TABLE 316.8 Summary of 2013 National Vaccine Advisory Committee's Standards for Adult Immunization Practices

AUDIENCE	SUMMARY OF STANDARDS
All providers	Incorporate immunization needs assessment into every clinical encounter. Strongly recommend needed vaccine(s) and either administer vaccine(s) or refer patient to a provider who can immunize. Stay up-to-date on, and educate patients about, vaccine recommendations. Implement systems to incorporate vaccine assessment into routine clinical care. Understand how to access immunization information systems (i.e., immunization registries).
Nonimmunizing providers	Routinely assess the immunization status of patients, recommend needed vaccine(s), and refer patient to an immunizing provider. Establish referral relationships with immunizing providers. Follow up to confirm patient receipt of recommended vaccine(s).
Immunizing providers	Ensure professional competencies in immunizations. Assess immunization status in every patient care and counseling encounter and strongly recommend needed vaccine(s). Ensure that receipt of vaccination is documented in patient medical record and immunization registry.
Professional health care–related organizations, associations, systems	Provide immunization education and training of members, including trainees. Provide resources and assistance to implement protocols and other systems to incorporate vaccine needs assessment and vaccination or referral into routine practice. Encourage members to be up-to-date on their own immunizations. Assist members in staying up-to-date on immunization information and recommendations. Partner with other immunization stakeholders to educate the public. Seek out collaboration opportunities with other immunization stakeholders. Collect and share best practices for immunization. Advocate policies that support adult immunization standards. Insurers, payers, entities that cover adult immunization services should ensure that their network is adequate to provide timely immunization access and augment with additional vaccine providers if necessary.
Public health departments	Determine community needs, vaccination capacity, and barriers to adult immunization. Provide access to all ACIP-recommended vaccinations for insured and uninsured adults and work toward becoming an in-network provider for immunization services for insured adults. Partner with immunization stakeholders and support activities and policies to improve awareness of adult vaccine recommendations, increase vaccination rates, and reduce barriers. Ensure professional competencies in immunizations. Collect, analyze, and disseminate immunization data. Provide outreach and education to providers and the public. Work to decrease disparities in immunization coverage and access. Increase immunization registry access and use by vaccine providers for adult patients. Develop capacity to bill for immunization of injured people. Ensure preparedness for identifying and responding to outbreaks of vaccine-preventable diseases. Promote adherence to applicable laws, regulations, and standards among adult immunization stakeholders.

ACIP, Advisory Committee on Immunization Practices.
From National Vaccine Advisory Committee. Recommendations from the National Vaccine Advisory Committee: standards for adult immunization practice. Public Health Rep. *2014;129:115–123.*

Key References

The complete reference list is available online at Expert Consult.

2. Ezeanolue E, Harriman K, Hunter P, et al. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf. Accessed June 15, 2019.
4. Orenstein WA, Paulson JA, Brady MT, et al. Global vaccination recommendations and thimerosal. *Pediatrics.* 2013;131:149–151.
5. Cooper LZ, Katz SL. Ban on thimerosal in draft treaty on mercury: why the AAP's position in 2012 is so important. *Pediatrics.* 2013;131:152–153.
6. Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices—United States, 2013-2014. *MMWR Recomm Rep.* 2013;62:1–43.
10. Van Damme P, Ward JW, Shouval D, et al. Hepatitis B vaccines. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines.* 7th ed. Philadelphia: Elsevier; 2018:342–374.
23. Siegrist CA. Vaccine immunology. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines.* 7th ed. Philadelphia: Elsevier; 2018: 16–34.
37. Ahmed SS, Ellis RW, Rappuoli R. Technologies for making new vaccines. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines.* 7th ed. Philadelphia: Elsevier; 2018:1283–1304.
39. Nabel GJ. Designing tomorrow's vaccines. *N Engl J Med.* 2013;368:551–560.
55. Edwards KM, Decker MD. Pertussis vaccines. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines.* 7th ed. Philadelphia: Elsevier; 2018:711–761.
59. 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–CE4.
60. Cohn AC, MacNeil JR, Clark TA, Centers for Disease Control and Prevention. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 2013;62:1–28.
62. The American College of Obstetrics and Gynecology Committee on Obstetric Practice. Update on immunization and pregnancy; tetanus, diphtheria, and pertussis vaccination. *Obstet Gynecol.* 2013;121: 1411–1414.
63. Ding Y, Yeh SH, Mink CA, et al. Cost-benefit analysis of hospital based postpartum vaccination with combined tetanus toxoid, reduced-diphtheria toxoid, and acellular pertussis vaccine (Tdap). *Vaccine.* 2013;31:2558–2564.
71. Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women—Advisory Committee on Immunization Practices (ACIP), 2012. *MMWR Morb Mortal Wkly Rep.* 2012;62:131–135.
91. Clemens JC, Desai SN, Qadri F, et al. Cholera vaccines. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines.* 7th ed. Philadelphia: Elsevier; 2018:185–197.
93. Kretsinger K, Broder KR, Cortese MM, et al. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for use of Tdap among health-care personnel. *MMWR Recomm Rep.* 2006;55:1–37.
120. Schiller JT, Markowitz LE, Hildesheim A, et al. Human papillomavirus vaccines. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines.* 7th ed. Philadelphia: Elsevier; 2018:430–455.
122. Centers for Disease Control and Prevention. Recommendations on the use of quadrivalent human papillomavirus vaccine in males—Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR Morb Mortal Wkly Rep.* 2011;60:1707–1708.
123. Markowitz LE, Hariri S, Lin C, et al. Reduction in human papillomavirus (HPV) prevalence among young women following HPV vaccine introduction in the United States, National Health and Nutrition Examination Surveys, 2003-2010. *J Infect Dis.* 2013;208:385–393.
129. Bresee JS, Fry AM, Sambhara S, et al. Inactivated influenza vaccines. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines.* 7th ed. Philadelphia: Elsevier; 2018:456–488.
141. Dauvillers Y, Arnulf I, Lecendreux M, et al. Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France. *Brain.* 2013;136:2486–2496.
157. McLean HQ, Fiebelkorn AP, Temte JL, Centers for Disease Control and Prevention. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2013;62:1–34.
196. Williamson ED, Oyston PCF. Plague vaccines. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines.* 7th ed. Philadelphia: Elsevier; 2018: 762–772.
213. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among

children aged 6-18 years with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2013;62:521–524.

215. Griffen MR, Zhu Y, Moore MR, et al. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. *N Engl J Med*. 2013;369:155–163.

241. Kennedy RB, Lane JM, Henderson DA, et al. Smallpox and vaccinia. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:1001–1030.

297. Advisory Committee on Immunization Practices; Centers for Disease Control and Prevention. Immunization of health-care personnel: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2011;60:1–45.

304. Ljungman P. Vaccination in the immunocompromised host. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:1355–1369.

318. Levine EM, Davey AS, Houston AM. Legal issues. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:1601–1630.

337. Wexler DL, Anderson TA, Quirk MR. Websites that contain information about immunization. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:1638–1644.

References

1. Rodewald LE, Orenstein WA, Hinman AR, et al. Immunization in the United States. In: Plotkin S, Orenstein WA, Offit P, eds. *Vaccines*. 6th ed. China: Elsevier; 2013:88–112.
2. Ezeanolue E, Harriman K, Hunter P, et al. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf. Accessed June 15, 2019.
3. Centers for Disease Control and Prevention. Thimerosal in vaccines: a joint statement of the American Academy of Pediatrics and the Public Health Service. *MMWR Morb Mortal Wkly Rep*. 1999;48:563–565.
4. Orenstein WA, Paulson JA, Brady MT, et al. Global vaccination recommendations and thimerosal. *Pediatrics*. 2013;131:149–151.
5. Cooper LZ, Katz SL. Ban on thimerosal in draft treaty on mercury: why the AAP's position in 2012 is so important. *Pediatrics*. 2013;131:152–153.
6. Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices—United States, 2013-2014. *MMWR Recomm Rep*. 2013;62:1–43.
7. Kroger AT, Atkinson WL, Pickering LK. General immunization practices. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:96–120.
8. Claman HN. The biology of the immune response. *JAMA*. 1992;268:2790–2796.
9. Poland GA, Ovsyannikova IG, Jacobson RM. Vaccine immunogenetics: bedside to bench to population. *Vaccine*. 2008;26:6183–6188.
10. Van Damme P, Ward JW, Shouval D, et al. Hepatitis B vaccines. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:342–374.
11. Fagarasan S, Honjo T. T-Independent immune response: new aspects of B cell biology. *Science*. 2000;290:89–92.

11a. Garcon N, Hem S, Friede M. Evolution of adjuvants across the century. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:61–74.

12. Schillie S, Harris A, Link-Gelles R, et al. Recommendations of the Advisory Committee on Immunization Practices for Use of a Hepatitis B Vaccine with a Novel Adjuvant. *MMWR Morb Mortal Wkly Rep*. 2018;67:455–458.
13. Shaw FE Jr, Guess HA, Roets JM, et al. Effect of anatomic injection site, age and smoking on the immune response to hepatitis B vaccination. *Vaccine*. 1989;7:425–430.
14. Lieberman JM, Marcy SM, Partridge S, et al. Evaluation of hepatitis A vaccine in infants: effect of maternal antibodies on the antibody response. Presented at Infectious Diseases Society of America 36th Annual Meeting. Denver, CO, November 12-15, 1998.
15. Mast EE, Margolis HS, 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 1: immunization of infants, children, and adolescents. *MMWR Recomm Rep*. 2005;54:1–38.
16. Ezekowitz RAB, Hoffmann JA, eds. *Innate Immunity*. Totowa, NJ: Humana Press; 2003.
17. Krogsgaard M, Davis MM. How T cells "see" antigen. *Nat Immunol*. 2005;6:239–245.
18. Kotb M, Calandra T. *Cytokines and Chemokinesin Infectious Diseases Handbook*. Totowa, NJ: Humana Press; 2003.
19. O'Garra A, Vieira P. Regulatory T cells and mechanisms of immune system control. *Nat Med*. 2004;10:801–805.
20. Pulendran B, Ahmed R. Translating innate immunity into immunological memory: implications for vaccine development. *Cell*. 2006;124:849–863.
21. Pulendran B, Palucka K, Banchereau J. Sensing pathogens and tuning immune responses. *Science*. 2001;293:253–256.
22. Petrilli V, Dostert C, Muruve DA, et al. The inflammasome: a danger sensing complex triggering innate immunity. *Curr Opin Immunol*. 2007;19:615–622.
23. Siegrist CA. Vaccine immunology. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:16–23.
24. Sercarz EE, Maverakis E. MHC-guided processing: binding of large antigen fragments. *Nat Rev Immunol*. 2003;3:621–629.
25. McHeyzer-Williams LJ, McHeyzer-Williams MG. Antigen-specific memory B cell development. *Annu Rev Immunol*. 2005;23:487–513.
26. Fulginiti VA, Eller JJ, Downie AW, et al. Altered reactivity to measles virus. Atypical measles in children previously immunized with inactivated measles virus vaccines. *JAMA*. 1967;202:1075–1080.
27. MacDonald NE, Halperin SA, Law BJ, et al. Induction of immunologic memory by conjugated vs plain meningococcal C polysaccharide vaccine in toddlers: a randomized controlled trial. *JAMA*. 1998;280:1685–1689.
28. Offit PA, Hackett CJ. Addressing parents' concerns: do vaccines cause allergic or autoimmune diseases? *Pediatrics*. 2003;111:653–659.
29. Stratton K, Wilson CB, McCormick MC, Institute of Medicine. *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction*. Washington, DC: National Academies Press; 2002.
30. DeStefano F, Gu D, Kramarz P, et al. Childhood vaccinations and risk of asthma. *Pediatr Infect Dis J*. 2002;21:498–504.
31. Iqbal S, Barlie JP, Thompson WW, et al. Number of antigens in early childhood vaccines and neuropsychological outcomes at age 7-10 years. *Pharmacoepidemiol Drug Saf*. 2013;22:1263–1270.
32. Offit PA, Quarles J, Gerber MA, et al. Addressing parents' concerns: do multiple vaccines overwhelm or weaken the infant's immune system? *Pediatrics*. 2002;109:124–129.
33. Deleted in review.
34. Eriksson K, Holmgren J. Recent advances in mucosal vaccines and adjuvants. *Curr Opin Immunol*. 2002;14:666–672.
35. Milgrom F, Abeyounis CJ, Kano K. *Principles of Immunological Diagnosis in Medicine*. Philadelphia: Lea & Febiger; 1981.
36. Romero-Steiner S, Libutti D, Pais LB, et al. Standardization of an opsonophagocytic assay for the measurement of functional antibody activity against *Streptococcus pneumoniae* using differentiated HL-60 cells. *Clin Diagn Lab Immunol*. 1997;4:415–422.
37. Ahmed SS, Ellis RW, Rappuoli R. Technologies for making new vaccines. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:1283–1304.
38. Dennehy PH. Rotavirus vaccines: an overview. *Clin Microbiol Rev*. 2008;21:198–208.
39. Nabel GJ. Designing tomorrow's vaccines. *N Engl J Med*. 2013;368:551–560.
40. Centers for Disease Control and Prevention. Measles—United States, 1999. *MMWR Morb Mortal Wkly Rep*. 2000;49:557–560.
41. Reef SE, Cochi SL. The evidence for the elimination of rubella and congenital rubella syndrome in the United States: a public health achievement. *Clin Infect Dis*. 2006;43:S123–S125.
42. Centers for Disease Control and Prevention. Recommendations of the International Task Force for Disease Eradication. *MMWR Recomm Rep*. 1993;42:1–38.
43. Centers for Disease Control and Prevention. Progress toward interruption of wild poliovirus transmission—worldwide, 2008. *MMWR Morb Mortal Wkly Rep*. 2009;58:308–312.
44. Centers for Disease Control and Prevention. Certification of poliomyelitis eradication—European Region, June 2002. *MMWR Morb Mortal Wkly Rep*. 2002;51:572–574.
45. Centers for Disease Control and Prevention. Certification of poliomyelitis eradication—Western Pacific Region, October 2000. *MMWR Morb Mortal Wkly Rep*. 2001;50:1–3.
46. Centers for Disease Control and Prevention. Certification of poliomyelitis eradication—the Americas, 1994. *MMWR Morb Mortal Wkly Rep*. 1994;43:720–722.
47. Peltola H, Kilpi T, Anttila M. Rapid disappearance of *Haemophilus influenzae* type b meningitis after routine childhood immunisation with conjugate vaccines. *Lancet*. 1992;340:592–594.
48. Centers for Disease Control and Prevention. Progress toward eliminating *Haemophilus influenzae* type b disease among infants and children—United States, 1987-1997. *MMWR Morb Mortal Wkly Rep*. 1998;47:993–998.
49. Centers for Disease Control and Prevention. Progress toward introduction of *Haemophilus influenzae* type b vaccine in low-income countries—worldwide, 2004-2007. *MMWR Morb Mortal Wkly Rep*. 2008;57:148–151.
50. Briere EC, Rubin L, Moro PL, et al. Prevention and control of *Haemophilus influenzae* type b disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2014;63:1–14.
51. Roush SW, Murphy TV. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *JAMA*. 2007;298:2155–2163.
52. Centers for Disease Control and Prevention. Invasive pneumococcal disease in children 5 years after conjugate vaccine introduction—eight states, 1998-2005. *MMWR Morb Mortal Wkly Rep*. 2008;57:144–148.
53. Truck J, Lazarus R, Jonsdottir I, et al. Correspondence pneumococcal polysaccharide vaccine efficacy and routine use of conjugate vaccines in infants: there is no need for a vaccine program in older adults at present. *Clin Infect Dis*. 2012;55:1577–1579, author reply 1579–1581.
54. Centers for Disease Control and Prevention. Pertussis vaccination: use of acellular pertussis vaccines among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 1997;46:1–25.
55. Edwards KM, Decker MD. Pertussis vaccines. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:711–761.
56. Centers for Disease Control and Prevention. Use of diphtheria toxoid-tetanus toxoid-acellular pertussis vaccine as a five-dose series. Supplemental recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2000;49:1–8.
57. Marin M, Guris D, Chaves SS, et al. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2007;56:1–40.
58. Izurieta HS, Strebel PM, Blake PA. Postlicensure effectiveness of varicella vaccine during an outbreak in a child care center. *JAMA*. 1997;278:1495–1499.
59. 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–CE4.
60. Cohn AC, MacNeil JR, Clark TA, Centers for Disease Control and Prevention. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2013;62:1–28.
61. Acosta AM, DeBolt C, Tasslimi A, et al Tdap vaccine effectiveness among adolescents in Washington. Presented at 62nd Annual Epidemic Intelligence Service Conference. Atlanta, April 22, 2013. http://www.cdc.gov/eis/downloads/2013-EIS-Conference.pdf.
62. The American College of Obstetrics and Gynecology Committee on Obstetric Practice. Update on immunization and pregnancy; tetanus, diphtheria, and pertussis vaccination. *Obstet Gynecol*. 2013;121:1411–1414.
63. Ding Y, Yeh SH, Mink CA, et al. Cost-benefit analysis of hospital based postpartum vaccination with combined tetanus toxoid, reduced-diphtheria toxoid, and acellular pertussis vaccine (Tdap). *Vaccine*. 2013;31:2558–2564.
64. Howson CP, Howe CJ, Fineberg HV, Institute of Medicine. *Adverse Effects of Pertussis and Rubella Vaccines*. Washington, DC: National Academies Press; 1991.
65. Stratton KR, Howe CJ, Johnston RB Jr. Adverse events associated with childhood vaccines other than pertussis and rubella. Summary of a report from the Institute of Medicine. *JAMA*. 1994;271:1602–1605.
66. Howson CP, Fineberg HV. Adverse events following pertussis and rubella vaccines. Summary of a report of the Institute of Medicine. *JAMA*. 1992;267:392–396.
67. Immunization Safety Review Committee, Board on Health Promotion, Institute of Medicine. *Immunization Safety Review: Vaccines and Autism*. Washington, DC: National Academies Press; 2004.
68. Destefano F, Offit PA, Fisher A. Safety of immunizations. In: Plotkin SA, Orenstein WA, Edwards KM, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:1584–1600.
69. Institute of Medicine. Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies, January 16, 2013. http://www.iom.edu/Reports/2013/The-Childhood-Immunization-Schedule-and-Safety.aspx. Accessed November 11, 2013.
70. Centers for Disease Control and Prevention. Safety of influenza vaccines. https://www.cdc.gov/flu/professionals/acip/2018-2019/background/safety-vaccines.htm, Accessed October 4, 2018.
71. Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women—Advisory Committee on Immunization Practices (ACIP), 2012. *MMWR Morb Mortal Wkly Rep*. 2012;62:131–135.
72. American Academy of Pediatrics. *Red Book: 2009 Report of the Committee on Infectious Diseases*. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009.
73. Robinson CL, Romero JR, Kempe A, Pellegrini C; Advisory Committee on Immunization Practices (ACIP) Child/Adolescent Immunization Work Group. Advisory

Committee on Immunization Practices recommended immunization schedule for children and adolescents aged 18 years or younger — United States, 2017. *MMWR Morb Mortal Wkly Rep*. 2017;66:134–135.

74. Centers for Disease Control and Prevention. Use of anthrax vaccine in response to terrorism: supplemental recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2002;51:1024–1026.
75. Centers for Disease Control and Prevention. Use of anthrax vaccine in the United States. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2010;59:1–26.
76. Friedlander AM, Pittman PR, Parker GW. Anthrax vaccine: evidence for safety and efficacy against inhalational anthrax. *JAMA*. 1999;282:2104–2106.
77. Marano N, Plikaytis BD, Martin SW, et al. Effects of a reduced dose schedule and intramuscular administration of anthrax vaccine adsorbed on immunogenicity and safety at 7 months: a randomized trial. *JAMA*. 2008;300:1532–1543.
78. Brachman PS, Gold H, Plotkin SA, et al. Field evaluation of a human anthrax vaccine. *Am J Public Health Nations Health*. 1962;52:632–645.
79. Abramowicz M. Anthrax vaccine. *Med Lett Drugs Ther*. 1998;40:52–53.
80. Sever JL, Brenner AI, Gale AD, et al. Safety of anthrax vaccine: a review by the Anthrax Vaccine Expert Committee (AVEC) of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS). *Pharmacoepidemiol Drug Saf*. 2002;11:189–202.
81. Lange JL, Lesikar SE, Rubertone MV, et al. Comprehensive systematic surveillance for adverse effects of anthrax vaccine adsorbed, US Armed Forces, 1998-2000. *Vaccine*. 2003;21:1620–1628.
82. Leppla SH, Robbins JB, Schneerson R, et al. Development of an improved vaccine for anthrax. *J Clin Invest*. 2002;110:141–144.
83. Campbell JD, Clement KH, Wasserman SS, et al. Safety, reactogenicity and immunogenicity of a recombinant protective antigen anthrax vaccine given to healthy adults. *Hum Vaccin*. 2007;3:205–211.
84. Centers for Disease Control and Prevention. Updated guidelines for using Interferon Gamma Release Assays to detect *Mycobacterium tuberculosis* infection—United States, 2010. *MMWR Morb Mortal Wkly Rep*. 2010;59:1–25.
85. Snider DE Jr, Rieder HL, Combs D, et al. Tuberculosis in children. *Pediatr Infect Dis J*. 1988;7:271–278.
86. Rodrigues LC, Diwan VK, Wheeler JG. Protective effect of BCG against tuberculous meningitis and miliary tuberculosis: a meta-analysis. *Int J Epidemiol*. 1993;22:1154–1158.
87. Colditz GA, Brewer TF, Berkey CS, et al. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *JAMA*. 1994;271:698–702.
88. Centers for Disease Control and Prevention. The role of BCG vaccine in the prevention and control of tuberculosis in the United States. A joint statement by the Advisory Council for the Elimination of Tuberculosis and the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 1996;45:1–18.
89. Clemens JC, Desai SN, Qadri F, et al. Cholera vaccines. In: Plotkin SA, Orenstein WA, Offit PA, Edwards KM, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:185–197.
90. Centers for Disease Control (CDC). Cholera vaccine. *MMWR Morb Mortal Wkly Rep*. 1988;37:617–618, 623–624.
91. Clemens JC, Desai SN, Qadri F, et al. Cholera vaccines. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:185–197.

91a. Harris JB, LaRocque RC, Qadri F, et al. Cholera. *Lancet*. 2012;379:2466–2476.

92. Centers for Disease Control and Prevention. Diphtheria, tetanus, and pertussis: recommendations for vaccine use and other preventive measures. Recommendations of the Immunization Practices Advisory committee (ACIP). *MMWR Recomm Rep*. 1991;40:1–28.
93. Kretsinger K, Broder KR, Cortese MM, et al. Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for use of Tdap among health-care personnel. *MMWR Recomm Rep*. 2006;55:1–37.
94. Centers for Disease Control and Prevention. *Haemophilus* b conjugate vaccines for prevention of *Haemophilus influenzae* type b disease among infants and children two months of age and older. Recommendations of the immunization practices advisory committee (ACIP). *MMWR Recomm Rep*. 1991;40:1–7.
95. Centers for Disease Control and Prevention. Recommendations for use of *Haemophilus* b conjugate vaccines and a combined diphtheria, tetanus, pertussis, and *Haemophilus* b vaccine. Recommendations of the advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 1993;42:1–15.
96. Centers for Disease Control and Prevention. Unlicensed use of combination of *Haemophilus influenzae* type b conjugate vaccine and diphtheria and tetanus toxoid and acellular pertussis vaccine for infants. *MMWR Morb Mortal Wkly Rep*. 1998;47:787.
97. Anderson EL, Decker MD, Englund JA, et al. Interchangeability of conjugated *Haemophilus influenzae* type b vaccines in infants. *JAMA*. 1995;273:849–853.
98. Greenberg DP, Lieberman JM, Marcy SM, et al. Enhanced antibody responses in infants given different sequences of heterogeneous *Haemophilus influenzae* type b conjugate vaccines. *J Pediatr*. 1995;126:206–211.
99. Bewley KM, Schwab JG, Ballanco GA, et al. Interchangeability of *Haemophilus influenzae* type b vaccines in the primary series: evaluation of a two-dose mixed regimen. *Pediatrics*. 1996;98:898–904.
100. Werzberger A, Mensch B, Kuter B, et al. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. *N Engl J Med*. 1992;327:453–457.
101. Vaqta package insert. https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110049.pdf. Accessed December 14, 2018.
102. Bell BP, Shapiro CN, Alter MJ, et al. The diverse patterns of hepatitis A epidemiology in the United States-implications for vaccination strategies. *J Infect Dis*. 1998;178:1579–1584.
103. Centers for Disease Control and Prevention. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 1996;45:1–30.
104. Prevention of hepatitis A through active or passive immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 1999;48:1–37.
105. Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2006;55:1–23.
106. Centers for Disease Control and Prevention (CDC); Advisory Committee on Immunization Practices. Updated recommendations from the Advisory Committee on Immunization Practices (ACIP) for use of hepatitis A vaccine in close contacts of newly arriving international adoptees. *MMWR Morb Mortal Wkly Rep*. 2009;58:1006–1007.
107. Foster M, Ramchandran S, Myatt K, et al Hepatitis A Virus Outbreaks Associated with Drug Use and Homelessness — California, Kentucky, Michigan, and Utah, 2017. https://www.cdc.gov/mmwr/volumes/67/wr/mm6743a3.htm?s_cid=mm6743a3_w. Accessed December 15, 2018.

107a. Doshani M, Weng M, Moore KL, et al. Recommendations of the advisory committee on immunization practices for the use of hepatitis a vaccine for persons experiencing homelessness. *MMWR Morb Mortal Wkly Rep*. 2019;68:153–156.

108. Shapiro CN, Letson GW, Kuehn D, et al. Effect of maternal antibody on immunogenicity of hepatitis A vaccine in infants. Presented at 35th Interscience Conference on Antimicrobial Agents and Chemotherapy. San Francisco, September 17-20, 1995.
109. Green MS, Cohen D, Lerman Y, et al. Depression of the immune response to an inactivated hepatitis A vaccine administered concomitantly with immune globulin. *J Infect Dis*. 1993;168:740–743.
110. Nelson NP, Link-Gelles R, Hofmeister MG, et al. Update: recommendations of the Advisory Committee on Immunization Practices for Use of Hepatitis A Vaccine for Postexposure Prophylaxis and for Preexposure Prophylaxis for International Travel. *MMWR Morb Mortal Wkly Rep*. 2018;67:1216–1220.
111. Centers for Disease Control and Prevention. Use of hepatitis B vaccination for adults with diabetes mellitus: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2011;60:1709–1711.
112. Schillie S, Vellozzi C, Reingold A, et al. Prevention of Hepatitis B Virus Infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 2018;67:1–31.
113. Centers for Disease Control and Prevention. Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR Recomm Rep*. 1991;40:1–25.
114. Centers for Disease Control and Prevention. Immunization of adolescents. Recommendations of the Advisory Committee on Immunization Practices, the American Academy of Pediatrics, the American Academy of Family Physicians, and the American Medical Association. *MMWR Recomm Rep*. 1996;45:1–16.
115. Middleman AB, Baker CJ, Kozinetz CA, et al. Duration of protection after infant hepatitis B vaccination series. *Pediatrics*. 2014;133:e1500–e1507.
116. Wise RP, Kiminyo KP, Salive ME. Hair loss after routine immunizations. *JAMA*. 1997;278:1176–1178.
117. Pirmohamed M, Winstanley P. Hepatitis B vaccine and neurotoxicity. *Postgrad Med J*. 1997;73:462–463.
118. DeStefano F, Verstraeten T, Jackson LA, et al. Vaccinations and risk of central nervous system demyelinating diseases in adults. *Arch Neurol*. 2003;60:504–509.
119. Institute of Medicine. Adverse Effects of Vaccines: Evidence and Causality, August 25, 2001. http://www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx. Accessed November 11, 2013.
120. Schiller JT, Markowitz LE, Hildesheim A, et al. Human papillomavirus vaccines. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:430–455.
121. Centers for Disease Control and Prevention. FDA licensure of quadrivalent human papillomavirus vaccine (HPV4, Gardasil) for use in males and guidance from the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2010;59:630–632.
122. Centers for Disease Control and Prevention. Recommendations on the use of quadrivalent human papillomavirus vaccine in males—Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR Morb Mortal Wkly Rep*. 2011;60:1707–1708.

122a. Centers for Disease Control and Prevention. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccine recommendations from the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2010;59:626–629.

123. Markowitz LE, Hariri S, Lin C, et al. Reduction in human papillomavirus (HPV) prevalence among young women following HPV vaccine introduction in the United States, National Health and Nutrition Examination Surveys, 2003-2010. *J Infect Dis*. 2013;208:385–393.
124. Meites E, Kempe A, Markowitz LE. Use of a 2-dose schedule for human papillomavirus vaccination - Updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2016;65:1405–1408.
125. Centers for Disease Control and Prevention. CDC seasonal flu vaccine effectiveness studies. https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm.
126. Osterholm MT, Kelly NS, Summer A, et al. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis*. 2012;12:655.
127. Centers for Disease Control and Prevention. Interim adjusted estimates of seasonal influenza vaccine effectiveness—United States, February 2013. *MMWR Morb Mortal Wkly Rep*. 2013;62:119.
128. Patriarca PA, Arden NH, Koplan JP, et al. Prevention and control of type A influenza infections in nursing homes. Benefits and costs of four approaches using vaccination and amantadine. *Ann Intern Med*. 1987;107:732–740.
129. Bresee JS, Fry AM, Sambhara S, et al. Inactivated influenza vaccines. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:456–488.
130. Hoberman A, Greenberg DP, Paradise JL, et al. Effectiveness of inactivated influenza vaccine in preventing acute otitis media in young children: a randomized controlled trial. *JAMA*. 2003;290:1608–1616.
131. Bridges CB, Harper SA, Fukuda K, et al. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2003;52:1–34, quiz CE1–CE4.
132. Flanner B, Chung J, Ferdinands J Preliminary Estimates of 2017–18 Seasonal Influenza Vaccine Effectiveness against Laboratory-Confirmed Influenza from the US Flu VE and HAIVEN Networks. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2018-06/flu-02-Flannery-508.pdf. Accessed October 30, 2018.
133. Jefferson T, Rivetti A, Di Pietrantonj C, et al. Vaccines for preventing influenza in healthy children. *Cochrane Database Syst Rev*. 2012;(8):CD004879.
134. Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and control of seasonal influenza with vaccines:

recommendations of the Advisory Committee on Immunization Practices, United States, 2015-16 influenza season. *MMWR Morb Mortal Wkly Rep*. 2016;65:1–54.

135. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, et al. Guillain-Barré syndrome following vaccination in the National Influenza Immunization Program, United States, 1976-1977. *Am J Epidemiol*. 1979;110:105–123.
136. Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barré syndrome and the 1992-1993 and 1993-1994 influenza vaccines. *N Engl J Med*. 1998;339:1797–1802.
137. Salmon DA, Proschan M, Forshee R, et al. Association between Guillain-Barré syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccine in the USA: a meta-analysis. *Lancet*. 2013;381:1461–1468.
138. Greene SK, Rett MD, Vellozzi C, et al. Guillain-Barré syndrome, influenza vaccination and antecedent respiratory and gastroinstestinal infections: a case-centered analysis in the Vaccine Safety Datalink, 2009-2011. *PLoS ONE*. 2013;8:e67185.
139. Kwong JC, Vasa PP, Campitelli MA, et al. Risk of Guillain-Barré syndrome after seasonal influenza vaccination and influenza healthcare encounters: a self-controlled study. *Lancet Infect Dis*. 2013;13:769–776.
140. Weibel D, Sturkenboom M, Black S, et al. Narcolepsy and adjuvanted pandemic (H1N1) 2009 vaccines – Multi-country assessment. *Vaccine*. 2018;36:6202–6211.
141. Dauvillers Y, Arnulf I, Lecendreux M, et al. Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France. *Brain*. 2013;136:2486–2496.
142. Melen K, Partinen M, Tynell J, et al. No serological evidence of influenza A H1N1pdm09 virus infection as a contributing factor in childhood narcolepsy after Pandemrix vaccination campaign in Finland. *PLoS ONE*. 2013;8:e68402.
143. Partinen M, Saarenpaa-Heikkila O, Ilveskoski I, et al. Increased incidence and clinical picture of childhood narcolepsy following the 2009 H1N1 pandemic vaccination campaign in Finland. *PLoS ONE*. 2012;7:e33723.
144. Miller E, Andrews N, Stellitano L. Risk of narcolepsy in children and young people receiving ASO3 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis. *BMJ*. 2013;346:f794.
145. Donahue JG, Kieke BA, King JP, et al. Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010-11 and 2011-12. *Vaccine*. 2017;35:5314–5322.
146. Murphy KR, Strunk RC. Safe administration of influenza vaccine in asthmatic children hypersensitive to egg proteins. *J Pediatr*. 1985;106:931–933.
147. Harper SA, Fukuda K, Cox NJ, et al. Using live, attenuated influenza vaccine for prevention and control of influenza: supplemental recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2003;52:1–8.
148. Zimmerman RK, Nowalk MP, Chung J, et al. 2014-2015 influenza vaccine effectiveness in the United States by vaccine type. *Clin Infect Dis*. 2016;63:1564–1573.
149. Jackson ML, Chung J, Jackson LA, et al. Influenza Vaccine Effectiveness in the United States during the 2015-2016 season. *N Engl J Med*. 2017;377:534–543.
150. FluMist package insert. https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM294307.pdf.
151. Duffy J, Lewis M, Harrington T, et al. Live attenuated influenza vaccine use and safety in children and adults with asthma. *Ann Allergy Asthma Immunol*. 2017;118:439–444.
152. Baxter R, Eaton A, Hansen J, et al. Safety of quadrivalent live attenuated influenza vaccin152e in subjects aged 2-49 years. *Vaccine*. 2017;35:1254–1258.
153. Hoke CH, Nisalak A, Sangawhipa N, et al. Protection against Japanese encephalitis by inactivated vaccines. *N Engl J Med*. 1988;319:608–614.
154. Fischer M, Lindsey N, Staples JE, Centers for Disease Control and Prevention. Japanese encephalitis vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2010;59:1–27.
155. Centers for Disease Control and Prevention. Use of Japanese encephalitis vaccine in children: recommendations of the Advisory Committee on Immunization Practices, 2013. *MMWR Morb Mortal Wkly Rep*. 2013;62:898–900.
156. Watson JC, Hadler SC, Dykewicz CA. Measle, mumps, and rubella—vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 1998;47:1–57.
157. McLean HQ, Fiebelkorn AP, Temte JL, Centers for Disease Control and Prevention. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2013;62:1–34.
158. Pabst HF, Spady DW, Marusyk RG, et al. Reduced measles immunity in infants in a well-vaccinated population. *Pediatr Infect Dis J*. 1992;11:525–529.
159. Marin M, Broder KR, Temte JL, Centers for Disease Control and Prevention. Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2010;59:1–12.
160. Macartney K, Gidding HF, Trinh L. Evaluation of combination measles-mumps-rubella-varicella vaccine introduction in Australia. *JAMA Pediatr*. 2017;171:992–998.
161. Adverse Events Following Immunization. Atlanta: Centers for Disease Control and Prevention; 1989.
162. Griffin MR, Ray WA, Mortimer EA, et al. Risk of seizures after measles-mumps-rubella immunization. *Pediatrics*. 1991;88:881–885.
163. Stratton KR, Howe CJ, Johnston RB Jr, eds. Measles and mumps vaccine. In: *Adverse Events Associated With Childhood Vaccines: Evidence Bearing on Causality*. Washington, DC: National Academies Press; 1994:118–186.
164. Hornig M, Briese T, Buie T, et al. Lack of association between measles, virus vaccine and autism with enteropathy: a case-control study. *PLoS ONE*. 2008;3:e3140.
165. Bilukha OO, Rosenstein N. Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2005;54:1–21.
166. Lepow ML, Beeler J, Randolph M, et al. Reactogenicity and immunogenicity of a quadrivalent combined meningococcal polysaccharide vaccine in children. *J Infect Dis*. 1986;154:1033–1036.
167. Richmond P, Borrow R, Miller E, et al. Meningococcal serogroup C conjugate vaccine is immunogenic in infancy and primes for memory. *J Infect Dis*. 1999;179:1569–1572.
168. Deleted in review.
169. Folaranmi T, Rubin L, Martin SW, et al. Use of serogroup B meningococcal vaccines in persons aged ≥10 years at increased risk for serogroup B meningococcal disease: recommendations of the Advisory Committee on Immunization Practices, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64:608–612.
170. MacNeil JR, Rubin L, Folaranmi T, et al. Use of serogroup B meningococcal vaccines in adolescents and young adults: recommendations of the Advisory Committee on Immunization Practices, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64:1171–1176.
171. Belshe RB, Edwards KM, Vesikari T, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. *N Engl J Med*. 2007;356:685–696.
172. MacNeil JR, Rubin LG, Patton M, et al. Recommendations for use of meningococcal conjugate vaccines in HIV-infected persons - Advisory Committee on Immunization Practices, 2016. *MMWR Morb Mortal Wkly Rep*. 2016;65:1189–1194.
173. Centers for Disease Control and Prevention. Notice to readers: updated recommendations of the Advisory Committee on Immunization Practices (ACIP) for the control and elimination of mumps. *MMWR Morb Mortal Wkly Rep*. 2006;55:629–630.
174. Marin M, Marlow M, Moore KL, et al. Recommendation of the Advisory Committee on Immunization Practices for Use of a Third Dose of Mumps Virus–Containing Vaccine in Persons at Increased Risk for Mumps During an Outbreak. *MMWR Morb Mortal Wkly Rep*. 2018;67:33–38.
175. Centers for Disease Control and Prevention. CDC guidance for public health authorities on use of a 3rd dose of MMR vaccine during mumps outbreaks. www.cdc.gov/mumps/health-departments/MMR3.html. Accessed October 31, 2018.
176. Liang JL, Tiwari T, Moro P. Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2018;67:1–46.
177. Gustafsson L, Hallander HO, Olin P, et al. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. *N Engl J Med*. 1996;334:349–355.
178. Greco D, Salmaso S, Mastrantonio P, et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. Progetto Pertosse Working Group. *N Engl J Med*. 1996;334:341–348.
179. Centers for Disease Control and Prevention. In: Hamborsky J, Kroger A, Wolfe S, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 13th ed. Washington D.C.: Public Health Foundation; 2015.
180. Misegades LK, Winter K, Harriman K, et al. Association of childhood pertussis with receipt of 5 doses of pertussis vaccine by time since last vaccine dose, California, 2010. *JAMA*. 2012;308:2126–2132.
181. Heijbel H, Rasmussen F, Olin P. Safety evaluation of one whole-cell and three acellular pertussis vaccines in Stockholm trial II. *Dev Biol Stand*. 1997;89:99–100.
182. Heijbel H, Ciofi degli Atti M, Harzer E, et al. Hypotonic hypo-responsive episodes in eight pertussis vaccine studies. *Dev Biol Stand*. 1997;89:101–103.
183. Reyes IS, Hsieh DT, Laux LC, et al. Alleged cases of vaccine encephalopathy rediagnosed years later as dravet syndrome. *Pediatrics*. 2011;128:e699–e702.
184. Gangarosa EJ, Galazka AM, Wolfe CR, et al. Impact of anti-vaccine movements on pertussis control: the untold story. *Lancet*. 1998;351:356–361.
185. Deen JL, Mink CA, Cherry JD, et al. Household contact study of *Bordetella* pertussis infections. *Clin Infect Dis*. 1995;21:1211–1219.
186. Izurieta HS, Kenyon TA, Strebel PM, et al. Risk factors for pertussis in young infants during an outbreak in Chicago in 1993. *Clin Infect Dis*. 1996;22:503–507.
187. Mink CM, Cherry JD, Christenson P, et al. A search for *Bordetella* pertussis infection in university students. *Clin Infect Dis*. 1992;14:464–471.
188. Wright SW, Edwards KM, Decker MD, et al. Pertussis infection in adults with persistent cough. *JAMA*. 1995;273:1044–1046.
189. Nennig ME, Shinefield HR, Edwards KM, et al. Prevalence and incidence of adult pertussis in an urban population. *JAMA*. 1996;275:1672–1674.
190. Edwards KM, Decker MD, Graham BS, et al. Adult immunization with acellular pertussis vaccine. *JAMA*. 1993;269:53–56.
191. Strebel P, Nordin J, Edwards K, et al. Population-based incidence of pertussis among adolescents and adults, Minnesota, 1995-1996. *J Infect Dis*. 2001;183:1353–1359.
192. Tanaka M, Vitek CR, Pascual FB, et al. Trends in pertussis among infants in the United States, 1980-1999. *JAMA*. 2003;290:2968–2975.
193. Ward JI, Cherry JD, Chang SJ, et al. Efficacy of an acellular pertussis vaccine among adolescents and adults. *N Engl J Med*. 2005;353:1555–1563.
194. Centers for Disease Control and Prevention. Updated recommendations for use of tetanus-toxoid, reduced-diphtheria toxoid, and acellular pertussis vaccine (Tdap) in adults aged 65 years and older—Advisory Committee on Immunization Practices (ACIP), 2012. *MMWR Morb Mortal Wkly Rep*. 2012;61:468–470.
195. Murphy TV, Slade BA, Broder KR, et al; Centers for Disease Control and Prevention. Prevention of pertussis, tetanus, and diphtheria among pregnant and postpartum women and their infants recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2008;57:1–51.
196. Williamson ED, Oyston PCF. Plague vaccines. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:762–772.
197. MacLeod CM, Hodges RG, Heidelberger M, et al. Prevention of pneumococcal pneumonia by immunization with specific capsular polysaccharides. *J Exp Med*. 1945;82:445–465.
198. Smit P, Oberholzer D, Hayden-Smith S, et al. Protective efficacy of pneumococcal polysaccharide vaccines. *JAMA*. 1977;238:2613–2616.
199. Austrian R, Douglas RM, Schiffman G, et al. Prevention of pneumococcal pneumonia by vaccination. *Trans Assoc Am Physicians*. 1976;89:184–194.
200. Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N Engl J Med*. 1991;325:1453–1460.
201. Butler JC, Breiman RF, Campbell JF, et al. Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. *JAMA*. 1993;270:1826–1831.
202. Centers for Disease Control and Prevention. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 1997;46:1–24.
203. Jackson LA, Neuzil KM, Yu O, et al. Effectiveness of pneumococcal polysaccharide vaccine in older adults. *N Engl J Med*. 2003;348:1747–1755.
204. Benin AL, O'Brien KL, Watt JP, et al. Effectiveness of the 23-valent polysaccharide vaccine against invasive pneumococcal disease in Navajo adults. *J Infect Dis*. 2003;188:81–89.
205. Kim DK, Riley LE, Harriman KH, et al. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older

- United States, 2017. *MMWR Morb Mortal Wkly Rep*. 2017;66:136–138.
206. Centers for Disease Control and Prevention. Pneumococcal vaccination for cochlear implant candidates and recipients: updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2003;52:739–740.
207. Centers for Disease Control and Prevention, Tomczyk S, Bennett NM, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2014;63:822–827.
208. Advisory Committee on Immunization Practices. Preventing pneumococcal disease among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2000;49:1–35.
209. Black SB, Shinefeld HR, Ling S, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than 5 years of age for prevention of pneumonia. *Pediatr Infect Dis J*. 2002;21:810–815.
210. O'Brien KL, Moulton LH, Reid R, et al. Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial. *Lancet*. 2003;362:355–361.
211. Nuorti JP, Whitney CG, Centers for Disease Control and Prevention. Prevention of pneumococcal disease among infants and children—use of 13-valent pneumococcal conjugate vaccine and 23-valent pnemococcal polysaccharide vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2010;59:1–18.
212. Centers for Disease Control and Prevention; Advisory Committee on Immunization Practices (ACIP). Updated recommendation from the Advisory Committee on Immunization Practices (ACIP) for use of 7-valent pneumococcal conjugate vaccine (PCV7) in children aged 24-59 months who are not completely vaccinated. *MMWR Morb Mortal Wkly Rep*. 2008;57:343–344.
213. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among children aged 6-18 years with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2013;62:521–524.
214. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med*. 2003;348:1737–1746.
215. Griffen MR, Zhu Y, Moore MR, et al. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. *N Engl J Med*. 2013;369:155–163.
216. Hsu HE, Shutt KA, Moore MR, et al. Effect of pneumococcal conjugate vaccine on pneumococcal meningitis. *N Engl J Med*. 2009;360:244–256.
217. Feikin DR, Kagucia EW, Loo JD, et al. Serotype-specific changes in invasive pneumococcal disease after pneumococcal conjugate vaccine introduction: a pooled analysis of multiple surveillance sites. *PLoS Med*. 2013;10:e1001517.
218. 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). *Morb Mortal Wkly Rep*. 2012;61:816–819.
219. Bonten JM, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med*. 2015;372:1114–1125.
220. Kobayashi M, Bennett NM, Gierke R, et al. Intervals between PCV13 and PPSV23 vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2015;64:944–947.
221. Centers for Disease Control and Prevention. Recommendations of the Advisory Committee on Immunization Practices: revised recommendations for routine poliomyelitis vaccination. *MMWR Morb Mortal Wkly Rep*. 1999;48:590.
222. Marin M, Patel M, Oberste S, et al. Guidance for assessment of poliovirus vaccination status and vaccination of children who have received poliovirus vaccine outside the United States. *MMWR Morb Mortal Wkly Rep*. 2017;66:23–25.
223. Khan F, Datta D. Progress toward polio eradication – Worldwide, January 2016-March 2018. *MMWR Morb Mortal Wkly Rep*. 2018;67:524–528.
224. Garon J, Seib K, Orenstein WA, et al. Polio endgame: the global switch from tOPV to bOPV. *Expert Rev Vaccines*. 2016;15:693–708.
225. Manning SE, Rupprecht CE, Fishbein D, et al; Centers for Disease Control and Prevention. Human rabies prevention—United States, 2008: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 2008;57:1–28.
226. Shill M, Baynes RD, Miller SD. Fatal rabies encephalitis despite appropriate post-exposure prophylaxis. A case report. *N Engl J Med*. 1987;316:1257–1258.
227. Centers for Disease Control and Prevention. Human rabies despite treatment with rabies immune globulin and human diploid cell rabies vaccine—Thailand. *MMWR Morb Mortal Wkly Rep*. 1987;36:759–760, 765.
228. Cortese MM, Parashar UD, Centers for Disease Control and Prevention. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2009;58:1–25.
229. Patel MM, Lopez-Collada V, Bulhoes M, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. *N Engl J Med*. 2011;364:2283–2292.
230. Haber P, Patel M, Pan Y, et al. Intussusception after rotavirus vaccine reported to U.S. VAERS, 2006-2012. *Pediatrics*. 2013;131:1042–1049.
231. Yih WK, Lieu TA, Kulldorff M, et al. Intussusception risk after rotavirus vaccination in U.S. infants. *New England Journal of Medicine*. 2014;370:503–512.
232. Weintraub ES, Baggs J, Duffy J, et al. Risk of intussusception after monovalent rotavirus vaccination. *New England Journal of Medicine*. 2014;370:513–519.
233. Tate JE, Mwenda JM, Armah G. Evaluation of intussusception after monovalent rotavirus vaccination in Africa. *New England Journal of Medicine*. 2018;378:1521–1528.
234. Patel MM, Glass R, Desai R, et al. Fulfilling the promise of rotavirus vaccines: how far have we come since licensure? *Lancet Infect Dis*. 2012;12:561–570.
235. Centers for Disease Control and Prevention. Rubella vaccination during pregnancy—United States, 1971-1988. *MMWR Morb Mortal Wkly Rep*. 1989;38:289–293.
236. Freestone DS, Prydie J, Smith SG, et al. Vaccination of adults with Wistar RA 27/3 rubella vaccine. *J Hyg (Lond)*. 1971;69:471–477.
237. Polk BF, Modlin JF, White JA, et al. A controlled comparison of joint reactions among women receiving one of two rubella vaccines. *Am J Epidemiol*. 1982;115:19–25.
238. Slater PE, Ben-Zvi T, Fogel A, et al. Absence of an association between rubella vaccination and arthritis in underimmune post-partum women. *Vaccine*. 1995;13:1529–1532.
239. Frenkel LM, Nielsen K, Garakian A, et al. A search for persistent rubella virus infection in persons with chronic symptoms after rubella and rubella immunization and in patients with juvenile rheumatoid arthritis. *Clin Infect Dis*. 1996;22:287–294.
240. Ray P, Black S, Shinefield H, et al. Risk of chronic arthropathy among women after rubella vaccination. Vaccine Safety Datalink Team. *JAMA*. 1997;278:551–556.
241. Kennedy RB, Lane JM, Henderson DA, et al. Smallpox and vaccinia. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:1001–1030.
242. Weltzin R, Liu J, Pugachev KV, et al. Clonal vaccinia virus grown in cell culture as a new smallpox vaccine. *Nat Med*. 2003;9:1125–1130.
243. Wharton M, Strikas RA, Harpaz R, et al. Recommendations for using smallpox vaccine in a pre-event vaccination program. Supplemental recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Healthcare Infection Control Practices Advisory Committee (HICPAC). *MMWR Recomm Rep*. 2003;52:1–16.
244. Cono J, Casey CG, Bell DM, Centers for Disease Control and Prevention. Smallpox vaccination and adverse reactions. Guidance for clinicians. *MMWR Recomm Rep*. 2003;52:1–28.
245. Talbot TR, Ziel E, Doersam JK, et al. Risk of vaccinia transfer to the hands of vaccinated persons after smallpox immunization. *Clin Infect Dis*. 2004;38:536–541.
246. Centers for Disease Control and Prevention. Supplemental recommendations on adverse events following smallpox vaccine in the pre-event vaccination program: recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2003;52:282–284.
247. Halsell JS, Riddle JR, Atwood JE, et al. Myopericarditis following smallpox vaccination among vaccinia-naive US military personnel. *JAMA*. 2003;289:3283–3289.
248. Relyveld EH, Henocq E, Bizzini B. Studies on untoward reactions to diphtheria and tetanus toxoids. *Dev Biol Stand*. 1979;43:33–37.
249. Pollard JD, Selby G. Relapsing neuropathy due to tetanus toxoid. Report of a case. *J Neurol Sci*. 1978;37:113–125.
250. Baxter R, Bakshi N, Fireman B, et al. Lack of association of Guillain-Barré syndrome with vaccinations. *Clin Infect Dis*. 2013;57:197–204.
251. Centers for Disease Control and Prevention. Update: vaccine side effects, adverse reactions, contraindications, and precautions. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 1996;45:1–35.
252. Centers for Disease Control and Prevention. Typhoid immunization. Recommendations of the immunization practices advisory committee (ACIP). *MMWR Recomm Rep*. 1990;39:1–5.
253. Centers for Disease Control and Prevention. Typhoid immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 1994;43:1–14.
254. Jackson BR, Iqbal S, Mahon B. Updated recommendations for the use of typhoid vaccine – Advisory Committee on Immunization Practices, United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64:305–308.
255. Bernstein HH, Rothstein EP, Watson BM, et al. Clinical survey of natural varicella compared with breakthrough varicella after immunization with live attenuated Oka/Merck varicella vaccine. *Pediatrics*. 1993;92: 833–837.
256. Kuter BJ, Weibel RE, Guess HA, et al. Oka/Merck varicella vaccine in healthy children: final report of a 2-year efficacy study and 7-year follow-up studies. *Vaccine*. 1991;9:643–647.
257. White CJ, Kuter BJ, Ngai A, et al. Modified cases of chickenpox after varicella vaccination: correlation of protection with antibody response. *Pediatr Infect Dis J*. 1992;11:19–23.
258. Watson BM, Piercy SA, Plotkin SA, et al. Modified chickenpox in children immunized with the Oka/Merck varicella vaccine. *Pediatrics*. 1993;91:17–22.
259. Vazquez M, LaRussa PS, Gershon AA, et al. Effectiveness over time of varicella vaccine. *JAMA*. 2004;291:851–855.
260. Vessey SJ, Chan CY, Kuter BJ, et al. Childhood vaccination against varicella: persistence of antibody, duration of protection, and vaccine efficacy. *J Pediatr*. 2001;139:297–304.
261. Marin M, Marti M, Kambhampati A, et al. Varicella vaccine effectiveness worldwide: a systematic review and meta-analysis. *Pediatrics*. 2016;137:1–10.
262. Kuter B, Matthews H, Shinefield H, et al. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. *Pediatr Infect Dis J*. 2004;23:132–137.
263. Kaplan JE, Masur H, Holmes KK, USPHS; Infectious Disease Society of America. Guidelines for preventing opportunistic infections among HIV-infected persons—2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2002;51:1–52.
264. Deleted in review.
265. Klein NP, Lewis E, Baxter R, et al. Measles-containing vaccines and febrile seizures in children aged 4 to 6 years. *Pediatrics*. 2012;129:809–814.
266. Watson B, Seward J, Yang A, et al. Postexposure effectiveness of varicella vaccine. *Pediatrics*. 2000;105:84–88.
267. Hall S, Galil K, Watson B, et al. The use of school-based vaccination clinics to control varicella outbreaks in two schools. *Pediatrics*. 2000;105:e17.
268. Lieu TA, Finkler LJ, Sorel ME, et al. Cost-effectiveness of varicella serotesting versus presumptive vaccination of school-age children and adolescents. *Pediatrics*. 1995;95:632–638.
269. Weinmann S, Chun C, Schmid S, et al. Incidence and clinical characteristics of herpes zoster among children in the varicella vaccine era, 2005-2009. *J Infect Dis*. 2013;208:1859–1868.
270. Varicella Vaccine Collaborative Study Group, Hardy I, Gershon AA, et al. The incidence of zoster after immunization with live attenuated varicella vaccine: a study in children with leukemia. *N Engl J Med*. 1991;325:1545–1550.
271. Levin MJ, Gershon AA, Weinberg A, et al. Immunization of HIV-infected children with varicella vaccine. *J Pediatr*. 2001;139:305–310.
272. Levin MJ, Gerson AA, Weinberg A, et al. Administration of live varicella vaccine to HIV-infected children with current or past significant depression of CD4(+) T cells. *J Infect Dis*. 2006;194:247–255.
273. Cetron MS, Marfin AA, Julian KG, et al. Yellow fever vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2002. *MMWR Recomm Rep*. 2002;51:1–11, quiz, CE1–CE4.

274. 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–CE4.
275. Tseng HF, Smith N, Harpaz R, et al. Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease. *JAMA*. 2011;305:160–166.
276. Centers for Disease Control and Prevention. Update: prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2007;56:1080–1084.
277. Centers for Disease Control and Prevention. Updated recommendations for use of VariZIG—United States, 2013. *MMWR Morb Mortal Wkly Rep*. 2013;62:574–576.
278. Arnon SS, Schechter R, Maslanka SE, et al. Human botulism immune globulin for the treatment of infant botulism. *N Engl J Med*. 2006;354:462–471.
279. Meissner HC, Long SS. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. *Pediatrics*. 2003;112:1447–1452.
280. Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. The PREVENT Study Group. *Pediatrics*. 1997;99:93–99.
281. Simoes EA, Sondheimer HM, Top FH Jr, et al. Respiratory syncytial virus immune globulin for prophylaxis against respiratory syncytial virus disease in infants and children with congenital heart disease. The Cardiac Study Group. *J Pediatr*. 1998;133:492–499.
282. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. *Pediatrics*. 1998;102:531–537.
283. Pickering LK, Baker CJ, Kimberlin DW, et al, eds. *American Academy of Pediatrics. Red Book*. 29th ed. 2012 Report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics; 2012:609–618.
284. http://pediatrics.aappublications.org/content/134/2/415.
285. Ellis EF, Henney CS. Adverse reactions following administration of human gamma globulin. *J Allergy*. 1969;43:45–54.
286. Siber GR, Werner BG, Halsey NA, et al. Interference of immune globulin with measles and rubella immunization. *J Pediatr*. 1993;122:204–211.
287. Centers for Disease Control and Prevention. Outbreak of hepatitis C associated with intravenous immunoglobulin administration—United States, October 1993-June 1994. *MMWR Morb Mortal Wkly Rep*. 1994;43:505–509.
288. Hepatitis C virus and intravenous anti-D immunoglobulin. *Commun Dis Rep CDR Wkly*. 1995;5:111.
289. Schiff RI. Transmission of viral infections through intravenous immune globulin. *N Engl J Med*. 1994;331:1649–1650.
290. Yu MY, Mason BL, Tankersley DL. Detection and characterization of hepatitis C virus RNA in immune globulins. *Transfusion*. 1994;34:596–602.
291. Khabbaz RF, Chamberland M. From prions to parasites: issues and concerns in blood safety. In: Scheld WM, Craig WA, Hughes JM, eds. *Emerging Infections*. Vol. 2. Washington, DC: American Society for Microbiology Press; 1998:295–309.
292. American College of Obstetricians and Gynecologists. *Selective Rho (D) Immune Globulin (RHIG)*. Chicago: American College of Obstetricians and Gynecologists; 1981.
293. King GE, Hadler SC. Simultaneous administration of childhood vaccines: an important public health policy that is safe and efficacious. *Pediatr Infect Dis J*. 1994;13:394–407.
294. Centers for Disease Control and Prevention. Combination vaccines for childhood immunization. *MMWR Recomm Rep*. 1999;48:1–14.
295. Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines. *MMWR Morb Mortal Wkly Rep*. 2018;67:103–108.
296. Staples JE, Gershman M, Fischer M. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2010;59:1–27.
297. Advisory Committee on Immunization Practices; Centers for Disease Control and Prevention. Immunization of health-care personnel: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2011;60:1–45.
298. Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med*. 2008;359:1555–1564.
299. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58:309–318.
300. Avery RK, Ljungman P. Prophylactic measures in the solid-organ recipient before transplantation. *Clin Infect Dis*. 2001;33:S15–S21.
301. Stark K, Gunther M, Schonfeld C, et al. Immunisations in solid-organ transplant recipients. *Lancet*. 2002;359:957–965.
302. Duchini A, Goss JA, Karpen S, et al. Vaccinations for adult solid-organ transplant recipients: current recommendations and protocols. *Clin Microbiol Rev*. 2003;16:357–364.
303. Pirofski LA, Casadevall A. Use of licensed vaccines for active immunization of the immunocompromised host. *Clin Microbiol Rev*. 1998;11:1–26.
304. Ljungman P. Vaccination in the immunocompromised host. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:1355–1369.
305. Sutcliffe CG, Moss WJ. Vaccination of human immunodeficiency virus-infected persons. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:1370–1382.
306. Ninane J, Grymonprez A, Burtonboy G, et al. Disseminated BCG in HIV infection. *Arch Dis Child*. 1988;63:1268–1269.
307. Centers for Disease Control and Prevention. Disseminated *Mycobacterium bovis* infection from BCG vaccination of a patient with acquired immunodeficiency syndrome. *MMWR Morb Mortal Wkly Rep*. 1985;34:227–228.
308. Centers for Disease Control and Prevention. Measles pneumonitis following measles-mumps-rubella vaccination of a patient with HIV infection, 1993. *MMWR Morb Mortal Wkly Rep*. 1996;45:603–606.
309. Kaplan SE, Benson C, Holmes KK, et al; Centers for Disease Control and Prevention. 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;58:1–198.
310. Siber GR, Snydman DR. Use of immune globulins in the prevention and treatment of infections. *Curr Clin Top Infect Dis*. 1992;12:208–256.
311. Ruuskanen O, Salmi TT, Halonen P. Measles vaccination after exposure to natural measles. *J Pediatr*. 1978;93:43–46.
312. Asano Y, Hirose S, Iwayama S, et al. Protective effect of immediate inoculation of a live varicella vaccine in household contacts in relation to the viral dose and interval between exposure and vaccination. *Biken J*. 1982;25:43–45.
313. Salzman MB, Garcia C. Postexposure varicella vaccination in siblings of children with active varicella. *Pediatr Infect Dis J*. 1998;17:256–257.
314. Pickering LK, Baker CJ, Freed GL, et al. Immunization programs for infants, children, adolescents, and adults; clinical practice guidelines by the Infectious Diseases Society of America (IDSA). *Clin Infect Dis*. 2009;49:817–840. Erratum in *Clin Infect Dis*. 2009;49:1465.
315. Centers for Disease Control and Prevention. Tetanus surveillance—United States, 2001-2008. *MMWR Morb Mortal Wkly Rep*. 2011;60:365–369.
316. Centers for Disease Control and Prevention. *Early Release of Selected Estimates Based on Data From the 2002 National Health Interview Survey*. Atlanta: Centers for Disease Control and Prevention; 2004.
317. Stewart AM. When vaccine injury claims go to court. *N Engl J Med*. 2009;360:2498–2500.
318. Levine EM, Davey AS, Houston AM. Legal issues. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:1601–1630.
319. Centers for Disease Control and Prevention. FDA approval for a combined hepatitis A and B vaccine. *MMWR Morb Mortal Wkly Rep*. 2001;50:806–807.
320. Centers for Disease Control and Prevention. FDA approval for infants of a *Haemophilus influenzae* type b conjugate and hepatitis B (recombinant) combined vaccine. *MMWR Morb Mortal Wkly Rep*. 1997;46:107–109.
321. Centers for Disease Control and Prevention. FDA approval of a *Haemophilus* b conjugate vaccine combined by reconstitution with an acellular pertussis vaccine. *MMWR Morb Mortal Wkly Rep*. 1996;45:993–995.
322. Centers for Disease Control and Prevention. FDA licensure of diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant), and poliovirus vaccine combined, (PEDIARIX) for use in infants. *MMWR Morb Mortal Wkly Rep*. 2003;52:203–204. Erratum in *MMWR Morb Mortal Wkly Rep*. 2003;52:379.
323. Centers for Disease Control and Prevention. Notice to readers: licensure of a combined live attenuated measles, mumps, rubella, and varicella vaccine. *MMWR Morb Mortal Wkly Rep*. 2005;54:1212–1214.
324. Centers for Disease Control and Prevention. Licensure of a diphtheria and tetanus toxoids and acellular pertussis adsorbed and inactivated poliovirus vaccine and guidance for use as a booster dose. *MMWR Morb Mortal Wkly Rep*. 2008;57:1078–1079.
325. Centers for Disease Control and Prevention. Licensure of a diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus, and *Haemophilus* B conjugate vaccine and guidance for use in infants and children. *MMWR Morb Mortal Wkly Rep*. 2008;57:1079–1080.
326. Centers for Disease Control and Prevention. National Childhood Vaccine Injury Act: requirements for permanent vaccination records and for reporting of selected events after vaccination. *MMWR Morb Mortal Wkly Rep*. 1988;37:197–200.
327. National Vaccine Advisory Committee. Recommendations from the National Vaccine Advisory Committee: standards for adult immunization practice. *Public Health Rep*. 2014;129:115–123.
328. Recommendations regarding interventions to improve vaccination coverage in children, adolescents, and adults. Task Force on Community Preventive Services. *Am J Prev Med*. 2000;18:92–96.
329. Shefer A, Briss P, Rodewald L, et al. Improving immunization coverage rates: an evidence-based review of the literature. *Epidemiol Rev*. 1999;21:96–142.
330. Cohn A, Rodewald LE, Orenstein WA, et al. Immunization in the United States. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:1421–1440.
331. Bushnell CJ The ABC's of practice-based immunization assessments. Presented at the 28th National Immunization Conference. Washington, DC, 1994.
332. Dini EF, Chaney M, Moolenaar RL, et al. Information as intervention: how Georgia used vaccination coverage data to double public sector vaccination coverage in seven years. *J Public Health Manag Pract*. 1996;2:45–49.
333. Deleted in review.
334. Linkins RW, Feikema SM. Immunization registries: the cornerstone of childhood immunization in the 21st century. *Pediatr Ann*. 1998;27:349–354.
335. U.S. Department of Health and Human Services. Maternal, Infant, and Child Health. http://www.healthypeople.gov/2020/topicsobjectives2020/objectiveslist.aspx?TopicId=23#564. Accessed November 11, 2013.
336. Centers for Disease Control and Prevention. Progress in immunization information systems—United States 2011. *MMWR Morb Mortal Wkly Rep*. 2013;62:48–51.
337. Wexler DL, Anderson TA, Quirk MR. Websites that contain information about immunization. In: Plotkin SA, Orenstein WA, Offit PA, et al, eds. *Plotkin's Vaccines*. 7th ed. Philadelphia: Elsevier; 2018:1638–1644.

E Zoonoses

317 Zoonoses

W. Ian Lipkin

SHORT VIEW SUMMARY

Definition
- A zoonosis is an infectious disease of humans that originates in animals.

Epidemiology
- Zoonoses account for up to 70% of emerging infectious diseases and include such varied examples as human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS), Ebola, severe acute respiratory syndrome (SARS), plague, rabies, influenza, Zika, and new variant Creutzfeldt-Jakob disease.

Diagnosis
- The majority of zoonotic diseases are diagnosed through molecular methods. Many appear in unexpected contexts; thus a comprehensive travel and exposure history can be critical.

Treatment
- With the notable exception of HIV/AIDS and influenza, most viral zoonoses have not been a focus for drug development. Accordingly, treatment is primarily supportive. In contrast, many bacterial zoonoses can be treated with antibiotics.

Prevention
- Vaccines are established for only a minority of zoonotic diseases. Prevention is best achieved by limiting exposure to reservoirs and vectors for transmission of infection.

Zoonoses, derived from the Greek words for animal *(zoo)* and the suffix modification indicating a state or condition *(sis),* are infectious diseases of humans that originate in animals. Infectious diseases that originate in humans and move into other animals are commonly described as reverse zoonoses. The majority of emerging viral diseases, up to 70%, represent zoonoses, with such prominent examples as human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS), influenza, West Nile virus (WNV) encephalitis, Nipah, Hendra, severe acute respiratory syndrome (SARS), Ebola, Marburg, hantavirus pulmonary syndrome (HPS) (Sin Nombre virus), Zika, and rabies. Common examples of nonviral zoonoses include Lyme disease (*Borrelia burgdorferi* in North America, *Borrelia afzelii* and *Borrelia garinii* in Europe), cat-scratch disease *(Bartonella henselae),* new variant Creutzfeldt-Jakob disease (vCJD), salmonellosis, and toxoplasmosis. Although secondary microbial contamination of agricultural products can cause significant disease, the term *zoonosis* does not apply unless there is direct transmission to humans from an infected animal.[1]

The majority of zoonotic disease can be attributed to anthropogenic change. Loss of wildlife habitat to development and consumption of bushmeat, necessitated by poverty or due to cultural preference, increase opportunities for cross-species jumps. Global warming may also increase the geographic range of phlebotomous arthropod vectors, such as mosquitos and ticks that serve as reservoirs and vectors for infectious agents. Given that there are more than 50,000 vertebrate species, for example, if we were to assume an average of 20 endemic viruses per vertebrate species, the potential reservoir of vertebrate viruses could be estimated at 1 million. Although it is unlikely all of them can be transmitted to humans and cause disease, it is sobering to consider the challenge of detecting and responding even to 1% of them—10,000 novel viruses.

ONE HEALTH INITIATIVE

The connection between human and animal microbiology was originally recognized by Virchow and Osler in the 1800s. The relationship has been emphasized through the One Health Initiative, which promotes coequal collaborations between practitioners and researchers in human and comparative medicine, and surveillance programs involving wildlife, domestic animals, and humans.[2,3] The catalytic event for the Initiative was the 1999 WNV outbreak in New York City, where two independent lines of research investigation converged. One that focused on high mortality in native corvids and exotic birds in the Bronx Zoo ultimately led to the culture and identification of the virus by the US Department of Agriculture (USDA). The other focused on human encephalitis cases that were initially attributed to the St. Louis encephalitis virus based on serology. WNV was subsequently implicated when brain material of victims was sequenced by Lipkin and colleagues at the University of California.[4] The cause of the human outbreak would have been ascertained earlier if the veterinary and medical practitioners had collaborated in sharing data and samples. A series of national and international meetings focused on emerging infectious diseases and concerns that the use of antibiotics as growth promoters in agriculture was promoting the development of antimicrobial resistance culminated in the One Health Resolution, signed by the presidents of the American Medical Association and American Veterinary Medical Association, with endorsements from the Centers for Disease Control and Prevention, the USDA, and the European Union.[5–7]

MECHANISMS OF TRANSMISSION

Mechanisms of transmission of zoonotic agents vary widely. Many are linked to food collection, processing, or consumption. The most dramatic examples are diseases associated with the slaughter and consumption of wild animals (bushmeat), such as Ebola, Marburg, SARS, monkeypox, and tularemia; however, less exotic meats are associated with transmission of *Salmonella,* highly pathogenic *Escherichia coli,* and prion diseases (new vCJD). Phlebotomous arthropods such as mosquitos, ticks, and flies may also serve as vectors for transmission of bacteria and viruses from birds and mammals to humans. Prominent examples include WNV, St. Louis encephalitis virus, tick-borne encephalitis virus (TBEV), Zika virus, Powassan virus, and *B. burgdorferi* (Lyme disease). Direct transmission can occur through exposure to infected urine or feces, as in

leptospirosis, toxoplasmosis, lymphocytic choriomeningitis, or HPS; through wound inoculation as in *Bartonella* infection (cat-scratch fever); or in rabies, the oldest recorded example of zoonotic disease and the only common one transmitted directly from infected animals to human by bite.

FACTORS IN THE EMERGENCE OF ZOONOTIC DISEASES

Travel and trade are increasingly global, carrying pathogens in addition to passengers and products to new locations. John F. Kennedy International Airport, for example, one of two international airports in the greater New York metropolitan area, receives nonstop flights from >100 international destinations and annually serves >12 million international passengers.[8] Similar traffic data apply in other major metropolitan areas. Given that an infected individual, mosquito, or other cargo can cross the world in less than 24 hours, clinicians and public health practitioners must be prepared to encounter known and novel agents in virtually any context.

The advent of global agribusiness and urbanization are also important factors in zoonotic diseases. The international food trade has burgeoned by more than 200% since 1975.[9] A hundred years ago, most fresh food was produced and consumed within a radius of a few kilometers. It is now not unusual for individuals to consume plants and animals harvested thousands of kilometers away.[11] Contamination of meat with prions, influenza viruses, and Rift Valley fever virus has been documented in international trade of livestock.[12] The centralization of food production and processing, particularly of ground meat or raw fruits and vegetables, has resulted in outbreaks of infectious diseases that may be distributed over large geographic areas.

Illegal trafficking in wildlife, as pets or food, is difficult to monitor. However, annual sales estimates in the United States alone exceed $10 billion for pets and $15 billion for bushmeat.[13] Analysis of bushmeat from bats, rodents, and primates confiscated in major ports has revealed evidence of foamy viruses, herpesviruses, and pathogenic bacteria.[14] Imported pets have been linked to outbreaks of human infection with poxviruses, *Salmonella,* and other pathogens.[14]

Attention has also increasingly focused on the role of land-use dynamics in infectious disease emergence.[15] Deforestation, the expansion of agriculture, and the extractive industries, particularly in tropical regions with high wildlife biodiversity, have led directly or indirectly to the emergence of HIV/AIDS, Nipah virus, and filoviruses.[16,17] The growth of suburbs in areas once only sparsely populated, particularly in the Northeastern United States, has been associated with an increase in the incidence of Lyme disease.

Global warming is already extending the geographic range of mosquitos and ticks that harbor and transmit plasmodia and arboviruses, resulting in outbreaks of malaria, dengue, and yellow fever in new locations.[18] Recent examples in North America include the appearance of dengue fever in Florida in 2010[19,20] and a surge in cases of West Nile encephalitis in Texas in 2012.[21] Mass migration due to war, natural disaster, poverty, and desertification can lead to increases in population density not only of humans but also of disease vectors, such as rodents and ectoparasites that carry pathogenic viruses and bacteria. In concert, these factors, malnutrition, lack of access to or refusal of vaccines, and exposure to contaminated food and water have enabled the emergence and transmission of infectious diseases.[22,23]

PREDICTION AND EARLY DETECTION OF EMERGING AND REEMERGING ZOONOTIC DISEASES

Rapid recognition and response are critical to reducing the mortality, morbidity, and economic and social costs of zoonotic outbreaks. An important factor in early outbreak detection has been the advent of tools for internet-based infectious disease surveillance. The first of these was ProMED-mail (Programme for Monitoring Emerging Infectious Diseases), created in 1994, which provides continuous, free email updates on new or evolving outbreaks and epidemics[24] in people, domestic animals, and wildlife. Reports submitted by readers are curated by a panel of experts who post submissions with commentary in several languages to a listserv of subscribers in close to 200 different countries. Another program, GPHIN (Global Public Health Intelligence Network),[25] a fee-based service, scans news services worldwide in several languages for information concerning outbreaks.

HealthMap[26] integrates reports from news media, ProMED-mail, and official documents into a user-friendly map that displays real-time updates of disease emergence. HealthMap also allows for public submission observations via its website or cellular phone applications.

An ideal surveillance system for zoonotic disease is one that allows identification of potential health threats before they move into the human population. By considering factors implicated as drivers in the emergence of zoonotic diseases, such as human demographics, agricultural production, land-use change, travel and trade patterns, climate, and wildlife distribution, risk algorithms can be developed and used to focus surveillance on sites, populations, professions, species of domestic animals, and wildlife in which there is an increased probability of known or novel high-threat pathogen emergence.[27] The two largest research programs with this focus are PREDICT, sponsored by the US Agency for International Development, and PREEMPT, sponsored the Defense Advanced Research Projects Agency.[27a,27b] PREDICT supports zoonotic surveillance and laboratory capacity in the developing world.[28] PREEMPT will develop models of viral emergence and strategies for eliminating potential human pathogens in wildlife before they jump to humans.[29] The global acknowledgment of the importance of rigorous, coordinated infectious disease surveillance, early detection, and transparency in data sharing was underscored in the International Health Regulations of 2005, signed by all member states of the United Nations.[30]

ZOONOTIC DISEASES

A chapter concerned with infectious agents that share the capacity to jump host species from domestic animals or wildlife into humans could be organized according to agent, mechanism of transmission, or clinical presentation. This chapter includes all three approaches. The following text provides an overview of a representative set of zoonotic diseases associated with bats, rodents, and other wildlife and domesticated animals. It is by no means complete, and others might highlight different choices. Nonetheless, it will provide a framework for thinking about the range of zoonotic diseases and the factors that contribute to their emergence and control. Table 317.1 indicates routes of transmission and associated syndromes.

INFECTIONS ASSOCIATED WITH WILDLIFE

Bats

Bats, order Chiroptera, comprising more than 1200 species, represent approximately 20% of mammalian species diversity and are found on every continent except Antarctica. They are divided into two suborders: the Megachiroptera (fruit bats and flying foxes) and the Microchiroptera (insectivorous and vampire bats). Bats are unique among mammals in their ability to fly, tendency to aggregate at high density, and capacity to harbor a wide range of viruses without apparent disease. The physiology of bats is poorly understood, and their tolerance for persistent infection with viruses that cause fatal disease in other mammals is an enigma. However, this is likely to change with recent investments in bat genomic sequencing and systems biology.

A wide range of highly pathogenic RNA viruses have been found to be carried by bats: henipaviruses associated with equine and human infections in Australia (Hendra virus); Nipah virus, responsible for human and pig infections in Malaysia and human infections in Bangladesh; filoviruses associated with human and great ape infections in central Africa (Ebola virus and Marburg virus); rabies virus; and the coronaviruses implicated in SARS and Middle East respiratory syndrome (MERS), which caused a recent outbreak of fatal respiratory and renal disease in the Middle East. The route of transmission can vary, even for the same virus. In Malaysia, farm workers became infected with Nipah virus through exposure to pigs that had consumed contaminated droppings of frugivorous bats; in Bangladesh, where pigs are not farmed, human Nipah virus infection has been associated with consumption of palm sap beverages contaminated by bats. In North America, silver-haired bats transmit rabies virus via a bite wound. Humans are typically infected with filoviruses (e.g., Ebola) through exposure to infected

TABLE 317.1 Examples of Zoonotic Diseases: Agents and Vectors

VECTOR		AGENT FAMILY	AGENT	DISEASE
Arthropod	Mosquito	Bunyaviridae	La Crosse encephalitis virus, California encephalitis virus	Encephalitis
			Rift Valley fever virus	Hemorrhagic fever
		Flaviviridae	Japanese encephalitis virus, St. Louis encephalitis virus, West Nile virus	Encephalitis
			Dengue virus, yellow fever virus, Zika virus	Hemorrhagic fever
		Togaviridae	Eastern equine encephalitis virus, western equine encephalitis virus, Venezuelan equine encephalitis virus, chikungunya virus, o'nyong-nyong fever virus	Encephalitis
	Tick	Bunyaviridae	Crimean-Congo hemorrhagic fever virus	Hemorrhagic fever
		Flaviviridae	Tick-borne encephalitis virus, Powassan encephalitis virus	Encephalitis
		Spirochaetaceae	Omsk hemorrhagic fever virus, Kyasanur Forest virus, Langat virus	Hemorrhagic fever
			Borrelia	Lyme disease
	Flea	Enterobacteriaceae	*Yersinia pestis*	Hemorrhagic fever (plague)
Mammal	Rodent	Arenaviridae	Lassa fever virus, Guanarito virus, Junin virus, Machupo virus, Sabia virus, Lujo virus	Hemorrhagic fever
			Lymphocytic choriomeningitis virus	Meningitis, encephalitis
		Bunyaviridae	Dobrava-Belgrade virus, Hantaan virus, Puumala virus, Seoul virus	Hemorrhagic fever
			Sin Nombre virus	Pulmonary
		Spirochaetaceae	*Leptospira*	Leptospirosis
	Rabbit	Francisellaceae	*Francisella tularensis*	Tularemia
	Bat	Filoviridae	Ebola virus, Bundibugyo virus, Sudan virus, Tai Forest virus, Marburg virus	Hemorrhagic fever
		Rhabdoviridae	Rabies virus, Chandipura virus	Encephalitis
		Paramyxoviridae	Hendra virus, Nipah virus	Pulmonary, encephalitis
		Coronaviridae	Severe acute respiratory syndrome (SARS) coronavirus, Middle Eastern coronavirus	Pulmonary
	Cattle	Prions	Bovine spongiform encephalopathy prion	Neurodegeneration
	Cat	Bartonellaceae	*Bartonella*	Hemorrhagic fever
		Sarcocystidae	*Toxoplasma*	Toxoplasmosis
Avian	Bird	Orthomyxoviridae	Influenza virus	Pulmonary

primate meat; however, there are instances in which infection may have occurred through consumption of infected bats or exposure to bat excreta in close quarters (e.g., caves and abandoned mines).

The SARS coronavirus is presumed to have entered the human population through intermediate species (civets) in live-animal markets. The major reservoir for the MERS coronavirus is the dromedary camel.[31,32] Although there are examples of human-to-human transmission of filoviruses and henipaviruses through contact with blood or other bodily fluids, the only bat-associated pathogen known to have established efficient transmission within the human population is the SARS coronavirus. Nipah virus, Hendra virus, SARS coronavirus, and MERS coronavirus cause respiratory disease and spread via aerosol. All are associated with high morbidity and mortality. However, the primary site of pathology in SARS and MERS is the lung, whereas Nipah and Hendra viruses cause encephalitis. Ebola virus and Marburg virus cause disseminated intravascular coagulation, resulting in hemorrhagic shock and multiorgan failure. Ebola virus, Marburg virus, and the arenaviruses and hantaviruses, described in the next section, are known collectively as hemorrhagic fever viruses in accord with the clinical manifestations of disease.

A diagnosis can be made based on clinical presentation in contexts in which others with similar presentation (including animals) have had a laboratory diagnosis. Although serology can be definitive, a laboratory diagnosis is typically made by means of an agent-specific polymerase chain reaction (PCR) assay. There is no established effective therapy for the diseases caused by SARS, MERS, Nipah, Hendra, Ebola, or Marburg viruses. A recombinant vesiculostomatitis virus vaccine expressing the surface glycoprotein of the Zaire ebolavirus was 100% effective in preventing disease in an open label trial in Guinea.[33] Monoclonal antibodies may reduce morbidity and mortality in disease caused by Nipah and Hendra viruses; therefore it is likely that a vaccine that elicits responses to similar antigenic targets would be effective. Rabies is typically fatal once the virus has entered the central nervous system; however, postexposure prophylaxis is effective, particularly when the exposed individual receives not only the vaccine, but also rabies immune globulin injected in proximity to the puncture wound.[34,35]

Rodents

Rodents, like bats, are globally distributed. They are the largest order of mammals, comprising more than 2200 species, and are implicated in transmission of both viruses and bacteria. The rodent-associated arenaviruses (named for their sandy appearance with electron microscopy; *arena* means "sand" in Latin) causing human disease include the Lassa fever virus, endemic in Western Africa; the lymphocytic choriomeningitis virus, found in both the Eastern and Western Hemispheres; and several South American viruses including Guanarito, Junín, Machupo, and Sabia. Another African arenavirus, Lujo virus, is presumed, but not proven, to have a rodent reservoir. Lassa fever is clinically similar to Ebola and Marburg; however, Lassa fever virus infection may be asymptomatic in up to 80% of cases, whereas asymptomatic filovirus infection is uncommon. The South American arenaviruses can cause hemorrhagic fever, but can also be associated with asymptomatic infection. Lymphocytic choriomeningitis virus has been implicated in aseptic meningitis and birth defects, particularly in the central nervous system. Although there is no specific drug for arenavirus infection, the nucleoside analogue ribavirin may have efficacy. Passive immunotherapy with hyperimmune plasma has been useful in Argentinean hemorrhagic fever (Junin virus infection).[36]

Leptospira, a genus named for its morphology (*leptos* is "thin" in Greek; *spiral* is "coil" in Latin), consists of spirochetes that persistently infect rodents, concentrating in the kidneys. Infectious organisms are excreted in urine, collect in standing water, and enter humans and other animals either through breaks in the skin or via the alimentary canal. Infection is correlated with the potential for exposure; hence, leptospirosis is common year round in the tropics and during warm wet months in temperate climate zones. Food markets, particularly those where rodents congregate and where there is opportunity for urine from infected animals to contaminate standing water, are high-risk environments for contraction of disease. The onset of disease is heralded by nonspecific symptoms such as fever, malaise, and headache. It may progress to meningitis, vasculitis, renal and liver failure, and disseminated intravascular coagulation. Antibiotics (penicillin, amoxicillin, and doxycycline) are effective in prophylaxis and as a therapeutic intervention. There are vaccines for some serotypes.

The Bunyaviridae family of RNA viruses includes several important human pathogens—hantaviruses, nairoviruses, and phleboviruses. Hantaviruses are transmitted through contact with rodent excreta; the other clinically significant bunyaviruses are transmitted through blood exchange by arthropod vectors, including mosquitos, ticks, and flies. Hantaviruses (named for the Hantan river in South Korea, where the first hantaviruses were identified) may cause hemorrhagic fever with renal failure (hemorrhagic fever with renal syndrome [HFRS])[37] or an acute respiratory distress syndrome (HPS).[38] HFRS is more common in Africa, Asia, and Europe. HPS has been reported only in North America. There is no hantavirus-specific drug or vaccine. Recovery from HFRS is not uncommon with supportive care; however, HPS is typically fatal. Crimean-Congo hemorrhagic fever virus, a nairovirus,

is distributed throughout Asia and Africa.[39] A wide range of small mammals may serve as reservoirs; domestic sheep, goats, cattle, and horses are typically intermediate hosts. The agent is most commonly transmitted by ticks; however, outbreaks have been linked to preparation or consumption of infected meat.[40] Manifestations of disease range from mild influenza-like illness to hemorrhagic fever.

Tick-borne encephalitis is a meningoencephalitis due to infection with the flavivirus TBEV.[41] TBEV is found in Europe and Asia. It is transmitted to humans from a wide range of infected hosts, including sheep, deer, and rodents. Infection is rarely fatal; however, neurologic sequelae are not uncommon. There are effective vaccines but no known antivirals.

The most common tick-borne illness in the United States is Lyme disease.[42] In North America, the causative agent is the spirochete *B. burgdorferi,* carried by the tick *Ixodes scapularis.* In Europe and Asia, the corresponding agents are *B. afzelii and B. garinii,* carried by *Ixodes ricinus* and *Ixodes persulcatus,* respectively. Early signs and symptoms of disease may include fever, lassitude, and headache. Some individuals have a classic "bull's-eye" skin rash known as erythema chronicum migrans, characterized by redness in the center and the periphery with central clearing. Later stages of the disease may include facial weakness (Bell palsy), peripheral neuropathy, and encephalomyelitis. Rodents are the reservoir for the spirochete; however, deer are also important to its life cycle as alternate reservoir hosts. Thus, human transmission is most common in suburban and rural areas, particularly where the density of vegetation is sufficiently thick to harbor large concentrations of rodents. Diagnosis is straightforward in the presence of the characteristic rash when there is a history of travel to an endemic area and a tick bite. However, many patients will not recall a tick bite, and up to 20% may not have the rash. Direct detection of the causative organism by means of culture or PCR analysis of the rash is definitive. Serology, the mainstay of laboratory diagnosis, is frequently inconclusive or misleading.[43]

Francisella tularensis, the causative agent of tularemia (also known as rabbit fever), infects a wide range of vertebrate and invertebrates. The most important reservoirs are rodents, deer, and rabbits. Humans become infected through contact with infected animals or hematophagous vectors, including mosquitoes, ticks, or flies. Thus, hunters, hikers, and farmers are at highest risk in endemic areas. Outbreaks of severe respiratory disease have been described in landscapers. The manifestations of infection vary with the route of exposure. Cutaneous inoculation typically results in a vesicular rash, which may or may not ulcerate, and regional lymphadenopathy. Ingestion results in oropharyngeal lesions. Inhalation can lead to fatal pneumonia. Ocular inoculation results in conjunctivitis. Without antibiotic treatment, some strains disseminate systemically and are associated with up to 30% mortality. The diagnosis is typically made based on clinical presentation, with confirmation by means of PCR or culture. The agent is sensitive to ciprofloxacin, aminoglycosides, and chloramphenicol. Vaccines are in development due to concerns that *F. tularensis* may be weaponized.[44]

Yersinia pestis, the causative agent of plague, is found in rodents throughout the world with the exception of Oceania. Infection is transmitted to humans primarily by fleas. However, transmission can also occur through ingestion and inhalation. Periodic pandemics, including the Black Death, have cost hundreds of millions of lives. Although outbreaks continue in the developing world, the majority of current reports in the United States note infections in single individuals. The manifestations of disease can vary from an influenza-like mild fever and lymphadenopathy (buboes) to pneumonia, shock, disseminated intravascular coagulation, and tissue necrosis. The diagnosis is typically made based on clinical presentation, with confirmation by means of PCR or culture. Like *F. tularensis, Y. pestis* is sensitive to ciprofloxacin, aminoglycosides, and chloramphenicol. It has the dubious distinction of being one of the first microbes to be used as a biologic weapon, in the 14th century, and remains a biosecurity concern.[45]

DISEASES ASSOCIATED WITH AGRICULTURAL AND OTHER DOMESTIC ANIMALS

Zoonotic agents associated with livestock, poultry, and companion animals include bacteria, fungi, parasites, and prions. Industrialization of food production has increased the probability of meat cross-contamination, in addition to animal-to-animal infection on feedlots. Outbreaks of disease due to *E. coli,* including the potentially fatal hemolytic-uremic syndrome, are commonly linked to contaminated ground beef. Infected poultry and eggs are frequently associated with outbreaks of *Salmonella* infection. The use of antibiotics as growth promoters in agriculture also encourages the emergence of antibiotic-resistant bacteria that contribute to human morbidity and mortality associated with infectious disease.[7]

vCJD is a progressive, fatal brain disorder caused by exposure to misfolded proteins (prions) in cattle. vCJD and an analogous disease known as bovine spongiform encephalopathy (BSE) catalyze conformational changes in host proteins. BSE was first identified in the United Kingdom in 1986 and peaked in incidence in 1993. The original infection is presumed to have been introduced when cattle were fed with meat (offal) from infected sheep or cows. An estimated 400,000 cows with BSE are estimated to have entered the food chain before the outbreak was terminated by culling cattle with behavior indicative of BSE, reducing the age of slaughter (so that titers would be lower in the event that an infected animal was inadvertently used for human consumption), and eliminating the practice of feeding offal to ruminants in 1997. At least 227 people exposed to BSE contracted vCJD. Susceptibility to disease is determined at least in part by the prion protein (PrP) genotype. The peak incidence of vCJD was observed in 2000 and tapered thereafter. Some investigators hold that a large wave of new cases is unlikely in the absence of recurrence of BSE. However, others note that the incubation period of kuru, a prion disorder associated with ritual cannibalism, due to essentially the same agent, may be as long as 27 years. The diagnosis of vCJD is made through brain or tonsillar biopsy based on histologic findings and/or the presence of protease-resistant PrP. There is no effective treatment or vaccine for prion diseases.

Rift Valley fever virus, a bunyavirus transmitted by mosquitoes, chiefly affects livestock but can cause human disease (Rift Valley fever), ranging from a mild febrile illness to meningitis or hemorrhage and multiorgan failure. Originally reported in Kenya, the virus has expanded in distribution across sub-Saharan Africa and the Arabian Peninsula.

A detailed discussion of influenza virus is beyond the scope of this chapter. Furthermore, influenza is not typically considered a zoonotic disease because human-to-human transmission is efficient and represents the large majority of cases of influenza A. Nonetheless, both birds and pigs play key roles in the maintenance of existing strains and the emergence of new ones. Only influenza A viruses are associated with pandemic disease, presumably because they have a higher propensity to evolve toward antigenic diversity and thus evade host immune surveillance than influenza B and C viruses. Wild aquatic birds are the natural hosts of the classic seasonal influenza viruses H1N1 and H3N2. Infection of free-range pigs by migrating aquatic birds or in live-animal markets where they may be housed near aquatic birds can lead to genetic reassortment (when more than one type of influenza virus is present) and adaption to humans. H5N1, popularly known as avian influenza, only rarely results in human disease but is frequently fatal when it does. A wide range of diagnostic assays is available for detection of influenza viruses. Vaccines are designed twice each year to reflect strains predicted to predominate during the influenza season in the Southern and Northern Hemispheres. Their efficacy fluctuates with the accuracy of those predictions, but, as a rule, they are less effective in inducing a protective immune response in the elderly. Efforts are underway to create universal influenza vaccines based on conserved regions of the virus hemagglutinin rather than those that evolve to evade the immune system.[46] The drug oseltamivir is effective for many strains.

Up to 30% of the world's population may have been exposed to the protozoan *Toxoplasma gondii*, including more than 60,000,000 people in the United States. Infection is contracted through ingestion of contaminated food or contact with feces of domestic cats, the natural host. In most instances, infection is asymptomatic or associated with a transient influenza-like illness; however, with immunosuppression in the context of HIV/AIDS, chemotherapy, or pregnancy, the parasite can cause a mass lesion in the brain, leading to focal neurologic deficits and seizures. Infection of the fetus during pregnancy can result in

miscarriage and abnormal brain development. Treatment varies with the immunologic status of the patient.

Eastern equine encephalitis virus (EEEV), western equine encephalitis virus (WEEV), and Venezuelan equine encephalitis virus (VEEV) are mosquito-borne alphaviruses that infect a wide range of vertebrates. Birds are the natural reservoirs. The nomenclature reflects the observation that horses with encephalitis are frequent sentinels for risk of human disease and roughly approximates the geographic distribution of the virus. EEEV is found throughout North, Central, and South America but is concentrated in the United States east of the Continental Divide. WEEV is found in the western United States. VEEV is found primarily in Central and South America. All are associated primarily with an influenza-like illness but may, in a small proportion of cases, progress to encephalitis. WNV is a mosquito-transmitted flavivirus associated with only mild, sporadic disease until the 1990s, when virulent strains appeared first in Europe and then in North America. Many vertebrate species are susceptible to infection; however, the primary reservoir is birds. Although most infections are asymptomatic or associated with mild influenza-like illness (West Nile fever), encephalitis and poliomyelitis can occur in individuals who are immunologically compromised because of advanced age or underlying medical conditions. Only supportive therapy is available for EEEV, WEEV, VEEV, and WNV encephalitis. Vaccines have been developed but are typically not used in humans, except where biomedical researchers concentrate VEEV and are at high risk for exposure.

Zika virus, identified in a rhesus monkey in 1947, is named for its site of isolation within the Zika forest in Uganda. It has been implicated in microcephaly and other neurodevelopmental damage in children whose mothers were infected during pregnancy and in Guillain-Barré syndrome in infected adults. Zika virus has both a sylvatic and an urban cycle. In the former, the virus is maintained in nonhuman primates by *Aedes* and *Anopheles* mosquitos. Humans appear to be the only reservoir in the urban cycle. Human-to-human transmission is most commonly mediated by *Aedes* mosquitos, but humans also can become infected through exposure to infected semen or blood products.[47] There is no known treatment for Zika; however, several vaccines are in development.

CONCLUSIONS

The majority of emerging and reemerging infectious diseases are zoonoses. Zoonoses are likely to increase in frequency owing to anthropogenic factors that include incursion into wildlife habitats, globalization of travel and trade, and climactic changes that influence the distribution of arboviral vectors, including mosquitos, phlebotomous flies, and ticks. Antimicrobial resistance is not a zoonosis in the strict sense of the term. Nonetheless, the threat of antimicrobial resistance is clearly exacerbated by the misuse of antibiotics in animal husbandry.

In viral zoonoses, interventions are currently limited to supportive care and in some instances, such as rabies and some hemorrhagic fevers, to immunotherapy with hyperimmune globulin or monoclonal antibodies. In contrast, specific antibiotic therapy has utility in bacterial zoonoses. Investments in biodefense focused on understanding viral biology and the development of antiviral drugs are rapidly leading to specific interventions that will reduce the morbidity and mortality of emerging viral infections. Accordingly, early differential diagnosis will become increasingly important not only for outbreak containment but also for ensuring that patients receive appropriate treatment.

References

1. Khabbaz R, Bell BP, Schuchat A, et al. Emerging and reemerging infectious disease threats. In: *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. 2015:158–177.
2. One Health Initiative. www.onehealthinitiative.com.
3. Smolinski MS, Hamburg MA, Lederberg J, eds. *Microbial Threats to Health: Emergence, Detection, and Response*. Washington (DC): National Academies Press; 2003.
4. Briese T, Jia XY, Huang C, et al. Identification of a Kunjin/West Nile-like flavivirus in brains of patients with New York encephalitis. *Lancet*. 1999;354:1261–1262.
5. Centers for Disease Control and Prevention (CDC). One Health History. https://www.cdc.gov/onehealth/basics/history/index.html.
6. Institute of Medicine (IOM). *Emerging Viral Diseases: The One Health Connection: Workshop Summary*. Washington (DC): IOM; 2015.
7. Combating Antimicrobial Resistance. *A One Health Approach to a Global Threat: Proceedings of a Workshop*. Washington (DC): National Academies Press; 2017.
8. U.S. Department of Transportation, Bureau of Transportation Statistics. U.S. Airlines and Foreign Airlines U.S. Passengers Continue to Increase from 2009; posted August 15, 2012. https://www.rita.dot.gov/bts/sites/rita.dot.gov.bts/files/press_releases/2012/bts017_12/html/bts017_12.html.
9. United Nations Department of Economic and Social Affairs. World Population Prospects, the 2010 Revision; posted August 15, 2011. http://esa.un.org/wpp/Documentation/WPP%202010%20publications.htm.
10. Deleted in review.
11. Maki DG. Don't eat the spinach—controlling foodborne infectious disease. *N Engl J Med*. 2006;355:1952–1955.
12. Newell DG, Koopmans M, Verhoef L, et al. Food-borne diseases—the challenges of 20 years ago still persist while new ones continue to emerge. *Int J Food Microbiol*. 2010;139(suppl 1):S3–S15.
13. U.S. Department of State, Wildlife Trafficking. Homepage. Posted October 2016. https://www.state.gov/e/oes/ecw/wlt/.
14. Smith KM, Anthony SJ, Switzer WM, et al. Zoonotic viruses associated with illegally imported wildlife products. *PLoS ONE*. 2012;7:e29505.
15. Karesh WB, Dobson A, Lloyd-Smith JO, et al. Ecology of zoonoses: natural and unnatural histories. *Lancet*. 2012;380:1936–1945.
16. Chua KB, Goh KJ, Wong KT, et al. Fatal encephalitis due to Nipah virus among pig-farmers in Malaysia. *Lancet*. 1999;354:1257–1259.
17. Pulliam JR, Epstein JH, Dushoff J, et al. Agricultural intensification, priming for persistence and the emergence of Nipah virus: a lethal bat-borne zoonosis. *J R Soc Interface*. 2012;9:89–101.
18. Shuman EK. Global climate change and infectious diseases. *N Engl J Med*. 2010;362:1061–1063.
19. Centers for Disease Control and Prevention. Locally acquired dengue—Key West, Florida, 2009-2010. *MMWR Morb Mortal Wkly Rep*. 2010;59:577–581.
20. Adalja AA, Sell TK, Bouri N, et al. Lessons learned during dengue outbreaks in the United States, 2001-2011. *Emerg Infect Dis*. 2012;18:608–614.
21. Centers for Disease Control Telebriefing on West Nile Virus Update; posted August 29, 2012. http://www.cdc.gov/media/releases/2012/t0829_west_nile_update.html.
22. Jones KE, Patel N, Levy M, et al. Global trends in emerging infectious diseases. *Nature*. 2008;451:990–994.
23. Morse SS. Factors and determinants of disease emergence. *Rev - Off Int Epizoot*. 2004;23:443–451.
24. Madoff LC. ProMED-mail: an early warning system for emerging diseases. *Clin Infect Dis*. 2004;39:227–232.
25. Mykhalovskiy E, Weir L. The Global Public Health Intelligence Network and early warning outbreak detection: a Canadian contribution to global public health. *Can J Public Health*. 2006;97:42–44.
26. Freifeld CC, Mandl KD, Reis BY, et al. HealthMap: global infectious disease monitoring through automated classification and visualization of Internet media reports. *J Am Med Inform Assoc*. 2008;15:150–157.
27. Lipkin WI. The changing face of pathogen discovery and surveillance. *Nat Rev Microbiol*. 2013;11:133–141.

27a. USAID. Emerging Pandemic Threats; last updated May 24, 2016. https://www.usaid.gov/news-information/fact-sheets/emerging-pandemic-threats-program. Accessed July 3, 2019.

27b. Ringeisen B. PREventing EMerging Pathogenic Threats (PREEMPT). https://www.darpa.mil/program/preventing-emerging-pathogenic-threats. Accessed July 3, 2019.

28. USAID. Emerging Pandemic Threats 2 Program; posted January 11, 2016. https://www.usaid.gov/news-information/fact-sheets/emerging-pandemic-threats-2-program.
29. Defense Advanced Research Projects Agency (DARPA). PREventing Emerging Pathogenic Threats (PREEMPT) Proposers Day; posted January 30, 2018. https://www.darpa.mil/attachments/PREEMPTOverview.pdf.
30. World Health Organization (WHO). Strengthening health security by implementing the International Health Regulations (2005); posted December 2005. www.who.int/ihr/about/en.
31. Reusken CB, Haagmans BL, Mueller MA, et al. Middle East respiratory syndrome coronavirus neutralising serum antibodies in dromedary camels: a comparative serological study. *Lancet*. 2013;13:859–866.
32. Alagaili AN, Briese T, Mishra N, et al. Middle East respiratory syndrome coronavirus infection in dromedary camels in Saudi Arabia. *MBio*. 2014;5:e00884–14.
33. Henao-Restrepo AM, Camacho A, Longini IM, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). *Lancet*. 2017;389:505–518.
34. World Health Organization (WHO). Rabies: Administration of rabies immunoglobulin. www.who.int/rabies/human/adminimmuno/en/.
35. World Health Organization (WHO). Rabies: Guide for post-exposure prophylaxis. www.who.int/rabies/human/postexp/en.
36. Enria DA, Briggler AM, Fernandez NJ, et al. Importance of dose of neutralizing antibodies in treatment of Argentine haemorrhagic fever with immune plasma. *Lancet*. 1984;2:255–256.
37. Zou LX, Chen MJ, Sun L. Haemorrhagic fever with renal syndrome: literature review and distribution analysis in China. *Int J Infect Dis*. 2016;43:95–100.
38. Hartline J, Mierek C, Knutson T, et al. Hantavirus infection in North America: a clinical review. *Am J Emerg Med*. 2013;31:978–982.
39. Bente DA, Forrester NL, Watts DM, et al. Crimean-Congo hemorrhagic fever: history, epidemiology, pathogenesis, clinical syndrome and genetic diversity. *Antiviral Res*. 2013;1000:159–189.
40. Fazlalipour M, Baniasadi V, Mirghiasi SM, et al. Crimean-Congo hemorrhagic fever due to consumption of raw meat: case reports for east-north of Iran. *Jpn J Infect Dis*. 2016;69:270–271.
41. Mansfield KL, Johnson N, Phipps LP, et al. Tick-borne encephalitis virus – a review of an emerging zoonosis. *J Gen Virol*. 2009;90(Pt 8):1781–1794.
42. Shapiro ED. Clinical practice. Lyme disease. *N Engl J Med*. 2014;370:1724–1731.
43. Marques AR. Laboratory diagnosis of Lyme disease: advances and challenges. *Infect Dis Clin North Am*. 2015;29:295–307.
44. Centers for Disease, Control & Prevention. Tularemia – United States, 2001-2010. *MMWR Morb Mortal Wkly Rep*. 2013;62:963–966.
45. Riedel S. Biological warfare and bioterrorism: a historical review. *Proc (Bayl Univ Med Cent)*. 2004;17:400–406.
46. Coughlan L, Palese P. Overcoming Barriers in the Path to a Universal Influenza Virus Vaccine. *Cell Host Microbe*. 2018;24:18–24.
47. Boyer S, Calvez E, Chouin-Carneiro T, et al. An overview of mosquito vectors of Zika virus. *Microbes Infect*. 2018;20:646–660.

318 Protection of Travelers

David O. Freedman

SHORT VIEW SUMMARY

- A pretravel office visit with an adult traveler to the developing world should follow a structured approach.

PERFORM RISK ASSESSMENT

- Exact itinerary, including regions within each country to be visited, dates of travel to assess risk of seasonal diseases, age, past vaccination and travel history, immune status, underlying illnesses, current medications, pregnancy status, allergies, purpose of trip, risk exposures (blood, body fluids, adventure or extensive outdoor exposures), urban versus rural travel, type of accommodations, travelers' risk tolerance, and financial limitations that may necessitate prioritization of interventions

ADMINISTER IMMUNIZATIONS

- Routine vaccinations that are not up-to-date, including measles-mumps-rubella (MMR), tetanus-diphtheria–acellular pertussis (Tdap), pneumococcal, varicella zoster virus
- Indicated routine travel vaccines, including hepatitis A, hepatitis B, typhoid, and influenza
- Indicated specialized vaccines, including yellow fever, rabies, polio, meningococcal, cholera, Japanese encephalitis, and tick-borne encephalitis in certain countries

PROVIDE MALARIA PREVENTION (IF INDICATED)

- Several equally effective drugs of choice may be indicated, including atovaquone-proguanil, mefloquine, and doxycycline. Ascertain which drug is best suited to the individual patient and itinerary.
- Educate on personal protection against arthropods.

TRAVELER'S DIARRHEA

- Recommend food and water precautions, as well as hand hygiene.
- Advise on use of loperamide and oral hydration if needed.
- Prescribe and educate on standby therapy with azithromycin (sometimes a quinolone) only for diarrhea that is disabling and prevents normal activities.

VECTOR-BORNE DISEASES

- Educate on personal protection measures for malaria, dengue, chikungunya, Zika virus infection, leishmaniasis, rickettsial disease, and sleeping sickness

TEACH ESSENTIAL PREVENTIVE BEHAVIORS

- Most travel-related health problems, including vaccine-preventable diseases, can be avoided through simple behaviors initiated by the traveler.
- Educate on appropriate strategies in the following categories (some topics are not applicable to all destinations): bloodborne and sexually transmitted diseases, safety and crime avoidance, transportation-associated and other injury prevention, swimming safety, rabies, skin/wound care, and tuberculosis.

DISCUSS OTHER APPLICABLE HEATH ISSUES

- Educate on and prescribe for altitude illness, motion sickness, traveler's thrombosis, or jet lag.
- Discuss minimal-risk conditions (e.g., hemorrhagic fevers) that are a frequent cause of patient anxiety.

MEDICAL KIT AND MEDICAL CARE ABROAD

- Contents of a personal health kit
- Finding destination medical facilities
- Evacuation insurance and supplemental health insurance

Pretravel management of an international traveler should be based on risk management principles. Prevention strategies and medical interventions need to be individualized according to both the itinerary and factors that are dependent on the traveler. A structured approach to patient interaction (Table 318.1) is the most efficient way to cover the necessary educational and preventive interventions. Because many of these measures will not be initiated until much later at the traveler's destination, clearly printed instructions in lay language are advisable. The worldwide epidemiology of travel-related diseases is constantly changing. A body of knowledge in travel medicine has been published, and online and print resources (Table 318.2) should be consulted frequently[1–3] to keep current.

EPIDEMIOLOGY OF TRAVEL-RELATED ILLNESS

In 2015 international tourist arrivals in all countries exceeded 1.2 billion people. In 2014 the total number of arrivals in countries with emerging markets nearly surpassed the number in developed countries. Depending on the destination, 6% to 87% of travelers become ill across all studies.[4–6] Of four studies that provide the best estimate, 43% to 79% of travelers who frequently visited developing nations (e.g., India, Tanzania, and Kenya) became ill; most of these illnesses were mild and self-limited such as diarrhea, respiratory infections, and skin disorders.[7] Some travelers return to their own countries with preventable life-threatening infections.[8] Yet 20% to 80% of travelers do not seek pretravel health consultation.[9,10] Data about the effect of pretravel advice are limited, although such advice has had a positive effect on the prevention of malaria. Travelers visiting friends and relatives in their country of origin constitute the group with the highest morbidity, especially from malaria and typhoid; this group requires special approaches to illness prevention and education.[11,12] Rates are significantly higher in summer. Approximately 8% of travelers consult a physician either during or after a trip, but less than 1% require hospitalization. Infectious diseases account for up to 10% of morbidity during travel but only 1% of deaths, with malaria the most common disease. Causes of death vary according to the population studied. At destinations that attract elderly adults, cardiovascular events predominate, whereas in developing countries, motor vehicle accidents and drowning prevail.

IMMUNIZATION

The choice of vaccines for an individual traveler is based on risk of exposure to vaccine-preventable diseases on the chosen itinerary; the severity of disease, if acquired; and any risks presented by the vaccine itself. Travelers differ in their tolerance of risk. Requests for immunization