglobulin-E syndrome. *Acta Paediatr* **2002**; 91:1271–2.
141. Zhang SY, Boisson-Dupuis S, Chappier A, et al. Inborn errors of interferon (IFN)-mediated immunity in humans: insights into the respective roles of IFN-alpha/beta, IFN-gamma, and IFN-lambda in host defense. *Immunol Rev* **2008**; 226:29–40.
142. Dupuis S, Jouanguy E, Al-Hajjar S, et al. Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. *Nat Genet* **2003**; 33:388–91.
143. Schubert MS, Moss RB. Selective polysaccharide antibody deficiency in familial DiGeorge syndrome. *Ann Allergy* **1992**; 69:231–8.
144. Gennery AR, Barge D, O'Sullivan JJ, Flood TJ, Abinun M, Cant AJ. Antibody deficiency and autoimmunity in 22q11.2 deletion syndrome. *Arch Dis Child* **2002**; 86:422–5.
145. Kirkpatrick CH. Specific polysaccharide antibody deficiency. *Ann Allergy Asthma Immunol* **2006**; 97:271.



146. Shrimpton A, Duddridge M, Ziegler-Heitbrock L. Vaccination with polysaccharide-conjugate-vaccines in adult patients with specific antibody deficiency. *Vaccine* **2006**; 24:3574–80.
147. Schubert R, Reichenbach J, Rose M, Zielen S. Immunogenicity of the seven valent pneumococcal conjugate vaccine in patients with ataxia-telangiectasia. *Pediatr Infect Dis J* **2004**; 23:269–70.
148. Sanal O, Ersoy F, Tezcan I, et al. Antibody response to a seven-valent pneumococcal conjugated vaccine in patients with ataxia-telangiectasia. *J Clin Immunol* **2004**; 24:411–7.
149. Stray-Pedersen A, Aaberge IS, Fruh A, Abrahamsen TG. Pneumococcal conjugate vaccine followed by pneumococcal polysaccharide vaccine; immunogenicity in patients with ataxia-telangiectasia. *Clin Exp Immunol* **2005**; 140:507–16.
150. Asindi AA, Bell EJ, Browning MJ, Stephenson JB. Vaccine-induced polioencephalomyelitis in Scotland. *Scott Med J* **1988**; 33:306–7.
151. Inaba H, Hori H, Ito M, et al. Polio vaccine virus-associated meningoencephalitis in an infant with transient hypogammaglobulinemia. *Scand J Infect Dis* **2001**; 33:630–1.
152. Martin J. Vaccine-derived poliovirus from long term excretors and the end game of polio eradication. *Biologicals* **2006**; 34:117–22.
153. Rezaei N, Aghamohammadi A, Read RC. Response to polysaccharide vaccination amongst pediatric patients with common variable immunodeficiency correlates with clinical disease. *Iran J Allergy Asthma Immunol* **2008**; 7:231–4.
154. Goldacker S, Draeger R, Warnatz K, et al. Active vaccination in patients with common variable immunodeficiency (CVID). *Clin Immunol* **2007**; 124:294–303.
155. Rezaei N, Siadat SD, Aghamohammadi A, et al. Serum bactericidal antibody response 1 year after meningococcal polysaccharide vaccination of patients with common variable immunodeficiency. *Clin Vaccine Immunol* **2010**; 17:524–8.
156. Hidalgo S, Garcia Erro M, Cisterna D, Freire MC. Paralytic poliomyelitis caused by a vaccine-derived polio virus in an antibody-deficient Argentinean child. *Pediatr Infect Dis J* **2003**; 22:570–2.
157. Misbah SA, Lawrence PA, Kurtz JB, Chapel HM. Prolonged faecal excretion of poliovirus in a nurse with common variable hypogammaglobulinaemia. *Postgrad Med J* **1991**; 67:301–3.
158. Shahmahmoodi S, Parvaneh N, Burns C, et al. Isolation of a type 3 vaccine-derived poliovirus (VDPV) from an Iranian child with X-linked agammaglobulinemia. *Virus Res* **2008**; 137:168–72.
159. Fiore L, Plebani A, Buttinelli G, et al. Search for poliovirus long-term excretors among patients affected by agammaglobulinemia. *Clin Immunol* **2004**; 111:98–102.
160. Halsey NA, Pinto J, Espinosa-Rosales F, et al. Search for poliovirus carriers among people with primary immune deficiency diseases in the United States, Mexico, Brazil, and the United Kingdom. *Bull World Health Organ* **2004**; 82:3–8.
161. Werther RL, Crawford NW, Boniface K, Kirkwood CD, Smart JM. Rotavirus vaccine induced diarrhea in a child with severe combined immune deficiency. *J Allergy Clin Immunol* **2009**; 124:600.
162. Patel NC, Hertel PM, Estes MK, et al. Vaccine-acquired rotavirus in infants with severe combined immunodeficiency. *N Engl J Med* **2010**; 362:314–9.
163. Uygungil B, Blesing JJ, Risma KA, McNeal MM, Rothenberg ME. Persistent rotavirus vaccine shedding in a new case of severe combined immunodeficiency: A reason to screen. *J Allergy Clin Immunol* **2010**; 125:270–1.
164. Azzari C, Gambineri E, Resti M, et al. Safety and immunogenicity of measles-mumps-rubella vaccine in children with congenital immunodeficiency (DiGeorge syndrome). *Vaccine* **2005**; 23:1668–71.
165. Moylett EH, Wasan AN, Noroski LM, Shearer WT. Live viral vaccines in patients with partial DiGeorge syndrome: clinical experience and cellular immunity. *Clin Immunol* **2004**; 112:106–12.
166. Perez EE, Bokszczyanin A, McDonald-McGinn D, Zackai EH, Sullivan KE. Safety of live viral vaccines in patients with chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). *Pediatrics* **2003**; 112:e325.
167. Al-Sukaiti N, Reid B, Lavi S, et al. Safety and efficacy of measles, mumps, and rubella vaccine in patients with DiGeorge syndrome. *J Allergy Clin Immunol* **2010**; 126:868–9.
168. Ermolovich MA, Fel'dman EV, Samoilovich EO, Kuzovkova NA, Levin VI. Characterization of the immune status of patients with vaccine-associated poliomyelitis. *Zh Mikrobiol Epidemiol Immunobiol* **2002**:42–50.
169. Mihatsch MJ, Ohnacker H, Just M, Nars PW. Lethal measles giant cell pneumonia after live measles vaccination in a case of thymic aplasia Gitlin. *Helv Paediatr Acta* **1972**; 27:143–6.
170. Monofo WJ, Haslam DB, Roberts RL, Zaki SR, Bellini WJ, Coffin CM. Disseminated measles infection after vaccination in a child with a congenital immunodeficiency. *J Pediatr* **1994**; 124:273–6.
171. Schuil J, van de Putte EM, Zwaan CM, Koole FD, Meire FM. Retinopathy following measles, mumps, and rubella vaccination in an immuno-incompetent girl. *Int Ophthalmol* **1998**; 22:345–7.
172. Bakare N, Menschik D, Tiernan R, Hua W, Martin D. Severe combined immunodeficiency (SCID) and rotavirus vaccination: reports to the Vaccine Adverse Events Reporting System (VAERS). *Vaccine* **2010**; 28:6609–12.
173. Egeler RM, Shapiro R, Loechelt B, Filipovich A. Characteristic immune abnormalities in hemophagocytic lymphohistiocytosis. *J Pediatr Hematol Oncol* **1996**; 18:340–5.
174. Yeganeh M, Heidarzade M, Pourpak Z, et al. Severe combined immunodeficiency: a cohort of 40 patients. *Pediatr Allergy Immunol* **2008**; 19:303–6.
175. Donovan RM, Moore E, Bush CE, Markowitz NP, Saravolatz LD. Changes in plasma HIV RNA levels and CD4 cell counts after vaccination of pediatric patients. *AIDS* **1997**; 11:1054–6.
176. Calmy A, Bel M, Nguyen A, et al. Strong serological responses and HIV RNA increase following AS03-adjuvanted pandemic immunization in HIV-infected patients. *HIV Med* **2012**; 13:207–18.
177. Weinberg A, Gona P, Nachman SA, et al. Antibody responses to hepatitis A virus vaccine in HIV-infected children with evidence of immunologic reconstitution while receiving highly active antiretroviral therapy. *J Infect Dis* **2006**; 193:302–11.
178. Abzug MJ, Pelton SI, Song LY, et al. Immunogenicity, safety, and predictors of response after a pneumococcal conjugate and pneumococcal polysaccharide vaccine series in human immunodeficiency virus-infected children receiving highly active antiretroviral therapy. *Pediatr Infect Dis J* **2006**; 25:920–9.
179. Abzug MJ, Song LY, Fenton T, et al. Pertussis booster vaccination in HIV-infected children receiving highly active antiretroviral therapy. *Pediatrics* **2007**; 120:e1190–202.
180. Levin MJ, Moscicki AB, Song LY, et al. Safety and immunogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine in HIV-infected children 7 to 12 years old. *J Acquir Immune Defic Syndr* **2010**:197–204.
181. Weinberg A, Song LY, Fenton T, et al. T cell responses of HIV-infected children after administration of inactivated or live attenuated influenza vaccines. *AIDS Res Hum Retroviruses* **2010**; 26:51–9.
182. Madhi SA, Kuwanda L, Saarinen L, et al. Immunogenicity and effectiveness of *Haemophilus influenzae* type b conjugate vaccine in HIV infected and uninfected African children. *Vaccine* **2005**; 23:5517–25.
183. Tedaldi EM, Baker RK, Moorman AC, et al. Hepatitis A and B vaccination practices for ambulatory patients infected with HIV. *Clin Infect Dis* **2004**; 38:1478–84.
184. Sutcliffe CG, Moss WJ. Do children infected with HIV receiving HAART need to be revaccinated? *Lancet Infect Dis* **2010**; 10:630–42.
185. Miotti PG, Nelson KE, Dallabetta GA, Farzadegan H, Margolick J, Clements ML. The influence of HIV infection on antibody responses to a two-dose regimen of influenza vaccine. *JAMA* **1989**; 262:779–83.
186. Chadwick EG, Chang G, Decker MD, Yogev R, Dimichele D, Edwards KM. Serologic response to standard inactivated influenza vaccine in



- human immunodeficiency virus-infected children. *Pediatr Infect Dis J* **1994**; 13:206–11.
187. Kroon FP, van Dissel JT, de Jong JC, van Furth R. Antibody response to influenza, tetanus and pneumococcal vaccines in HIV-seropositive individuals in relation to the number of CD4+ lymphocytes. *AIDS* **1994**; 8:469–76.
  188. Vigano A, Zuccotti GV, Pacci M, et al. Humoral and cellular response to influenza vaccine in HIV-infected children with full viroimmunologic response to antiretroviral therapy. *J Acquir Immune Defic Syndr* **2008**; 48:289–96.
  189. Madhi SA, Maskew M, Koen A, et al. Trivalent inactivated influenza vaccine in African adults infected with human immunodeficient virus: double blind, randomized clinical trial of efficacy, immunogenicity, and safety. *Clin Infect Dis* **2011**; 52:128–37.
  190. O'Brien WA, Grovit-Ferbas K, Namazi A, et al. Human immunodeficiency virus-type 1 replication can be increased in peripheral blood of seropositive patients after influenza vaccination. *Blood* **1995**; 86:1082–9.
  191. Rosok B, Voltersvik P, Bjerknes R, Axelsson M, Haaheim LR, Asjo B. Dynamics of HIV-1 replication following influenza vaccination of HIV+ individuals. *Clin Exp Immunol* **1996**; 104:203–7.
  192. Glesby MJ, Hoover DR, Farzadegan H, Margolick JB, Saah AJ. The effect of influenza vaccination on human immunodeficiency virus type 1 load: a randomized, double-blind, placebo-controlled study. *J Infect Dis* **1996**; 174:1332–6.
  193. Tasker SA, O'Brien WA, Treanor JJ, et al. Effects of influenza vaccination in HIV-infected adults: a double-blind, placebo-controlled trial. *Vaccine* **1998**; 16:1039–42.
  194. Crum-Cianflone NF, Eberly LE, Duplessis C, et al. Immunogenicity of a monovalent 2009 influenza A (H1N1) vaccine in an immunocompromised population: a prospective study comparing HIV-infected adults with HIV-uninfected adults. *Clin Infect Dis* **2011**; 52:138–46.
  195. Flynn P, Nachman S, Spector SA. H1N1 immunization in HIV-1 perinatally infected children and youth. *J Infect Dis* **2012**; 206:421–30.
  196. Madhi SA, Adrian P, Kuwanda L, et al. Long-term immunogenicity and efficacy of a 9-valent conjugate pneumococcal vaccine in human immunodeficient virus infected and non-infected children in the absence of a booster dose of vaccine. *Vaccine* **2007**; 25:2451–7.
  197. Dworkin MS, Ward JW, Hanson DL, Jones JL, Kaplan JE. Pneumococcal disease among human immunodeficiency virus-infected persons: incidence, risk factors, and impact of vaccination. *Clin Infect Dis* **2001**; 32:794–800.
  198. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med* **2003**; 349:1341–8.
  199. Nachman S, Kim S, King J, et al. Safety and immunogenicity of a heptavalent pneumococcal conjugate vaccine in infants with human immunodeficiency virus type 1 infection. *Pediatrics* **2003**; 112:66–73.
  200. Arpadi SM, Back S, O'Brien J, Janoff EN. Antibodies to pneumococcal capsular polysaccharides in children with human immunodeficiency virus infection given polyvalent pneumococcal vaccine. *J Pediatr* **1994**; 125:77–9.
  201. King JC Jr., Vink PE, Farley JJ, et al. Comparison of the safety and immunogenicity of a pneumococcal conjugate with a licensed polysaccharide vaccine in human immunodeficiency virus and non-human immunodeficiency virus-infected children. *Pediatr Infect Dis J* **1996**; 15:192–6.
  202. Tangsinmankong N, Kamchaisatian W, Day NK, Sleasman JW, Emmanuel PJ. Immunogenicity of 23-valent pneumococcal polysaccharide vaccine in children with human immunodeficiency virus undergoing highly active antiretroviral therapy. *Ann Allergy Asthma Immunol* **2004**; 92:558–64.
  203. Madhi SA, Klugman KP, Kuwanda L, Cutland C, Kayhty H, Adrian P. Quantitative and qualitative anamnestic immune responses to pneumococcal conjugate vaccine in HIV-infected and HIV-uninfected children 5 years after vaccination. *J Infect Dis* **2009**; 199:1168–76.
  204. Lesprit P, Pedrono G, Molina JM, et al. Immunological efficacy of a prime-boost pneumococcal vaccination in HIV-infected adults. *AIDS* **2007**; 21:2425–34.
  205. French N, Gordon SB, Mwalukomo T, et al. A trial of a 7-valent pneumococcal conjugate vaccine in HIV-infected adults. *N Engl J Med* **2010**; 362:812–22.
  206. Hung CC, Chen MY, Hsieh SM, Hsiao CF, Sheng WH, Chang SC. Clinical experience of the 23-valent capsular polysaccharide pneumococcal vaccination in HIV-1-infected patients receiving highly active antiretroviral therapy: a prospective observational study. *Vaccine* **2004**; 22:2006–12.
  207. Grau I, Pallares R, Tubau F, et al. Epidemiologic changes in bacteremic pneumococcal disease in patients with human immunodeficiency virus in the era of highly active antiretroviral therapy. *Arch Intern Med* **2005**; 165:1533–40.
  208. Watera C, Nakiyingi J, Miiro G, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-infected Ugandan adults: 6-year follow-up of a clinical trial cohort. *AIDS* **2004**; 18:1210–3.
  209. French N, Nakiyingi J, Carpenter LM, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet* **2000**; 355:2106–11.
  210. Gibb D, Giacomelli A, Masters J, et al. Persistence of antibody responses to *Haemophilus influenzae* type b polysaccharide conjugate vaccine in children with vertically acquired human immunodeficiency virus infection. *Pediatr Infect Dis J* **1996**; 15:1097–101.
  211. Madhi SA, Petersen K, Khoosal M, et al. Reduced effectiveness of *Haemophilus influenzae* type b conjugate vaccine in children with a high prevalence of human immunodeficiency virus type 1 infection. *Pediatr Infect Dis J* **2002**; 21:315–21.
  212. Daza P, Banda R, Misoya K, et al. The impact of routine infant immunization with *Haemophilus influenzae* type b conjugate vaccine in Malawi, a country with high human immunodeficiency virus prevalence. *Vaccine* **2006**; 24:6232–9.
  213. Borrow R, Southern J, Andrews N, et al. Comparison of antibody kinetics following meningococcal serogroup C conjugate vaccine between healthy adults previously vaccinated with meningococcal A/C polysaccharide vaccine and vaccine-naïve controls. *Vaccine* **2001**; 19:3043–50.
  214. Richmond P, Kaczmarek E, Borrow R, et al. Meningococcal C polysaccharide vaccine induces immunologic hyporesponsiveness in adults that is overcome by meningococcal C conjugate vaccine. *J Infect Dis* **2000**; 181:761–4.
  215. Siberry GK, Williams PL, Lujan-Zilbermann J, et al. Phase I/II, open-label trial of safety and immunogenicity of meningococcal (groups A, C, Y, and W-135) polysaccharide diphtheria toxoid conjugate vaccine in human immunodeficiency virus-infected adolescents. *Pediatr Infect Dis J* **2010**; 29:391–6.
  216. Siberry GK, Warshaw MG, Williams PL, et al. Safety and immunogenicity of quadrivalent meningococcal conjugate vaccine in 2- to 10-year-old human immunodeficiency virus-infected children. *Pediatr Infect Dis J* **2012**; 31:47–52.
  217. de Martino M, Podda A, Galli L, et al. Acellular pertussis vaccine in children with perinatal human immunodeficiency virus-type 1 infection. *Vaccine* **1997**; 15:1235–8.
  218. Farquhar C, Wamalwa D, Selig S, et al. Immune responses to measles and tetanus vaccines among Kenyan human immunodeficiency virus type 1 (HIV-1)-infected children pre- and post-highly active antiretroviral therapy and revaccination. *Pediatr Infect Dis J* **2009**; 28:295–9.
  219. Melvin AJ, Mohan KM. Response to immunization with measles, tetanus, and *Haemophilus influenzae* type b vaccines in children who have human immunodeficiency virus type 1 infection and are treated with highly active antiretroviral therapy. *Pediatrics* **2003**; 111:e641–4.
  220. Rosenblatt HM, Song LY, Nachman SA, et al. Tetanus immunity after diphtheria, tetanus toxoids, and acellular pertussis vaccination in children with clinically stable HIV infection. *J Allergy Clin Immunol* **2005**; 116:698–703.

221. Tovo PA, de Martino M, Gabiano C, Galli L. Pertussis immunization in HIV-1-infected infants: a model to assess the effects of repeated T cell-dependent antigen administrations on HIV-1 progression. *Italian Register for HIV infection in children. Vaccine* **2000**; 18:1203–9.
222. Xu WM, Cui YT, Wang L, et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multi-centre, randomized, double-blind, placebo-controlled study. *J Viral Hepat* **2009**; 16:94–103.
223. Pickering LK, Baker CJ, Kimberlin DW, Long SS. *Red Book: 2012 report of the Committee on Infectious Diseases*. 29 ed. Elk Grove Village: American Academy of Pediatrics, **2012**.
224. Collier AC, Corey L, Murphy VL, Handsfield HH. Antibody to human immunodeficiency virus (HIV) and suboptimal response to hepatitis B vaccination. *Ann Intern Med* **1988**; 109:101–5.
225. Pasricha N, Datta U, Chawla Y, et al. Immune responses in patients with HIV infection after vaccination with recombinant hepatitis B virus vaccine. *BMC Infect Dis* **2006**; 6:65.
226. Veiga AP, Casseb J, Duarte AJ. Humoral response to hepatitis B vaccination and its relationship with T CD45RA+ (naive) and CD45RO+ (memory) subsets in HIV-1-infected subjects. *Vaccine* **2006**; 24:7124–8.
227. Cornejo-Juarez P, Volkow-Fernandez P, Escobedo-Lopez K, Vilar-Compte D, Ruiz-Palacios G, Soto-Ramirez LE. Randomized controlled trial of hepatitis B virus vaccine in HIV-1-infected patients comparing two different doses. *AIDS Res Ther* **2006**; 3:9.
228. Kim HN, Harrington RD, Van Rompaey SE, Kitahata MM. Independent clinical predictors of impaired response to hepatitis B vaccination in HIV-infected persons. *Int J STD AIDS* **2008**; 19:600–4.
229. Keet IP, van Doornum G, Safary A, Coutinho RA. Insufficient response to hepatitis B vaccination in HIV-positive homosexual men. *AIDS* **1992**; 6:509–10.
230. Abzug MJ, Warshaw M, Rosenblatt HM, et al. Immunogenicity and immunologic memory after hepatitis B virus booster vaccination in HIV-infected children receiving highly active antiretroviral therapy. *J Infect Dis* **2009**; 200:935–46.
231. Laurence JC. Hepatitis A and B immunizations of individuals infected with human immunodeficiency virus. *Am J Med* **2005**; 118 (Suppl 10A):75S–83.
232. Overton ET, Sungkanuparph S, Powderly WG, Seyfried W, Groger RK, Aberg JA. Undetectable plasma HIV RNA load predicts success after hepatitis B vaccination in HIV-infected persons. *Clin Infect Dis* **2005**; 41:1045–8.
233. Cruciani M, Mengoli C, Serpelloni G, et al. Serologic response to hepatitis B vaccine with high dose and increasing number of injections in HIV infected adult patients. *Vaccine* **2009**; 27:17–22.
234. Zuin G, Principi N, Tornaghi R, et al. Impaired response to hepatitis B vaccine in HIV infected children. *Vaccine* **1992**; 10:857–60.
235. Irungu E, Mugo N, Ngure K, et al. Immune response to hepatitis B virus vaccination among HIV-1 infected and uninfected adults in Kenya. *J Infect Dis* **2013**; 207:402–10.
236. Rey D, Krantz V, Partisani M, et al. Increasing the number of hepatitis B vaccine injections augments anti-HBs response rate in HIV-infected patients. Effects on HIV-1 viral load. *Vaccine* **2000**; 18:1161–5.
237. Solfaro C, Fiammengo P, Balbo L, Madon E, Tovo PA. Hepatitis B vaccination in HIV-1-infected children: double efficacy doubling the paediatric dose. *AIDS* **1996**; 10:1169–70.
238. Flynn M, Kort R. XVII International AIDS Conference: From Evidence to Action—Epidemiology. *J Int AIDS Soc* **2009**; 12 (Suppl 1):S2.
239. Lao-Araya M, Puthanakit T, Aupibul L, Taecharoenkul S, Sirisanthana T, Sirisanthana V. Prevalence of protective level of hepatitis B antibody 3 years after revaccination in HIV-infected children on antiretroviral therapy. *Vaccine* **2011**; 29:3977–81.
240. Poovorawan Y, Chongsrisawat V, Theamboonlers A, et al. Long-term benefit of hepatitis B vaccination among children in Thailand with transient hepatitis B virus infection who were born to hepatitis B surface antigen-positive mothers. *J Infect Dis* **2009**; 200:33–8.
241. Jongjirawan Y, Ungulkraiwit P, Sungkanuparph S. Isolated antibody to hepatitis B core antigen in HIV-1 infected patients and a pilot study of vaccination to determine the anamnestic response. *J Med Assoc Thai* **2006**; 89:2028–34.
242. Gandhi RT, Wurcel A, McGovern B, et al. Low prevalence of ongoing hepatitis B viremia in HIV-positive individuals with isolated antibody to hepatitis B core antigen. *J Acquir Immune Defic Syndr* **2003**; 34:439–41.
243. Kemper CA, Haubrich R, Frank I, et al. Safety and immunogenicity of hepatitis A vaccine in human immunodeficiency virus-infected patients: a double-blind, randomized, placebo-controlled trial. *J Infect Dis* **2003**; 187:1327–31.
244. Wallace MR, Brandt CJ, Earhart KC, et al. Safety and immunogenicity of an inactivated hepatitis A vaccine among HIV-infected subjects. *Clin Infect Dis* **2004**; 39:1207–13.
245. Sudjaritruk T, Sirisanthana T, Sirisanthana V. Antibody responses to hepatitis A virus vaccination in Thai HIV-infected children with immune recovery after antiretroviral therapy. *Pediatr Infect Dis J* **2011**; 30:256–9.
246. Crum-Cianflone NF, Wilkins K, Lee AW, et al. Long-term durability of immune responses after hepatitis A vaccination among HIV-infected adults. *J Infect Dis* **2011**; 203:1815–23.
247. Barbi M, Biffi MR, Binda S, et al. Immunization in children with HIV seropositivity at birth: antibody response to polio vaccine and tetanus toxoid. *AIDS* **1992**; 6:1465–9.
248. Kroon FP, van Dissel JT, Labadie J, van Loon AM, van Furth R. Antibody response to diphtheria, tetanus, and poliomyelitis vaccines in relation to the number of CD4+ T lymphocytes in adults infected with human immunodeficiency virus. *Clin Infect Dis* **1995**; 21:1197–203.
249. Wilkin T, Lee JY, Lensing SY, et al. Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in HIV-1-infected men. *J Infect Dis* **2010**; 202:1246–53.
250. Palefsky JM, Holly EA, Ralston ML, Jay N, Berry JM, Darragh TM. High incidence of anal high-grade squamous intra-epithelial lesions among HIV-positive and HIV-negative homosexual and bisexual men. *AIDS* **1998**; 12:495–503.
251. Cortese MM, Parashar UD. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* **2009**; 58:1–25.
252. Madhi SA, Cunliffe NA, Steele D, et al. Effect of human rotavirus vaccine on severe diarrhea in African infants. *N Engl J Med* **2010**; 362:289–98.
253. Steele AD, Madhi SA, Louw CE, et al. Safety, Reactogenicity, and immunogenicity of human rotavirus vaccine RIX4414 in human immunodeficiency virus-positive infants in South Africa. *Pediatr Infect Dis J* **2011**; 30:125–30.
254. Palumbo P, Hoyt L, Demasio K, Oleske J, Connor E. Population-based study of measles and measles immunization in human immunodeficiency virus-infected children. *Pediatr Infect Dis J* **1992**; 11:1008–14.
255. Aupibul L, Puthanakit T, Siriakorn S, Sirisanthana T, Sirisanthana V. Prevalence of protective antibody against measles in HIV-infected children with immune recovery after highly active antiretroviral therapy. *HIV Med* **2006**; 7:467–70.
256. Bekker V, Scherpbier H, Pajkrt D, Jurriaans S, Zaaijer H, Kuijpers TW. Persistent humoral immune defect in highly active antiretroviral therapy-treated children with HIV-1 infection: loss of specific antibodies against attenuated vaccine strains and natural viral infection. *Pediatrics* **2006**; 118:e315–22.
257. Berkelhamer S, Borock E, Elsen C, Englund J, Johnson D. Effect of highly active antiretroviral therapy on the serological response to additional measles vaccinations in human immunodeficiency virus-infected children. *Clin Infect Dis* **2001**; 32:1090–4.
258. Brena AE, Cooper ER, Cabral HJ, Pelton SI. Antibody response to measles and rubella vaccine by children with HIV infection. *J Acquir Immune Defic Syndr* **1993**; 6:1125–9.

259. Lima M, De Menezes Succi RC, Nunes Dos Santos AM, Weckx LY, De Moraes-Pinto MI. Rubella immunization in human immunodeficiency virus type 1-infected children: cause for concern in vaccination strategies. *Pediatr Infect Dis J* **2004**; 23:604–7.
260. Aурpibul L, Puthanakit T, Sirisanthana T, Sirisanthana V. Response to measles, mumps, and rubella revaccination in HIV-infected children with immune recovery after highly active antiretroviral therapy. *Clin Infect Dis* **2007**; 45:637–42.
261. Scott P, Moss WJ, Gilani Z, Low N. Measles vaccination in HIV-infected children: systematic review and meta-analysis of safety and immunogenicity. *J Infect Dis* **2011**; 204 (Suppl 1):S164–78.
262. No authors listed. Measles pneumonia following measles-mumps-rubella vaccination of a patient with HIV infection, 1993. *MMWR Morb Mortal Wkly Rep* **1996**; 45:603–6.
263. Sprauer MA, Markowitz LE, Nicholson JK, et al. Response of human immunodeficiency virus-infected adults to measles-rubella vaccination. *J Acquir Immune Defic Syndr* **1993**; 6:1013–6.
264. Goyal S, Pai SK, Kelkar R, Advani SH. Hepatitis B vaccination in acute lymphoblastic leukemia. *Leuk Res* **1998**; 22:193–5.
265. Yu JW, Borkowski A, Danzig L, Reiter S, Kavan P, Mazer BD. Immune response to conjugated meningococcal C vaccine in pediatric oncology patients. *Pediatr Blood Cancer* **2007**; 49:918–23.
266. Ercan TE, Soycan LY, Apak H, et al. Antibody titers and immune response to diphtheria-tetanus-pertussis and measles-mumps-rubella vaccination in children treated for acute lymphoblastic leukemia. *J Pediatr Hematol Oncol* **2005**; 27:273–7.
267. Polychronopoulou-Androulakaki S, Panagiotou JP, Kostaridou S, Kyrtzopoulou A, Haidas S. Immune response of immunocompromised children with malignancies to a recombinant hepatitis B vaccine. *Pediatr Hematol Oncol* **1996**; 13:425–31.
268. Rokicka-Milewska R, Jackowska T, Sopylo B, Kacperska E, Seyfried H. Active immunization of children with leukemias and lymphomas against infection by hepatitis B virus. *Acta Paediatr Jpn* **1993**; 35:400–3.
269. Zengin E, Sarper N. Humoral immunity to diphtheria, tetanus, measles, and hemophilus influenzae type b in children with acute lymphoblastic leukemia and response to re-vaccination. *Pediatr Blood Cancer* **2009**; 53:967–72.
270. Patel SR, Ortin M, Cohen BJ, et al. Revaccination of children after completion of standard chemotherapy for acute leukemia. *Clin Infect Dis* **2007**; 44:635–42.
271. Alanko S, Pelliniemi TT, Salmi TT. Recovery of blood B-lymphocytes and serum immunoglobulins after chemotherapy for childhood acute lymphoblastic leukemia. *Cancer* **1992**; 69:1481–6.
272. Alanko S, Salmi TT, Pelliniemi TT. Recovery of blood T-cell subsets after chemotherapy for childhood acute lymphoblastic leukemia. *Pediatr Hematol Oncol* **1994**; 11:281–92.
273. Alanko S, Salmi TT, Pelliniemi TT. Recovery of natural killer cells after chemotherapy for childhood acute lymphoblastic leukemia and solid tumors. *Med Pediatr Oncol* **1995**; 24:373–8.
274. Mustafa MM, Buchanan GR, Winick NJ, et al. Immune recovery in children with malignancy after cessation of chemotherapy. *J Pediatr Hematol Oncol* **1998**; 20:451–7.
275. Pao M, Papadopoulos EB, Chou J, et al. Response to pneumococcal (PNCRM7) and haemophilus influenzae conjugate vaccines (HIB) in pediatric and adult recipients of an allogeneic hematopoietic cell transplantation (alloHCT). *Biol Blood Marrow Transplant* **2008**; 14:1022–30.
276. Ljungman P, Andersson J, Aschan J, et al. Influenza A in immunocompromised patients. *Clin Infect Dis* **1993**; 17:244–7.
277. Earle CC. Influenza vaccination in elderly patients with advanced colorectal cancer. *J Clin Oncol* **2003**; 21:1161–6.
278. Robertson JD, Nagesh K, Jowitz SN, et al. Immunogenicity of vaccination against influenza, *Streptococcus pneumoniae* and *Haemophilus influenzae* type B in patients with multiple myeloma. *Br J Cancer* **2000**; 82:1261–5.
279. Nordoy T, Husebekk A, Aaberge IS, et al. Humoral immunity to viral and bacterial antigens in lymphoma patients 4–10 years after high-dose therapy with ABMT. Serological responses to revaccinations according to EBMT guidelines. *Bone Marrow Transplant* **2001**; 28:681–7.
280. Nordoy T, Kolstad A, Tuck MK, Aaberge IS, Husebekk A, Kaminski MS. Radioimmunotherapy with iodine-131 tositumomab in patients with low-grade non-Hodgkin's B-cell lymphoma does not induce loss of acquired humoral immunity against common antigens. *Clin Immunol* **2001**; 100:40–8.
281. Mazza JJ, Yale SH, Arrowood JR, et al. Efficacy of the influenza vaccine in patients with malignant lymphoma. *Clin Med Res* **2005**; 3:214–20.
282. Centkowski P, Brydak L, Machala M, et al. Immunogenicity of influenza vaccination in patients with non-Hodgkin lymphoma. *J Clin Immunol* **2007**; 27:339–46.
283. Lo W, Whimbey E, Elting L, Couch R, Cabanillas F, Bodey G. Antibody response to a two-dose influenza vaccine regimen in adult lymphoma patients on chemotherapy. *Eur J Clin Microbiol Infect Dis* **1993**; 12:778–82.
284. Yri OE, Torfoss D, Hungnes O, et al. Rituximab blocks protective serological response to influenza A(H1N1) 2009 vaccination in lymphoma patients during or within six months after treatment. *Blood* **2011**; 122:1946–53.
285. Bedognetti D, Zoppoli G, Massucco C, et al. Impaired response to influenza vaccine associated with persistent memory B cell depletion in non-Hodgkin's lymphoma patients treated with rituximab-containing regimens. *J Immunol* **2011**; 186:6044–55.
286. Elting LS, Whimbey E, Lo W, Couch R, Andreeff M, Bodey GP. Epidemiology of influenza A virus infection in patients with acute or chronic leukemia. *Support Care Cancer* **1995**; 3:198–202.
287. Anderson H, Petrie K, Berrisford C, Charlett A, Thatcher N, Zambon M. Seroconversion after influenza vaccination in patients with lung cancer. *Br J Cancer* **1999**; 80:219–20.
288. Brydak LB, Guzy J, Starzyk J, Machala M, Gozdz SS. Humoral immune response after vaccination against influenza in patients with breast cancer. *Support Care Cancer* **2001**; 9:65–8.
289. Meerveld-Eggink A, de Weerd O, van der Velden AM, et al. Response to influenza virus vaccination during chemotherapy in patients with breast cancer. *Ann Oncol* **2011**; 22:2031–5.
290. Nordoy T, Aaberge IS, Husebekk A, et al. Cancer patients undergoing chemotherapy show adequate serological response to vaccinations against influenza virus and *Streptococcus pneumoniae*. *Med Oncol* **2002**; 19:71–8.
291. Vilar-Compte D, Cornejo P, Valle-Salinas A, et al. Influenza vaccination in patients with breast cancer: a case-series analysis. *Med Sci Monit* **2006**; 12:CR332–6.
292. Avritscher EB, Cooksley CD, Geraci JM, et al. Cost-effectiveness of influenza vaccination in working-age cancer patients. *Cancer* **2007**; 109:2357–64.
293. Levine AM, Overturf GD, Field RF, Holdorf D, Paganini-Hill A, Feinstein DI. Use and efficacy of pneumococcal vaccine in patients with Hodgkin disease. *Blood* **1979**; 54:1171–5.
294. Siber GR, Weitzman SA, Aisenberg AC, Weinstein HJ, Schiffman G. Impaired antibody response to pneumococcal vaccine after treatment for Hodgkin's disease. *N Engl J Med* **1978**; 299:442–8.
295. Addiego JE Jr., Ammann AJ, Schiffman G, Baehner R, Higgins G, Hammond D. Response to pneumococcal polysaccharide vaccine in patients with untreated Hodgkin's disease. *Children's Cancer Study Group Report. Lancet* **1980**; 2:450–2.
296. Frederiksen B, Specht L, Henrichsen J, Pedersen FK, Pedersen-Bjerggaard J. Antibody response to pneumococcal vaccine in patients with early stage Hodgkin's disease. *Eur J Haematol* **1989**; 43:45–9.
297. Grimfors G, Soderqvist M, Holm G, Lefvert AK, Bjorkholm M. A longitudinal study of class and subclass antibody response to pneumococcal vaccination in splenectomized individuals with special reference to patients with Hodgkin's disease. *Eur J Haematol* **1990**; 45:101–8.



298. Landgren O, Bjorkholm M, Konradsen HB, et al. A prospective study on antibody response to repeated vaccinations with pneumococcal capsular polysaccharide in splenectomized individuals with special reference to Hodgkin's lymphoma. *J Intern Med* **2004**; 255:664–73.
299. Cherif H, Landgren O, Konradsen HB, Kalin M, Bjorkholm M. Poor antibody response to pneumococcal polysaccharide vaccination suggests increased susceptibility to pneumococcal infection in splenectomized patients with hematological diseases. *Vaccine* **2006**; 24:75–81.
300. Molrine DC, George S, Tarbell N, et al. Antibody responses to polysaccharide and polysaccharide-conjugate vaccines after treatment of Hodgkin disease. *Ann Intern Med* **1995**; 123:828–34.
301. Sinisalo M, Vilpo J, Itala M, Vakevainen M, Taurio J, Aittoniemi J. Antibody response to 7-valent conjugated pneumococcal vaccine in patients with chronic lymphocytic leukaemia. *Vaccine* **2007**; 26:82–7.
302. Chan CY, Molrine DC, George S, et al. Pneumococcal conjugate vaccine primes for antibody responses to polysaccharide pneumococcal vaccine after treatment of Hodgkin's disease. *J Infect Dis* **1996**; 173:256–8.
303. Ammann AJ, Schiffman G, Addiego JE, Wara WM, Wara DW. Immunization of immunosuppressed patients with pneumococcal polysaccharide vaccine. *Rev Infect Dis* **1981**; 3 (Suppl):S160–7.
304. Hammarstrom V, Pauksen K, Bjorkstrand B, Simonsson B, Oberg G, Ljungman P. Tetanus immunity in autologous bone marrow and blood stem cell transplant recipients. *Bone Marrow Transplant* **1998**; 22:67–71.
305. Chung SM, Sohn JH, Kim TY, et al. Fulminant hepatic failure with hepatitis B virus reactivation after rituximab treatment in a patient with resolved hepatitis B. *Korean J Gastroenterol* **2010**; 55:266–9.
306. Yagci M, Acar K, Sucak GT, Yamac K, Haznedar R. Hepatitis B virus vaccine in lymphoproliferative disorders: a prospective randomized study evaluating the efficacy of granulocyte-macrophage colony stimulating factor as a vaccine adjuvant. *Eur J Haematol* **2007**; 79:292–6.
307. Pullukcu H, Ertem E, Karaca Y, Yamazhan T, Sertoz RY, Altuglu I. Efficacy of accelerated hepatitis B vaccination program in patients being actively treated for hematologic malignancies. *Int J Infect Dis* **2008**; 12:166–70.
308. Ljungman P, Nahi H, Linde A. Vaccination of patients with hematological malignancies with one or two doses of influenza vaccine: a randomised study. *Br J Haematol* **2005**; 130:96–8.
309. Takata T, Suzumiya Y, Ishikawa T, Takamatsu Y, Ikematsu H, Tamura K. Attenuated antibody reaction for the primary antigen but not for the recall antigen of influenza vaccination in patients with non-Hodgkin B-cell lymphoma after the administration of rituximab-CHOP. *J Clin Exp Hematol* **2009**; 49:9–13.
310. Horwitz SM, Negrin RS, Blume KG, et al. Rituximab as adjuvant to high-dose therapy and autologous hematopoietic cell transplantation for aggressive non-Hodgkin lymphoma. *Blood* **2004**; 103:777–83.
311. Lum LG, Seigneuret MC, Storb R. The transfer of antigen-specific humoral immunity from marrow donors to marrow recipients. *J Clin Immunol* **1986**; 6:389–96.
312. Lum LG, Munn NA, Schanfield MS, Storb R. The detection of specific antibody formation to recall antigens after human bone marrow transplantation. *Blood* **1986**; 67:582–7.
313. Lum LG. The kinetics of immune reconstitution after human marrow transplantation. *Blood* **1987**; 69:369–80.
314. Lum LG, Noges JE, Beatty P, et al. Transfer of specific immunity in marrow recipients given HLA-mismatched, T cell-depleted, or HLA-identical marrow grafts. *Bone Marrow Transplant* **1988**; 3:399–406.
315. Saxon A, Mitsuyasu R, Stevens R, Champlin RE, Kimata H, Gale RP. Designed transfer of specific immune responses with bone marrow transplantation. *J Clin Invest* **1986**; 78:959–67.
316. Wahren B, Gahrton G, Linde A, et al. Transfer and persistence of viral antibody-producing cells in bone marrow transplantation. *J Infect Dis* **1984**; 150:358–65.
317. Witherspoon RP, Storb R, Ochs HD, et al. Recovery of antibody production in human allogeneic marrow graft recipients: influence of time posttransplantation, the presence or absence of chronic graft-versus-host disease, and antithymocyte globulin treatment. *Blood* **1981**; 58:360–8.
318. Witherspoon RP, Matthews D, Storb R, et al. Recovery of in vivo cellular immunity after human marrow grafting. Influence of time post-grafting and acute graft-versus-host disease. *Transplantation* **1984**; 37:145–50.
319. Wimperis JZ, Brenner MK, Prentice HG, et al. Transfer of a functioning humoral immune system in transplantation of T-lymphocyte-depleted bone marrow. *Lancet* **1986**; 1:339–43.
320. Molrine DC, Hibberd PL. Vaccines for transplant recipients. *Infect Dis Clin North Am* **2001**; 15:273–305, xii.
321. Molrine DC, Guinan EC, Antin JH, et al. Donor immunization with *Haemophilus influenzae* type b (HIB)-conjugate vaccine in allogeneic bone marrow transplantation. *Blood* **1996**; 87:3012–8.
322. Ljungman P, Wiklund-Hammarsten M, Duraj V, et al. Response to tetanus toxoid immunization after allogeneic bone marrow transplantation. *J Infect Dis* **1990**; 162:496–500.
323. Ljungman P, Duraj V, Magnus L. Response to immunization against polio after allogeneic marrow transplantation. *Bone Marrow Transplant* **1991**; 7:89–93.
324. Engelhard D, Handscher R, Naparstek E, et al. Immune response to polio vaccination in bone marrow transplant recipients. *Bone Marrow Transplant* **1991**; 8:295–300.
325. Parkkali T, Stenvik M, Ruutu T, Hovi T, Volin L, Ruutu P. Randomized comparison of early and late vaccination with inactivated poliovirus vaccine after allogeneic BMT. *Bone Marrow Transplant* **1997**; 20:663–8.
326. Ljungman P, Lewensohn-Fuchs I, Hammarstrom V, et al. Long-term immunity to measles, mumps, and rubella after allogeneic bone marrow transplantation. *Blood* **1994**; 84:657–63.
327. Machado CM, Goncalves FB, Pannuti CS, Dullely FL, de Souza VA. Measles in bone marrow transplant recipients during an outbreak in Sao Paulo, Brazil. *Blood* **2002**; 99:83–7.
328. Parkman R, Weinberg KI. Immunological reconstitution following bone marrow transplantation. *Immunol Rev* **1997**; 157:73–8.
329. Cristofani LM, Weinberg A, Peixoto V, et al. Administration of live attenuated varicella vaccine to children with cancer before starting chemotherapy. *Vaccine* **1991**; 9:873–6.
330. Tsolia M, Gershon AA, Steinberg SP, Gelb L. Live attenuated varicella vaccine: evidence that the virus is attenuated and the importance of skin lesions in transmission of varicella-zoster virus. National Institute of Allergy and Infectious Diseases Varicella Vaccine Collaborative Study Group. *J Pediatr* **1990**; 116:184–9.
331. Hardy I, Gershon AA, Steinberg SP, LaRussa P. The incidence of zoster after immunization with live attenuated varicella vaccine. A study in children with leukemia. Varicella Vaccine Collaborative Study Group. *N Engl J Med* **1991**; 325:1545–50.
332. Ljungman P, Ward KN, Crooks BN, et al. Respiratory virus infections after stem cell transplantation: a prospective study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant* **2001**; 28:479–84.
333. Ljungman P, de la Camara R, Perez-Bercoff L, et al. Outcome of pandemic H1N1 infections in hematopoietic stem cell transplant recipients. *Haematologica* **2011**; 96:1231–5.
334. Choi SM, Boudreaux AA, Xie H, Englund JA, Corey L, Boeckh M. Differences in clinical outcomes after 2009 influenza A/H1N1 and seasonal influenza among hematopoietic cell transplant recipients. *Blood* **2011**; 117:5050–6.
335. Engelhard D, Zakay-Rones Z, Shapira MY, et al. The humoral immune response of hematopoietic stem cell transplantation recipients to AS03-adjuvanted A/California/7/2009 (H1N1)v-like virus vaccine during the 2009 pandemic. *Vaccine* **2011**; 29:1777–82.
336. Pauksen K, Linde A, Hammarstrom V, et al. Granulocyte-macrophage colony-stimulating factor as immunomodulating factor together with influenza vaccination in stem cell transplant patients. *Clin Infect Dis* **2000**; 30:342–8.



337. de Lavallade H, Garland P, Sekine T, et al. Repeated vaccination is required to optimize seroprotection against H1N1 in the immunocompromised host. *Haematologica* **2011**; 96:307–14.
338. Avetisyan G, Aschan J, Hassan M, Ljungman P. Evaluation of immune responses to seasonal influenza vaccination in healthy volunteers and in patients after stem cell transplantation. *Transplantation* **2008**; 86:257–63.
339. Haining WN, Evans JW, Seth NP, et al. Measuring T cell immunity to influenza vaccination in children after haemopoietic stem cell transplantation. *Br J Haematol* **2004**; 127:322–5.
340. Gueller S, Allwinn R, Mousset S, et al. Enhanced immune response after a second dose of an AS03-adjuvanted H1N1 influenza A vaccine in patients after hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* **2011**; 17:1546–50.
341. Engelhard D, Cordonnier C, Shaw PJ, et al. Early and late invasive pneumococcal infection following stem cell transplantation: a European Bone Marrow Transplantation survey. *Br J Haematol* **2002**; 117:444–50.
342. Winston DJ, Schiffman G, Wang DC, et al. Pneumococcal infections after human bone-marrow transplantation. *Ann Intern Med* **1979**; 91:835–41.
343. Kulkarni S, Powles R, Treleaven J, et al. Chronic graft versus host disease is associated with long-term risk for pneumococcal infections in recipients of bone marrow transplants. *Blood* **2000**; 95:3683–6.
344. Youssef S, Rodriguez G, Rolston KV, Champlin RE, Raad II, Safdar A. Streptococcus pneumoniae infections in 47 hematopoietic stem cell transplantation recipients: clinical characteristics of infections and vaccine-breakthrough infections, 1989–2005. *Medicine (Baltimore)* **2007**; 86:69–77.
345. Giebink GS, Warkentin PI, Ramsay NK, Kersey JH. Titers of antibody to pneumococci in allogeneic bone marrow transplant recipients before and after vaccination with pneumococcal vaccine. *J Infect Dis* **1986**; 154:590–6.
346. Avanzini MA, Carra AM, Maccario R, et al. Antibody response to pneumococcal vaccine in children receiving bone marrow transplantation. *J Clin Immunol* **1995**; 15:137–44.
347. Guinan EC, Molrine DC, Antin JH, et al. Polysaccharide conjugate vaccine responses in bone marrow transplant patients. *Transplantation* **1994**; 57:677–84.
348. Parkkali T, Kaythy H, Ruutu T, Volin L, Eskola J, Ruutu P. A comparison of early and late vaccination with *Haemophilus influenzae* type b conjugate and pneumococcal polysaccharide vaccines after allogeneic BMT. *Bone Marrow Transplant* **1996**; 18:961–7.
349. Winston DJ, Ho WG, Schiffman G, Champlin RE, Feig SA, Gale RP. Pneumococcal vaccination of recipients of bone marrow transplants. *Arch Intern Med* **1983**; 143:1735–7.
350. Cordonnier C, Labopin M, Chesnel V, et al. Randomized study of early versus late immunization with pneumococcal conjugate vaccine after allogeneic stem cell transplantation. *Clin Infect Dis* **2009**; 48:1392–401.
351. Molrine DC, Antin JH, Guinan EC, et al. Donor immunization with pneumococcal conjugate vaccine and early protective antibody responses following allogeneic hematopoietic cell transplantation. *Blood* **2003**; 101:831–6.
352. Meisel R, Kuypers L, Dirksen U, et al. Pneumococcal conjugate vaccine provides early protective antibody responses in children after related and unrelated allogeneic hematopoietic stem cell transplantation. *Blood* **2007**; 109:2322–6.
353. Kumar D, Chen MH, Welsh B, et al. A randomized, double-blind trial of pneumococcal vaccination in adult allogeneic stem cell transplant donors and recipients. *Clin Infect Dis* **2007**; 45:1576–82.
354. Cordonnier C, Labopin M, Chesnel V, et al. Immune response to the 23-valent polysaccharide pneumococcal vaccine after the 7-valent conjugate vaccine in allogeneic stem cell transplant recipients: results from the EBMT IDWP01 trial. *Vaccine* **2010**; 28:2730–4.
355. Hammarstrom V, Pauksen K, Azinge J, Oberg G, Ljungman P. Pneumococcal immunity and response to immunization with pneumococcal vaccine in bone marrow transplant patients: the influence of graft versus host reaction. *Support Care Cancer* **1993**; 1:195–9.
356. Barra A, Cordonnier C, Preziosi MP, et al. Immunogenicity of *Haemophilus influenzae* type b conjugate vaccine in allogeneic bone marrow recipients. *J Infect Dis* **1992**; 166:1021–8.
357. Avanzini MA, Carra AM, Maccario R, et al. Immunization with *Haemophilus influenzae* type b conjugate vaccine in children given bone marrow transplantation: comparison with healthy age-matched controls. *J Clin Immunol* **1998**; 18:193–201.
358. Parkkali T, Olander RM, Ruutu T, et al. A randomized comparison between early and late vaccination with tetanus toxoid vaccine after allogeneic BMT. *Bone Marrow Transplant* **1997**; 19:933–8.
359. Kochethu G, Clark FJ, Craddock CF. Pertussis: should we vaccinate post transplant? *Bone Marrow Transplant* **2006**; 37:793–4.
360. Florax A, Ehler K, Becker K, Vormoor J, Groll AH. *Bordetella pertussis* respiratory infection following hematopoietic stem cell transplantation: time for universal vaccination? *Bone Marrow Transplant* **2006**; 38:639–40.
361. Small TN, Zelenetz AD, Noy A, et al. Pertussis immunity and response to tetanus-reduced diphtheria-reduced pertussis vaccine (Tdap) after autologous peripheral blood stem cell transplantation. *Biol Blood Marrow Transplant* **2009**; 15:1538–42.
362. Papadopoulos E, Young J, Kernan NA, Boulard F, Castro-Malaspina H, O'Reilly RJ. Use of the tetanus toxoid, reduced dose diphtheria and pertussis vaccine (Tdap) in allogeneic transplant (alloHCT) recipients. *Blood* **2008**; 112:2214.
363. Nagler A, Ilan Y, Adler R, et al. Successful immunization of autologous bone marrow transplantation recipients against hepatitis B virus by active vaccination. *Bone Marrow Transplant* **1995**; 15:475–8.
364. Jaffe D, Papadopoulos EB, Young JW, et al. Immunogenicity of recombinant hepatitis B vaccine (rHBV) in recipients of unrelated or related allogeneic hematopoietic cell (HC) transplants. *Blood* **2006**; 108:2470–5.
365. Nakano T, Shimono Y, Sugiyama K, et al. Clinical features of measles in immunocompromised children. *Acta Paediatr Jpn* **1996**; 38:212–7.
366. Kaplan LJ, Daum RS, Smaron M, McCarthy CA. Severe measles in immunocompromised patients. *JAMA* **1992**; 267:1237–41.
367. Machado CM, de Souza VA, Sumita LM, da Rocha IF, Dulley FL, Pannuti CS. Early measles vaccination in bone marrow transplant recipients. *Bone Marrow Transplant* **2005**; 35:787–91.
368. Spoulou V, Giannaki M, Vounatsou M, Bakoula C, Grafakos S. Long-term immunity to measles, mumps and rubella after MMR vaccination among children with bone marrow transplants. *Bone Marrow Transplant* **2004**; 33:1187–90.
369. King SM, Saunders EF, Petric M, Gold R. Response to measles, mumps and rubella vaccine in paediatric bone marrow transplant recipients. *Bone Marrow Transplant* **1996**; 17:633–6.
370. Ljungman P, Fridell E, Lonnqvist B, et al. Efficacy and safety of vaccination of marrow transplant recipients with a live attenuated measles, mumps, and rubella vaccine. *J Infect Dis* **1989**; 159:610–5.
371. Kusmaul SC, Horn BN, Dvorak CC, Abramovitz L, Cowan MJ, Weintrub PS. Safety of the live, attenuated varicella vaccine in pediatric recipients of hematopoietic SCTs. *Bone Marrow Transplant* **2010**; 45:1602–6.
372. Van Thiel DH, Gavalier JS. Response to HBV vaccination in patients with severe liver disease. Absence of an HLA effect. *Dig Dis Sci* **1992**; 37:1447–51.
373. Danziger-Isakov L, Kumar D. Guidelines for vaccination of solid organ transplant candidates and recipients. *Am J Transplant* **2009**; 9 (Suppl 4):S258–62.
374. No authors listed. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* **2009**; 9 (Suppl 3):S1–155.
375. Kotton CN, Hibberd PL. Travel medicine and the solid organ transplant recipient. *Am J Transplant* **2009**; 9 (Suppl 4):S273–81.
376. Kumar D, Blumberg EA, Danziger-Isakov L, et al. Influenza vaccination in the organ transplant recipient: review and summary recommendations. *Am J Transplant* **2011**; 11:2020–30.

377. Campbell AL, Herold BC. Immunization of pediatric solid-organ transplantation candidates: immunizations in transplant candidates. *Pediatr Transplant* **2005**; 9:652-61.
378. Laube GF, Berger C, Goetschel P, Leumann E, Neuhaus TJ. Immunization in children with chronic renal failure. *Pediatr Nephrol* **2002**; 17:638-42.
379. Flynn JT, Frisch K, Kershaw DB, Sedman AB, Bunchman TE. Response to early measles-mumps-rubella vaccination in infants with chronic renal failure and/or receiving peritoneal dialysis. *Adv Perit Dial* **1999**; 15:269-72.
380. Benden C, Danziger-Isakov LA, Astor T, et al. Variability in immunization guidelines in children before and after lung transplantation. *Pediatr Transplant* **2007**; 11:882-7.
381. Wu JF, Ni YH, Chen HL, Hsu HY, Lai HS, Chang MH. Humoral immunogenicity to measles, rubella, and varicella-zoster vaccines in biliary atresia children. *Vaccine* **2009**; 27:2812-5.
382. Prelog M, Pohl M, Ermisch B, et al. Demand for evaluation of vaccination antibody titers in children considered for renal transplantation. *Pediatr Transplant* **2007**; 11:73-6.
383. Duchini A, Hendry RM, Redfield DC, Pockros PJ. Influenza infection in patients before and after liver transplantation. *Liver Transpl* **2000**; 6:531-42.
384. Furth SL, Neu AM, Case B, Lederman HM, Steinhoff M, Fivush B. Pneumococcal polysaccharide vaccine in children with chronic renal disease: a prospective study of antibody response and duration. *J Pediatr* **1996**; 128:99-101.
385. Linnemann CC Jr., First MR, Schiffman G. Response to pneumococcal vaccine in renal transplant and hemodialysis patients. *Arch Intern Med* **1981**; 141:1637-40.
386. Linnemann CC Jr., First MR, Schiffman G. Revaccination of renal transplant and hemodialysis recipients with pneumococcal vaccine. *Arch Intern Med* **1986**; 146:1554-6.
387. Kruger S, Seyfarth M, Sack K, Kreft B. Defective immune response to tetanus toxoid in hemodialysis patients and its association with diphtheria vaccination. *Vaccine* **1999**; 17:1145-50.
388. Lin CC, Chen CL, Concejero A, et al. Active immunization to prevent de novo hepatitis B virus infection in pediatric live donor liver recipients. *Am J Transplant* **2007**; 7:195-200.
389. Wachs ME, Amend WJ, Ascher NL, et al. The risk of transmission of hepatitis B from HBsAg(-), HBCAb(+), HBIGM(-) organ donors. *Transplantation* **1995**; 59:230-4.
390. Crosnier J, Jungers P, Courouce AM, et al. Randomised placebo-controlled trial of hepatitis B surface antigen vaccine in French haemodialysis units: II, haemodialysis patients. *Lancet* **1981**; 1:797-800.
391. Stevens CE, Alter HJ, Taylor PE, Zang EA, Harley EJ, Szmunes W. Hepatitis B vaccine in patients receiving hemodialysis. Immunogenicity and efficacy. *N Engl J Med* **1984**; 311:496-501.
392. Villeneuve E, Vincelette J, Villeneuve JP. Ineffectiveness of hepatitis B vaccination in cirrhotic patients waiting for liver transplantation. *Can J Gastroenterol* **2000**; 14 (Suppl B):59B-62B.
393. Carey W, Pimentel R, Westveer MK, Vogt D, Broughan T. Failure of hepatitis B immunization in liver transplant recipients: results of a prospective trial. *Am J Gastroenterol* **1990**; 85:1590-2.
394. Arslan M, Wiesner RH, Sievers C, Egan K, Zein NN. Double-dose accelerated hepatitis B vaccine in patients with end-stage liver disease. *Liver Transpl* **2001**; 7:314-20.
395. Engler SH, Sauer PW, Golling M, et al. Immunogenicity of two accelerated hepatitis B vaccination protocols in liver transplant candidates. *Eur J Gastroenterol Hepatol* **2001**; 13:363-7.
396. Aziz A, Aziz S, Li DS, et al. Efficacy of repeated high-dose hepatitis B vaccine (80 microg) in patients with chronic liver disease. *J Viral Hepat* **2006**; 13:217-21.
397. Schumann A, Lindemann M, Valentin-Gamazo C, et al. Adoptive immune transfer of hepatitis B virus specific immunity from immunized living liver donors to liver recipients. *Transplantation* **2009**; 87:103-11.
398. Keeffe EB, Iwarson S, McMahon BJ, et al. Safety and immunogenicity of hepatitis A vaccine in patients with chronic liver disease. *Hepatology* **1998**; 27:881-6.
399. Arslan M, Wiesner RH, Poterucha JJ, Zein NN. Safety and efficacy of hepatitis A vaccination in liver transplantation recipients. *Transplantation* **2001**; 72:272-6.
400. Dumot JA, Barnes DS, Younossi Z, et al. Immunogenicity of hepatitis A vaccine in decompensated liver disease. *Am J Gastroenterol* **1999**; 94:1601-4.
401. Geel AL, Landman TS, Kal JA, van Doornum GJ, Weimar W. Varicella zoster virus serostatus before and after kidney transplantation, and vaccination of adult kidney transplant candidates. *Transplant Proc* **2006**; 38:3418-9.
402. Broyer M, Tete MJ, Guest G, Gagnadoux MF, Rouzioux C. Varicella and zoster in children after kidney transplantation: long-term results of vaccination. *Pediatrics* **1997**; 99:35-9.
403. Furth SL, Hogg RJ, Tarver J, Moulton LH, Chan C, Fivush BA. Varicella vaccination in children with chronic renal failure. A report of the Southwest Pediatric Nephrology Study Group. *Pediatr Nephrol* **2003**; 18:33-8.
404. Webb NJ, Fitzpatrick MM, Hughes DA, et al. Immunisation against varicella in end stage and pre-end stage renal failure. Trans-Pennine Paediatric Nephrology Study Group. *Arch Dis Child* **2000**; 82:141-3.
405. Donati M, Zuckerman M, Dhawan A, et al. Response to varicella immunization in pediatric liver transplant recipients. *Transplantation* **2000**; 70:1401-4.
406. Nithichaiyo C, Chongsrisawat V, Hutagalung Y, Bock HL, Poovorawa Y. Immunogenicity and adverse effects of live attenuated varicella vaccine (Oka-strain) in children with chronic liver disease. *Asian Pac J Allergy Immunol* **2001**; 19:101-5.
407. Furth SL, Fivush BA. Varicella vaccination in pediatric kidney transplant candidates. *Pediatr Transplant* **2002**; 6:97-100.
408. Sanchez-Fructuoso AI, Prats D, Naranjo P, et al. Influenza virus immunization effectiveness in kidney transplant patients subjected to two different triple-drug therapy immunosuppression protocols: mycophenolate versus azathioprine. *Transplantation* **2000**; 69:436-9.
409. Versluis DJ, Beyer WE, Masurel N, Wenting GJ, Weimar W. Impairment of the immune response to influenza vaccination in renal transplant recipients by cyclosporine, but not azathioprine. *Transplantation* **1986**; 42:376-9.
410. Soesman NM, Rimmelzwaan GF, Nieuwkoop NJ, et al. Efficacy of influenza vaccination in adult liver transplant recipients. *J Med Virol* **2000**; 61:85-93.
411. Dengler TJ, Strnad N, Buhning I, et al. Differential immune response to influenza and pneumococcal vaccination in immunosuppressed patients after heart transplantation. *Transplantation* **1998**; 66:1340-7.
412. Fraund S, Wagner D, Pethig K, Drescher J, Girgsdies OE, Haverich A. Influenza vaccination in heart transplant recipients. *J Heart Lung Transplant* **1999**; 18:220-5.
413. Magnani G, Falchetti E, Pollini G, et al. Safety and efficacy of two types of influenza vaccination in heart transplant recipients: a prospective randomised controlled study. *J Heart Lung Transplant* **2005**; 24:588-92.
414. Furth SL, Neu AM, McColley SA, Case B, Steinhoff M, Fivush B. Immune response to influenza vaccination in children with renal disease. *Pediatr Nephrol* **1995**; 9:566-8.
415. Madan RP, Tan M, Fernandez-Sesma A, et al. A prospective, comparative study of the immune response to inactivated influenza vaccine in pediatric liver transplant recipients and their healthy siblings. *Clin Infect Dis* **2008**; 46:712-8.
416. Hayney MS, Welter DL, Francois M, Reynolds AM, Love RB. Influenza vaccine antibody responses in lung transplant recipients. *Prog Transplant* **2004**; 14:346-51.
417. Blumberg EA, Fitzpatrick J, Stutman PC, Hayden FG, Brozena SC. Safety of influenza vaccine in heart transplant recipients. *J Heart Lung Transplant* **1998**; 17:1075-80.

418. Burbach G, Bienzle U, Stark K, et al. Influenza vaccination in liver transplant recipients. *Transplantation* **1999**; 67:753–5.
419. Mazzone PJ, Mossad SB, Mawhorter SD, Mehta AC, Schilz RJ, Maurer JR. The humoral immune response to influenza vaccination in lung transplant patients. *Eur Respir J* **2001**; 18:971–6.
420. Salles MJ, Sens YA, Boas LS, Machado CM. Influenza virus vaccination in kidney transplant recipients: serum antibody response to different immunosuppressive drugs. *Clin Transplant* **2010**; 24:E17–23.
421. Mazzone PJ, Mossad SB, Mawhorter SD, Mehta AC, Maurer JR. Cell-mediated immune response to influenza vaccination in lung transplant recipients. *J Heart Lung Transplant* **2004**; 23:1175–81.
422. Hurst FP, Lee JJ, Jindal RM, Agodoa LY, Abbott KC. Outcomes associated with influenza vaccination in the first year after kidney transplantation. *Clin J Am Soc Nephrol* **2011**; 6:1192–7.
423. Baluch A, Humar A, Eurich D, et al. Randomized controlled trial of high-dose intradermal versus standard-dose intramuscular influenza vaccine in organ transplant recipients. *Am J Transplant* **2013**; 13:1026–33.
424. Kazancioglu R, Sever MS, Yuksel-Onel D, et al. Immunization of renal transplant recipients with pneumococcal polysaccharide vaccine. *Clin Transplant* **2000**; 14:61–5.
425. Blumberg EA, Brozena SC, Stutman P, Wood D, Phan HM, Musher DM. Immunogenicity of pneumococcal vaccine in heart transplant recipients. *Clin Infect Dis* **2001**; 32:307–10.
426. McCashland TM, Preheim LC, Gentry MJ. Pneumococcal vaccine response in cirrhosis and liver transplantation. *J Infect Dis* **2000**; 181:757–60.
427. Kumar D, Rotstein C, Miyata G, Arlen D, Humar A. Randomized, double-blind, controlled trial of pneumococcal vaccination in renal transplant recipients. *J Infect Dis* **2003**; 187:1639–45.
428. Kumar D, Welsh B, Siegal D, Chen MH, Humar A. Immunogenicity of pneumococcal vaccine in renal transplant recipients—three year follow-up of a randomized trial. *Am J Transplant* **2007**; 7:633–8.
429. Kumar D, Chen MH, Wong G, et al. A randomized, double-blind, placebo-controlled trial to evaluate the prime-boost strategy for pneumococcal vaccination in adult liver transplant recipients. *Clin Infect Dis* **2008**; 47:885–92.
430. Lin PL, Michaels MG, Green M, et al. Safety and immunogenicity of the American Academy of Pediatrics—recommended sequential pneumococcal conjugate and polysaccharide vaccine schedule in pediatric solid organ transplant recipients. *Pediatrics* **2005**; 116:160–7.
431. Barton M, Wasfy S, Dipchand AI, et al. Seven-valent pneumococcal conjugate vaccine in pediatric solid organ transplant recipients: a prospective study of safety and immunogenicity. *Pediatr Infect Dis J* **2009**; 28:688–92.
432. Enke BU, Bokenkamp A, Offner G, Bartmann P, Brodehl J. Response to diphtheria and tetanus booster vaccination in pediatric renal transplant recipients. *Transplantation* **1997**; 64:237–41.
433. Duca P, Del Pont JM, D'Agostino D. Successful immune response to a recombinant hepatitis B vaccine in children after liver transplantation. *J Pediatr Gastroenterol Nutr* **2001**; 32:168–70.
434. Sanchez-Fueyo A, Rimola A, Grande L, et al. Hepatitis B immunoglobulin discontinuation followed by hepatitis B virus vaccination: A new strategy in the prophylaxis of hepatitis B virus recurrence after liver transplantation. *Hepatology* **2000**; 31:496–501.
435. Di Paolo D, Lenci I, Trinito MO, Tisone G, Angelico M. Extended HBV vaccination in liver transplant recipients for HBV-related cirrhosis: report of two successful cases. *Dig Liver Dis* **2005**; 37:793–8.
436. Arslan M, Wiesner RH, Poterucha JJ, Gross JB Jr., Zein NN. Hepatitis A antibodies in liver transplant recipients: evidence for loss of immunity posttransplantation. *Liver Transpl* **2000**; 6:191–5.
437. Gunther M, Stark K, Neuhaus R, Reinke P, Schroder K, Bienzle U. Rapid decline of antibodies after hepatitis A immunization in liver and renal transplant recipients. *Transplantation* **2001**; 71:477–9.
438. Kwak EJ, Julian K. Human papillomavirus infection in solid organ transplant recipients. *Am J Transplant* **2009**; 9 (Suppl 4):S151–60.
439. Khan S, Erlichman J, Rand EB. Live virus immunization after orthotopic liver transplantation. *Pediatr Transplant* **2006**; 10:78–82.
440. Levitsky J, Te HS, Faust TW, Cohen SM. Varicella infection following varicella vaccination in a liver transplant recipient. *Am J Transplant* **2002**; 2:880–2.
441. Posfay-Barbe KM, Pittet LF, Sottas C, et al. Varicella-zoster immunization in pediatric liver transplant recipients: safe and immunogenic. *Am J Transplant* **2012**; 12:2974–85.
442. Lawal A, Basler C, Branch A, Gutierrez J, Schwartz M, Schiano TD. Influenza vaccination in orthotopic liver transplant recipients: absence of post administration ALT elevation. *Am J Transplant* **2004**; 4:1805–9.
443. Kimball P, Verbeke S, Flattery M, Rhodes C, Tolman D. Influenza vaccination does not promote cellular or humoral activation among heart transplant recipients. *Transplantation* **2000**; 69:2449–51.
444. White-Williams C, Brown R, Kirklín J, et al. Improving clinical practice: should we give influenza vaccinations to heart transplant patients? *J Heart Lung Transplant* **2006**; 25:320–3.
445. Danziger-Isakov L, Cherkassky L, Siegel H, et al. Effects of influenza immunization on humoral and cellular alloreactivity in humans. *Transplantation* **2010**; 89:838–44.
446. Lu Y, Jacobson DL, Ashworth LA, et al. Immune response to influenza vaccine in children with inflammatory bowel disease. *Am J Gastroenterol* **2009**; 104:444–53.
447. Mamula P, Markowitz JE, Piccoli DA, Klimov A, Cohen L, Baldassano RN. Immune response to influenza vaccine in pediatric patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* **2007**; 5:851–6.
448. Kanakoudi-Tsakalidou F, Trachana M, Pratsidou-Gertsi P, Tsitsami E, Kyriazopoulou-Dalaina V. Influenza vaccination in children with chronic rheumatic diseases and long-term immunosuppressive therapy. *Clin Exp Rheumatol* **2001**; 19:589–94.
449. Elkayam O, Bashkin A, Mandelboim M, et al. The effect of infliximab and timing of vaccination on the humoral response to influenza vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. *Semin Arthritis Rheum* **2009**; 39:1062–7.
450. Abu-Shakra M, Press J, Varsano N, et al. Specific antibody response after influenza immunization in systemic lupus erythematosus. *J Rheumatol* **2002**; 29:2555–7.
451. Holvast A, Huckriede A, Wilschut J, et al. Safety and efficacy of influenza vaccination in systemic lupus erythematosus patients with quiescent disease. *Ann Rheum Dis* **2006**; 65:913–8.
452. Fomin I, Caspi D, Levy V, et al. Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNF alpha blockers. *Ann Rheum Dis* **2006**; 65:191–4.
453. van Assen S, Holvast A, Benne CA, et al. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. *Arthritis Rheum* **2010**; 62:75–81.
454. Mori S, Ueki Y, Hirakata N, Oribe M, Hidaka T, Oishi K. Impact of tocilizumab therapy on antibody response to influenza vaccine in patients with rheumatoid arthritis. *Ann Rheum Dis* **2012**; 71:2006–10.
455. Shinoki T, Hara R, Kaneko U, et al. Safety and response to influenza vaccine in patients with systemic-onset juvenile idiopathic arthritis receiving tocilizumab. *Mod Rheumatol* **2012**; 22:871–6.
456. Saad CG, Borba EF, Aikawa NE, et al. Immunogenicity and safety of the 2009 non-adjuvanted influenza A/H1N1 vaccine in a large cohort of autoimmune rheumatic diseases. *Ann Rheum Dis* **2011**; 70:1068–73.
457. Elkayam O, Amir S, Mendelson E, et al. Efficacy and safety of vaccination against pandemic 2009 influenza A (H1N1) virus among patients with rheumatic diseases. *Arthritis Care Res (Hoboken)* **2011**; 23:1062–7.
458. Gabay C, Bel M, Combesure C, et al. Impact of synthetic and biologic disease-modifying antirheumatic drugs on antibody responses to the AS03-adjuvanted pandemic influenza vaccine: a prospective, open-label, parallel-cohort, single-center study. *Arthritis Rheum* **2011**; 63:1486–96.
459. Kapetanovic MC, Saxne T, Sjöholm A, Truedsson L, Jonsson G, Geborek P. Influence of methotrexate, TNF blockers and prednisolone



- on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. *Rheumatology (Oxford)* **2006**; 45:106–11.
460. Visvanathan S, Keenan GF, Baker DG, Levinson AI, Wagner CL. Response to pneumococcal vaccine in patients with early rheumatoid arthritis receiving infliximab plus methotrexate or methotrexate alone. *J Rheumatol* **2007**; 34:952–7.
  461. Mease PJ, Ritchlin CT, Martin RW, et al. Pneumococcal vaccine response in psoriatic arthritis patients during treatment with etanercept. *J Rheumatol* **2004**; 31:1356–61.
  462. Bingham CO 3rd, Looney RJ, Deodhar A, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. *Arthritis Rheum* **2010**; 62:64–74.
  463. Mori S, Ueki Y, Akeda Y, et al. Pneumococcal polysaccharide vaccination in rheumatoid arthritis patients receiving tocilizumab therapy. *Ann Rheum Dis* **2013**.
  464. Farmaki E, Kanakoudi-Tsakalidou F, Spoulou V, et al. The effect of anti-TNF treatment on the immunogenicity and safety of the 7-valent conjugate pneumococcal vaccine in children with juvenile idiopathic arthritis. *Vaccine* **2010**; 28:5109–13.
  465. Zonneveld-Huijssoon E, Ronaghy A, Van Rossum MA, et al. Safety and efficacy of meningococcal c vaccination in juvenile idiopathic arthritis. *Arthritis Rheum* **2007**; 56:639–46.
  466. Elkayam O, Yaron M, Caspi D. Safety and efficacy of vaccination against hepatitis B in patients with rheumatoid arthritis. *Ann Rheum Dis* **2002**; 61:623–5.
  467. Cush J. Herpes Zoster (Shingles) Vaccine Guidelines for Immunosuppressed Patients. American College of Rheumatology Hotline **2008**. Available at: [http://www.rheumatology.org/publications/hotline/2008\\_08\\_01\\_shingles.asp](http://www.rheumatology.org/publications/hotline/2008_08_01_shingles.asp).
  468. Borte S, Liebert UG, Borte M, Sack U. Efficacy of measles, mumps and rubella revaccination in children with juvenile idiopathic arthritis treated with methotrexate and etanercept. *Rheumatology (Oxford)* **2009**; 48:144–8.
  469. Heijstek MW, Kamphuis S, Armbrust W, et al. Effects of the live attenuated measles-mumps-rubella booster vaccination on disease activity in patients with juvenile idiopathic arthritis: a randomized trial. *JAMA* **2013**; 309:2449–56.
  470. Chalmers A, Scheifele D, Patterson C, et al. Immunization of patients with rheumatoid arthritis against influenza: a study of vaccine safety and immunogenicity. *J Rheumatol* **1994**; 21:1203–6.
  471. Holvast A, van Assen S, de Haan A, et al. Effect of a second, booster, influenza vaccination on antibody responses in quiescent systemic lupus erythematosus: an open, prospective, controlled study. *Rheumatology (Oxford)* **2009**; 48:1294–9.
  472. Wallin L, Quintilio W, Locatelli F, Cassel A, Silva MB, Skare TL. Safety and efficiency of influenza vaccination in systemic lupus erythematosus patients. *Acta Reumatol Port* **2009**; 34:498–502.
  473. Kuruma KA, Borba EF, Lopes MH, de Carvalho JF, Bonfa E. Safety and efficacy of hepatitis B vaccine in systemic lupus erythematosus. *Lupus* **2007**; 16:350–4.
  474. Elkayam O, Paran D, Caspi D, et al. Immunogenicity and safety of pneumococcal vaccination in patients with rheumatoid arthritis or systemic lupus erythematosus. *Clin Infect Dis* **2002**; 34:147–53.
  475. Vernacchio L, Neufeld EJ, MacDonald K, et al. Combined schedule of 7-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal vaccine in children and young adults with sickle cell disease. *J Pediatr* **1998**; 133:275–8.
  476. Shatz DV, Schinsky MF, Pais LB, Romero-Steiner S, Kirton OC, Carlone GM. Immune responses of splenectomized trauma patients to the 23-valent pneumococcal polysaccharide vaccine at 1 versus 7 versus 14 days after splenectomy. *J Trauma* **1998**; 44:760–5; discussion 65–6.
  477. Shatz DV, Romero-Steiner S, Elie CM, Holder PF, Carlone GM. Antibody responses in postsplenectomy trauma patients receiving the 23-valent pneumococcal polysaccharide vaccine at 14 versus 28 days post-operatively. *J Trauma* **2002**; 53:1037–42.
  478. Konradsen HB, Rasmussen C, Ejstrup P, Hansen JB. Antibody levels against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b in a population of splenectomized individuals with varying vaccination status. *Epidemiol Infect* **1997**; 119:167–74.
  479. Newcomer W, Santosham M, Bengston S, Panny S, Dover G. Immunogenicity of *Haemophilus influenzae* type b polysaccharide and *Neisseria meningitidis* outer membrane protein complex conjugate vaccine in infants and children with sickle cell disease. *Pediatr Infect Dis J* **1993**; 12:1026–7.
  480. Jakacki R, Luery N, McVerry P, Lange B. *Haemophilus influenzae* diphtheria protein conjugate immunization after therapy in splenectomized patients with Hodgkin disease. *Ann Intern Med* **1990**; 112:143–4.
  481. No authors listed. Recommendation of the Advisory Committee on Immunization Practices (ACIP) for use of quadrivalent meningococcal conjugate vaccine (MenACWY-D) among children aged 9 through 23 months at increased risk for invasive meningococcal disease. *MMWR Morb Mortal Wkly Rep* **2011**; 60:1391–2.
  482. Administration FaD. Product approval information: package insert. Menactra (meningococcal (groups A, C, Y and W-135) polysaccharide diphtheria toxoid conjugate vaccine), **2011**. Available at: <http://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm131170.pdf>. Accessed 12 April 2011.
  483. Rubin LG, Papsin B, Cochlear implants in children: surgical site infections and prevention and treatment of acute otitis media and meningitis. *Pediatrics* **2010**; 126:381–91.
  484. Rose M, Hey C, Kujumdshiev S, Gall V, Schubert R, Zielen S. Immunogenicity of pneumococcal vaccination of patients with cochlear implants. *J Infect Dis* **2004**; 190:551–7.

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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, *Haemophilus 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- $\gamma$ /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