67. Postexposure Prophylaxis for Selected Infectious Diseases

RECOMMENDATION

Postexposure prophylaxis should be provided to selected persons with exposure or possible exposure to Haemophilus influenzae type b, hepatitis A, hepatitis B, meningococcal, rabies, or tetanus pathogens (see ***Clinical Intervention***). See Chapter 66 for recommendations on postexposure prophylaxis against influenza A.

HAEMOPHILUS INFLUENZAE TYPE B DISEASE

Burden of Suffering

The incidence of invasive *H. influenzae* type b (Hib) disease (e.g., meningitis, epiglottitis, septic arthritis) has decreased dramatically in recent years, most likely due to the immunization of infants and young children with effective vaccines, with 1,174 cases reported in 1994.[1] The incidence of invasive Hib disease among children less than 5 years of age decreased from 41/100,000 in 1987 to fewer than 2/100,000 in 1994.[2] Most cases occur during infancy,[3,4] but many children remain susceptible to infection until age 4–5 years. Young children are at especially increased risk if they are exposed to infected persons at home or in day care.[3,5–7] Most secondary cases of Hib disease in household contacts occur within 1–2 weeks of the primary case.[5]

Efficacy of Prophylaxis

Rifampin prophylaxis can reduce the risk of secondary infection in persons exposed to Hib. A randomized controlled clinical trial and an uncontrolled trial have shown that a 4-day antibiotic regimen can reduce both the rate of asymptomatic carriage of Hib and the incidence of secondary infection in household and day care contacts of infected persons.[8,9] Postexposure prophylaxis for Hib may prove unnecessary eventually, given widespread childhood immunization with the Hib conjugate vaccine (see Chapter 65). In addition to protecting the vaccinated child against Hib infection, conjugate vaccine appears to decrease Hib pharyngeal colonization,[10,11] which would also reduce Hib transmission to unvaccinated children.

HEPATITIS A AND B

Burden of Suffering

Epidemics caused by hepatitis A virus (HAV) remain a major public health problem, with 26,796 cases reported in 1994 in the U.S.[1] HAV is transmitted through the fecal-oral route, and the most frequent source of infection is household or sexual contact with a person who has hepatitis A. Day care centers have become an important source of epidemic HAV infection.[12] In the U.S. each year, hepatitis B virus (HBV) causes an estimated 200,000 to 300,000 acute infections and 4,000–5,000 deaths from chronic liver disease and hepatocellular carcinoma.[13] More than 1 million Americans have chronic HBV infection. HBV may be transmitted by perinatal (see Chapter 24), percutaneous, sexual, or mucosal exposure.[14]

Efficacy of Prophylaxis

Since the 1940s, passive immunization with immune globulin (IG), administered within 2 weeks of exposure, has been shown to be an effective means of preventing or markedly attenuating clinical hepatitis A in persons exposed to HAV.[15] Studies in household contacts have shown that IG can reduce the incidence of clinical hepatitis A by 80–90%.[16] The earlier that IG is given after exposure the more likely it is that protection will result.[16] Adverse effects of IG include local symptoms and, less commonly, systemic symptoms such as headache, chills, and nausea.[12] Serious adverse effects with IG have been rare.[13] There is no evidence of transmission of HBV, human immunodeficiency virus, or other viruses in the U.S. by IG prepared for intramuscular injection.[13] Hepatitis C transmission has been reported with intravenous administration of an immune globulin product.[16a]

Immunogenic inactivated hepatitis A vaccines, recently licensed in the U.S., have been shown to be highly protective against hepatitis A (see Chapters 65 and 66).[17,18] Because an adequate immune response does not develop for 1–2 weeks after vaccine administration,[17,19–22] the vaccine alone is likely to be inadequate for postexposure prophylaxis. Vaccine may be given simultaneously with IG for individuals with both immediate and continued risk of hepatitis A. Although studies have reported lower mean antibody titers when the vaccine is administered concomitantly with IG, vaccine seroconversion rates appear to be adequate.[20,23,24]

Administration of hepatitis B immune globulin (HBIG) promptly after exposure and 1 month later has a combined efficacy of about 75% in protecting susceptible persons with perinatal, percutaneous, sexual, or mucosal exposure to HBV.[25–28] Hepatitis B vaccine is highly immunogenic and efficacious and can be used to provide both preexposure and postexposure protection (see Chapters 24, 65, and 66).[29] Two recombinant DNA hepatitis B vaccines are currently licensed in the U.S. and, in recom-

mended dosages, provide similar seroconversion rates. Combined active-passive immunization has the advantage of providing both immediate and long-term protection.[30] For infants born to mothers who are infected with HBV, the combination of HBIG given at birth and hepatitis B vaccine given at birth and ages 1 and 6 months is 85–90% effective in preventing perinatal HBV transmission (see Chapter 24).[31–34] Regimens involving a vaccine series alone have shown 70–85% efficacy in preventing perinatal transmission (see Chapters 24 and 65).

MENINGOCOCCAL INFECTION

Burden of Suffering

Infection with *Neisseria meningitidis* serotypes A, B, C, X, Y, Z, 29-E, and W-135 can lead to meningitis and fulminant septicemia. Meningococcal infections occur sporadically, with 2,886 cases reported in the U.S. in 1994.[1] The estimated incidence during 1989–1991 in the U.S. was 1/100,000 persons annually.[35] The potential exists for epidemic meningococcal disease.

Efficacy of Prophylaxis

Both chemoprophylaxis and vaccination are available for postexposure prophylaxis against meningococcal infection, although vaccines are not routinely recommended for postexposure prophylaxis. Rifampin prophylaxis in contacts of patients with meningococcal infection can reduce the rate of meningococcal colonization, thereby reducing the risk of secondary infection.[36–38] Rifampin dosage schedules effective in eliminating meningococci in adults have included 600 mg taken once daily for 4 days or twice daily for 2 days.[36–40] One study has shown that a single intramuscular dose of ceftriaxone is at least as effective as oral rifampin in eliminating pharyngeal carriage in family contacts;[39] its efficacy has only been confirmed for serogroup A strains.

Due to the relatively long interval (as long as 14–30 days) that can occur between primary and secondary cases,[41,42] meningococcal vaccines also may be efficacious for postexposure prophylaxis against serogroups contained in the vaccine.[43] A quadrivalent vaccine effective against meningococcal serogroups A, C, Y, and W-135,[12,44] is available in the U.S. and has been effective in interrupting epidemic disease in other developed countries.[45,46] The serogroup A component is immunogenic in children ≥3 months of age,[47] but children less than 2 years of age do not always respond to the vaccine's other components. The current vaccine does not provide adequate long-term protection. A satisfactory vaccine to prevent group B meningococcal disease has yet to be developed. One vaccine against group B meningococcus was estimated to be 74% effective in children aged 4–6 years but was not proven ef-

fective in younger children.[48] Conjugate meningococcal vaccines, which may be more immunogenic, are currently being evaluated.[49,50] The serogroup specificity of currently available meningococcal vaccines requires that the infecting organism be properly characterized.

RABIES

Burden of Suffering

In the absence of adequate prophylaxis, persons infected with rabies almost always die from rabies encephalitis.[51] Human rabies is an uncommon disease in the U.S., with only 33 cases diagnosed from 1977 to 1994, 15 of which were associated with exposure to dogs outside the country or at the U.S.-Mexican border.[52] Bat-associated rabies virus has been associated with at least 10 cases.[52] Wild animals now constitute the largest source of human infection acquired in the U.S. A recent outbreak among raccoons in the northeastern states has been responsible for a large increase in the incidence of animal rabies, although no human transmission has been reported.[53] In the U.S., squirrels, chipmunks, and other rodents have not been implicated in any human cases.[51] More than 18,000 persons receive postexposure prophylaxis yearly for rabies.[54] Another 10,000 persons at increased risk receive preexposure prophylaxis.

Efficacy of Prophylaxis

Currently recommended postexposure prophylaxis consists of wound cleansing, human rabies immune globulin (HRIG) administered at the site of the bite and into the gluteal muscle, and a vaccination series administered into the deltoid muscle. Two vaccine preparations, human diploid cell vaccine (HDCV) and rabies vaccine, adsorbed (RVA) are available in the U.S. No vaccine failure has been reported in the U.S. in anyone who received postexposure prophylaxis using the current regimen.[55] Field experience has shown that this regimen provides adequate virus-neutralizing antibody titers.[56–59] Studies from developing countries have reported adequate antibody titers and clinical efficacy with varied dosages, schedules, and routes of administration of potent rabies vaccines (HDCV and others).[55,60–62b] Deviations from current recommendations, including gluteal HDCV administration, inadequate wound cleansing, and incorrect use of HRIG, may have been responsible for 13 rabies cases that occurred after administration of postexposure prophylaxis in other countries.[63–66] Two cohort studies have shown that gluteal, as opposed to deltoid, administration of HDCV results in lower antibody titers.[67,68] Reported adverse effects of HDCV include systemic allergic reactions[69] and, rarely, Guillain-Barré-like illnesses.[70–72]

Preexposure rabies vaccination is recommended for persons at high risk of rabies exposure. A three-dose series of HDCV (1.0 mL intramuscularly [IM] or 0.1 mL intradermally) or RVA (1.0 mL IM), given in the deltoid region on days 0, 7, and 21 or 28, provides an antibody response in virtually all individuals, lasting at least 2 years.[73–76] Recent studies have reported a continuous decline in antibody levels over time.[77,78] A two-dose booster is therefore recommended after an exposure. One rabies case has been reported following preexposure rabies vaccination;[79] this patient did not receive the recommended two-dose booster following exposure. Immune complex hypersensitivity develops in 6% of persons given a HDCV booster dose after the initial series.[69,80,81] A recent randomized clinical trial reports that purified HDCV used for boosters causes fewer severe and urticarial reactions.[82]

TETANUS

Burden of Suffering

Largely as a result of childhood immunization, tetanus has become uncommon in the U.S., with only 51 cases reported in 1994.[1] Tetanus remains a serious disease with 24% of recent cases resulting in death. Reports may underrepresent tetanus mortality by as much as 60%.[83] Most persons with tetanus had not received a primary immunization series.[84] Seventy-eight percent of cases followed an acute injury, half of which were puncture wounds. At least half of cases of tetanus and deaths from tetanus occur in persons over the age of 60.[1,84] In the third National Health and Nutrition Examination Survey (NHANES III), the prevalence of immunity to tetanus declined with increasing age beginning at age 40.[85] More than 80% of persons aged 6–39 years, but only 28% of persons 70 years and older, had protective antibody levels.

Efficacy of Prophylaxis

The use of equine tetanus immune globulin (TIG) resulted in a dramatic decline in the incidence of clinical tetanus during World War I.[86,87] Numerous animal trials[88,89] and an uncontrolled experiment involving two humans[90] established the protective serum antitoxin level at 0.01 unit/mL, although there have been several case reports of clinical tetanus despite higher serum antitoxin levels.[91–93] In unimmunized individuals, the combination of 250 units human TIG and 0.5 mL adsorbed tetanus toxoid provides a serum antitoxin level of 0.01 unit/mL immediately that lasts beyond 4 weeks.[94–98] Individuals who have completed a primary vaccination series (three doses and one booster) have serum antitoxin levels of ≥0.01 unit/mL for at least 20 years.[99–101] Booster immunization results in

a vigorous anamnestic response after periods as long as 20–30 years following a three-dose primary vaccination series;[100,101] recent data suggest, however, that some individuals who receive their first booster 17–20 years after a primary vaccination series may not develop protective antitoxin levels immediately.[102] There is animal evidence to suggest that protection begins before a rise in antitoxin is detected.[103] Furthermore, tetanus is unlikely in persons who have received a primary vaccination series at any time.[83,104] Serious adverse effects of tetanus toxoid are rare, although several case reports and a case series have described allergic or Arthus-like reactions and peripheral neuropathy following frequent boosters.[105,106]

Recommendations of Other Groups

The Advisory Committee on Immunization Practices,[13,54,55,74,107–109] the American Academy of Pediatrics,[12] and the American College of Physicians[110] have issued recommendations on postexposure prophylaxis for Hib disease, hepatitis A and B, meningococcal infection, rabies, and tetanus that are similar to those described below. The American College of Obstetricians and Gynecologists has issued detailed guidelines on the use of vaccines during pregnancy.[111]

CLINICAL INTERVENTION

Postexposure prophylaxis is recommended for selected persons with exposure or possible exposure to *H. influenzae* type b, hepatitis A, hepatitis B, meningococcal, rabies, or tetanus pathogens ("A" recommendation). Details are given below.

H. influenzae Type b Disease Oral rifampin prophylaxis should be prescribed promptly for patients with Hib disease and for all their household contacts regardless of age, if at least one of the contacts is a child less than 4 years of age who has not been fully vaccinated with a licensed Hib conjugate vaccine. Experts define a household contact as a person residing with the index patient or a nonresident who spent 4 hours or more with the index patient for at least 5 of the 7 days preceding the day of hospital admission of the index patient.[12] The dosage of rifampin for children and adults is 20 mg/kg (maximum 600 mg) as a single daily dose for 4 days. The dose for infants younger than 1 month of age has not been established, but experts recommend reducing the dose to 10 mg/kg/day.[12] Published guidelines also recommend postexposure prophylaxis for all day care attendees and staff, regardless of vaccination status, when 2 or more cases have occurred within 60 days and unvaccinated or incompletely vaccinated children attend.[12] When a single case has occurred in a day care center, rifampin prophylaxis should be given to all attendees and staff

only if unvaccinated or incompletely vaccinated children less than 2 years of age are present in the center for at least 25 hours per week.[12] Day care contacts of children with Hib disease should receive rifampin prophylaxis using the same regimen as for household contacts. All children who are less than 5 years of age and who are unvaccinated or incompletely vaccinated should be brought up to date by administration of the recommended doses of a licensed Hib conjugate vaccine (see Chapter 65).

Hepatitis A. Immune globulin should be administered at a dose of 0.02 mL/kg IM as soon as possible within 2 weeks of exposure to sexual and close household contacts of persons with hepatitis A, staff and children at day care centers where a hepatitis A case is recognized, staff and patients at custodial institutions where HAV transmission is documented, and food handlers at food service establishments where a food handler is diagnosed with hepatitis A. Detailed published protocols are available.[12,13,110] Hepatitis A vaccine is recommended for persons ≥2 years of age who are at high risk for infection (see Chapters 65 and 66).

Hepatitis B. The use of HBIG and hepatitis B vaccine is recommended to prevent HBV infection in the following circumstances: birth of an infant to a hepatitis B surface antigen (HBsAg)-positive mother (see Chapter 24), percutaneous or permucosal exposure to HBsAg-positive blood, sexual exposure to an HBsAg-positive person, and household exposure of an infant less than 1 year of age to a primary caregiver who has acute HBV infection. For needlesticks and other percutaneous exposures, and for sexual exposures, the precise protocol for postexposure prophylaxis against hepatitis B depends on the nature of the exposure, the availability from the source of exposure of blood for testing, the HBsAg status of the source, and the hepatitis B vaccination and vaccine-response status of the exposed person. Detailed guidelines are available.[12,13] See Chapter 24 for detailed recommendations on prenatal screening and perinatal postexposure prophylaxis against HBV infection, and Chapters 65 and 66 for recommendations regarding routine use of hepatitis B vaccine in children and adults.

Meningococcal Infection. Oral rifampin prophylaxis is indicated for household or day care contacts of persons with meningococcal infection, as well as for those with direct exposure to oral secretions (e.g., kissing) of an index patient. The dose is 600 mg for adults, 10 mg/kg for children 1–12 years of age, and 5 mg/kg for infants 3 months to 1 year of age, given twice daily for 2 days (for a total of four doses). Rifampin is contraindicated during pregnancy. There is currently insufficient evidence to recommend for or against the use of ceftriaxone for routine meningococcal prophylaxis ("C" recommendation). Ceftriaxone at a dose of 250 mg IM for adults and 125 mg IM for children is efficacious for eliminating meningococcal carriage of serogroup A strains of meningococcus. In outbreaks

caused by serogroup A strains, the use of meningococcal vaccine is recommended in addition to antibiotic prophylaxis for all persons ≥3 months of age. In outbreaks caused by serogroup C, Y, and W-135 strains, vaccination is recommended for persons ≥2 years of age. [12]

Rabies. Postexposure prophylaxis against rabies should be instituted if a possible exposure to rabies has occurred. Criteria for making this assessment, which include the type of animal (e.g., carnivorous wild animals, bats), the circumstances of the attack (e.g., unprovoked attack), and the type of exposure (e.g., bite), are available in published guidelines[55,110] and from local health departments. HRIG is given at a dose of 20 IU/kg; half of the dose is infiltrated around the wound, and the remainder is given intramuscularly at another site. The upper outer gluteal region of the buttocks is preferred because of the large volume administered. HDCV or RVA is administered in the deltoid muscle in five 1.0 mL injections on days 0, 3, 7, 14, and 28. Persons who were immunized before the incident require only two 1.0 mL doses of vaccine on days 0 and 3, and do not require HRIG. Preexposure prophylaxis with three injections (1.0 mL IM or 0.1 mL intradermally) of vaccine (days 0, 7, and 21 or 28) is recommended for those at high risk of contact with rabies virus, including rabies laboratory workers, veterinarians, animal handlers, and persons planning to spend more than 1 month in countries where rabies is endemic. Persons with frequent exposure should have their antibody level checked every 6 months and receive booster injections if antibody titers are below protective levels. Published guidelines suggest more frequent testing for certain continuously exposed laboratory workers. [55,110]

Tetanus. All individuals who have not completed a primary vaccination series of at least three doses and who present with wounds should receive 0.5 mL IM adsorbed tetanus toxoid. Diphtheria and tetanus toxoids and whole-cell or acellular pertussis vaccine adsorbed (DTP or DTaP, respectively) or diphtheria and tetanus toxoids adsorbed (DT) (as appropriate) for patients less than 7 years old and tetanus and diphtheria toxoids adsorbed (Td) for patients ≥7 years old, are preferred so that adequate levels of diphtheria and pertussis immunity are maintained (see Chapters 65 and 66). For a wound that is serious and/or contaminated (e.g., with dirt, feces), the incompletely vaccinated patient should receive both vaccine and human TIG (250 units IM at a separate site). Although there is inadequate evidence on which to make a recommendation for or against TIG prophylaxis for clean, minor wounds in inadequately immunized persons, experts recommend against the routine use of human TIG.[12,109,110] For individuals presenting with a wound who have completed a primary vaccination series of at least three doses, tetanus toxoid is recommended if more than 10 years have elapsed since the last dose or if only three doses of fluid

toxoid (which was used prior to the availability of adsorbed toxoid) were received. There is insufficient evidence to document increased risk after a shorter interval for major or contaminated wounds, but expert opinion supports vaccination when more than 5 years have elapsed.[12,109,110] Human TIG is not recommended for persons who have completed a primary vaccination series. All wounds should be properly cleaned and debrided.

Influenza. See Chapter 66 for recommendations regarding the use of amantadine and rimantadine to protect against influenza A.

The draft update of this chapter was prepared for the U.S. Preventive Services Task Force by Robert Reid, MD, MPH, Carolyn DiGuiseppi, MD, MPH, Cameron Grant, MBChB, and Modena Wilson, MD, MPH.

REFERENCES

1. Centers for Disease Control and Prevention. Final 1994 reports of notifiable diseases. MMWR 1995;44:537–543.
2. Centers for Disease Control. Progress toward elimination of *Haemophilus influenzae* type b disease among infants and children—United States, 1993–1994. MMWR 1995;44:545–550.
3. Redmond SR, Pichichero ME. *Haemophilus influenzae* type b disease: an epidemiologic study with special reference to day-care centers. JAMA 1984;252:2581–2584.
4. Casto DT, Edwards DL. Preventing *Haemophilus influenzae* type b disease. Clin Pharmacol 1985;4:637–648.
5. Ward JI, Fraser DW, Baraff LJ, et al. *Haemophilus influenzae* meningitis: a national study of secondary spread in household contacts. N Engl J Med 1979;301:122–126.
6. Fleming DW, Leibenhaut MH, Albanes D, et al. Secondary *Haemophilus influenzae* type b in day-care facilities: risk factors and prevention. JAMA 1985;254:509–514.
7. Makintubee S, Istre GR, Ward JI. Transmission of invasive *Haemophilus influenzae* type b disease in day care settings. J Pediatr 1987;111:180–186.
8. Band JD, Fraser DW, Ajello G. Prevention of *Haemophilus influenzae* type b disease. JAMA 1984;251: 2381–2386.
9. Granoff DM, Gilsdorf J, Gessert C, et al. *Haemophilus influenzae* type B disease in a day care center: eradication of carrier state by rifampin. Pediatrics 1979;63:397–401.
10. Murphy TV, Pastor P, Medley F, et al. Decreased *Haemophilus* colonization in children vaccinated with *Haemophilus influenzae* type b conjugate vaccine. J Pediatr 1993;122:517–523.
11. Barbour ML, Mayon-White RT, Coles C, et al. The impact of conjugate vaccine on carriage of *Haemophilus influenzae* type b. J Infect Dis 1995;171:93–98.
12. American Academy of Pediatrics. 1994 Red Book: report of the Committee on Infectious Diseases. 23rd ed. Elk Grove, IL: American Academy of Pediatrics, 1994.
13. Immunization Practices Advisory Committee. Protection against viral hepatitis. MMWR 1990;39(RR-2):1–26.
14. Gerberding JL. Management of occupational exposures to blood-borne viruses. N Engl J Med 1995;332:444–451.
15. Hollinger FB, Glombicki AP. Hepatitis A virus. In: Mandell GL, Douglas RG, Bennett JE, eds. Principles and practice of infectious diseases. 3rd ed. New York: Churchill Livingstone, 1990:1383–1399.
16. Mosley JW, Reisler DM, Brachott D, et al. Comparison of two lots of immune serum globulin for prophylaxis of infectious hepatitis. Am J Epidemiol 1968;87:539–550.
16a. Bresee JS, Mast E, Alter MJ, et al. Hepatitis C associated with intravenous immunoglobulin administration [abstr]. Presented at the 44th Annual Epidemic Intelligence Service Conference, Atlanta, GA, March 27–31, 1995.

17. 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.
18. Innis BL, Snitbhan R, Kunasol P, et al. Protection against hepatitis A by an inactivated vaccine. JAMA 1994;271:1328–1334.
19. Briem H, Safary A. Immunogenicity and safety in adults of hepatitis A virus vaccine administered as a single dose with a booster 6 months later. J Med Virol 1994;44:443–445.
20. Leentvaar-Kuijpers A, Coutinho RA, Brulein V, et al. Simultaneous passive and active immunization against hepatitis A. Vaccine 1992;10(Suppl 1):S138–S141.
21. Van Damme P, Mathei C, Thoelen S, et al. Single dose inactivated hepatitis A vaccine: rationale and clinical assessment of the safety and immunogenicity. J Med Virol 1994;44:435–441.
22. Jilg W, Bittner R, Bock HL, et al. Vaccination against hepatitis A: comparison of different short-term immunization schedules. Vaccine 1992;10(Suppl 1):S126–S128.
23. Green MS, Cohen D, Lerman Y, et al. Depression of the immune response to an inactivated hepatitis A vaccine administered concomitantly with imune globulin. J Infect Dis 1993;168:740–743.
24. Wagner G, Lavanchy D, Darioli R, et al. Simultaneous active and passive immunization against hepatitis A studied in a population of travelers. Vaccine 1993;11:1027–1032.
25. Maynard JE. Passive immunization against hepatitis B: a review of recent studies and comment on current aspects of control. Am J Epidemiol 1978;107:77–86.
26. Hoofnagle JH, Seeff LB, Bales ZB, et al. Passive-active immunity from hepatitis B immune globulin: reanalysis of a Veterans Administrative cooperative study of needle stick hepatitis, the Veterans Administration Cooperative Study Group. Ann Intern Med 1979;91:813–818.
27. Perrillo RP, Campbell CR, Strang S, et al. Immune globulin and hepatitis B immune globulin: prophylactic measures for intimate contacts exposed to acute type B hepatitis. Arch Intern Med 1984;144:81–85.
28. Beasley RP, Hwang LY, Stevens CE, et al. Efficacy of hepatitis B immune globulin for prevention of perinatal transmission of the hepatitis B carrier state: final report of a randomized double-blind, placebo-controlled trial. Hepatology 1983;3:135–141.
29. Centers for Disease Control. 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 1991;40(RR-13):1–25.
30. Palmovic D. Prevention of hepatitis B infection in health care workers after accidental exposure. J Infect 1987;15:221–224.
31. Stevens CE, Taylor PE, Tong MJ, et al. Yeast-recombinant hepatitis B vaccine: efficacy with hepatitis B immune globulin in prevention of perinatal hepatitis B virus transmission. JAMA 1987;257:2612–2616.
32. Beasley RP, Hwang LY, Lee GC, et al. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis immune globulin and hepatitis B vaccine. Lancet 1983;2:1099–1102.
33. Wong VC, Ip HM, Reesink HW, et al. Prevention of HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg by administration of hepatitis-B vaccine and hepatitis-B immunoglobulin: double-blind randomised, placebo-controlled study. Lancet 1984;1:921–926.
34. Stevens CE, Toy PT, Tong MJ, et al. Perinatal hepatitis B transmission in the United States: prevention by passive-active immunization. JAMA 1985;253:1740–1745.
35. Jackson LA, Wenger JD, Meningococcal Disease Study Group. Laboratory-based surveillance for meningococcal disease in selected areas, United States—1989–1991. MMWR 1993;42(SS-2):21–30.
36. Kaiser AB, Hennekens CH, Saslaw MS, et al. Seroepidemiology and chemoprophylaxis of disease due to sulfonamide resistant *Neisseria meningitidis* in a civilian population. J Infect Dis 1974;130:217–224.
37. Munford RS, Sussuarana de Vasconcelos ZJ, Phillips CJ, et al. Eradication of carriage of *Neisseria meningitidis* in families: a study in Brazil. J Infect Dis 1974;129:644–649.
38. Guttler RB, Counts GW, Avent CK, et al. Effect of rifampin and minocycline on meningococcal carrier rates. J Infect Dis 1971;124:199–205.
39. Schwartz B, Al-Tobaiqi A, Al-Ruwais A, et al. Comparative efficacy of ceftriaxone and rifampin in eradicating pharyngeal carriage of group A *Neisseria meningitidis*. Lancet 1988;1:1239–1242.
40. Deal WB, Sanders E. Efficacy of rifampin in treatment of meningococcal carriers. N Engl J Med 1969;281:641–645.
41. Munford RS, Taunay AE, Morais JS, et al. Spread of meningococcal infection within households. Lancet 1974;1:1275–1278.
42. Meningococcal Disease Surveillance Group. Meningococcal disease: secondary attack rate and chemoprophylaxis in the United States, 1974. JAMA 1976;235:261–265.

43. Greenwood BM, Hassan-King M, Whittle HC. Prevention of secondary cases of meningococcal disease in household contacts by vaccination. BMJ 1978;2:1317–1318.
44. Jones DM. Meningococcal vaccines [editorial]. J Med Microbiol 1993;38:77–78.
45. Lennon D, Gellin B, Hood D, et al. Successful intervention in a group A meningococcal outbreak in Auckland, New Zealand. Pediatr Infect Dis J 1992;11:617–623.
46. Biselli R, Fattorossi A, Matricardi PM, et al. Dramatic reduction of meningococcal meningitis among military recruits in Italy after introduction of specific vaccination. Vaccine 1993;11:578–581.
47. Peltola H, Makela HP, Kayhty H, et al. Clinical efficacy of meningococcal group A capsular polysaccharide vaccine in children three months to five years of age. N Engl J Med 1977;297:686–691.
48. de Moraes JC, Perkins BA, Camargo MC, et al. Protective efficacy of a serogroup B meningococcal vaccine in Sao Paulo, Brazil. Lancet 1992;340:1074–1078.
49. Twumasi PA Jr, Kumah S, Leach A, et al. A trial of a group A plus group C meningococcal polysaccharide-protein conjugate vaccine in African infants. J Infect Dis 1995;171:632–638.
50. Bjune G, Nokleby H, Hareide B. Clinical trials using a new Norwegian vaccine against disease caused by group B meningococci. Tidsskr Nor Laegeforen 1990;110:614–617.
51. Fishbein DB, Robinson LE. Rabies. N Engl J Med 1993;329:1632–1638.
52. Centers for Disease Control and Prevention. Human rabies—Alabama, Tennessee, and Texas, 1994. MMWR 1995;44:269–272.
53. Centers for Disease Control and Prevention. Raccoon rabies epizootic—United States, 1993. MMWR 1994;43: 269–273.
54. Centers for Disease Control. Update on adult immunizations: recommendations of the Immunization Practices Advisory Committee. MMWR 1991;40(RR-12):36–39.
55. Centers for Disease Control. Rabies prevention—United States, 1991: recommendations of the Immunization Practices Advisory Committee. MMWR 1991;40(RR-3):1–19.
56. Berlin BS, Mitchell JR, Burgoyne GH, et al. Rhesus diploid vaccine (adsorbed), a new rabies vaccine: II. results of clinical studies simulating prophylactic therapy for rabies exposure. JAMA 1983;249:2663–2665.
57. Helmick CG, Johnstone C, Sumner J, et al. A clinical study of Merieux human rabies immune globulin. J Biol Stand 1982;10:357–367.
58. Anderson LJ, Sikes RK, Langkop CW, et al. Postexposure trial of a human diploid cell strain rabies vaccine. J Infect Dis 1980;142:133–138.
59. Bahmanyar M, Fayaz A, Nour-Salehi S, et al. Successful protection of humans exposed to rabies infection: post exposure treatment with the new human diploid cell rabies vaccine and antirabies serum. JAMA 1976;236:2751–2754.
60. Chutivongse S, Wilde H, Supich C, et al. Postexposure prophylaxis for rabies with antiserum and intradermal vaccination. Lancet 1990;2:896–898.
61. Warrell MJ, Nicholson KG, Warrell DA, et al. Economical multiple-site intradermal immunization with human diploid cell strain vaccine is effective for post exposure rabies prophylaxis. Lancet 1985;1: 1059–1062.
62. Vodopija I, Sureau P, Smerdel S, et al. Interaction of rabies vaccine with human rabies immunoglobulin and reliability of the 2-1-1 schedule application for postexposure treatment. Vaccine 1988; 6:283–286.
62a. Suntharasamai P, Warrell MJ, Warrell DA, et al. New purified vero cell vaccine prevents rabies in patients bitten by rabid animals. Lancet 1986;2:129–131.
62b. Sehgal S, Bhattacharya D, Bhardwaj M. Clinical evaluation of purified vero-cell rabies vaccine in patients bitten by rabid animals in India. J Commun Dis 1994;26:139–146.
63. 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.
64. Wilde H, Choomkasien O, Hemachudka T, et al. Failure of rabies postexposure treatment in Thailand. Vaccine 1989;7:49–52.
65. Centers for Disease Control. Human rabies despite treatment with rabies immune globulin and human diploid cell vaccine—Thailand. MMWR 1987;36:759–760, 765.
66. Review: rabies vaccine failures. Lancet 1988;1:917–918.
67. Reid-Sanden FL, Fishbein DB, Stevens CA, et al. Administration of rabies vaccine in the gluteal area: a continuing problem [letter]. Arch Intern Med 1991;151:821.
68. Fishbein DB, Sawyer LA, Reid-Sanden FL. Administration of human diploid-cell vaccine in the gluteal area [letter]. N Engl J Med 1988;318:214–215.

69. Centers for Disease Control. Systemic allergic reactions following immunization with human diploid cell rabies vaccine. MMWR 1984;33:185–187.
70. Bernard KW, Smith PW, Kader FJ, et al. Neuroparalytic illness and human diploid cell rabies vaccine. JAMA 1982;248:3136–3138.
71. Boe E, Nyland H. Guillain-Barré syndrome after vaccination with human diploid cell rabies vaccine Scand J Infect Dis 1980;12:231–232.
72. Knittel T, Ramadori G, Mayet WJ. Guillain-Barré syndrome and human diploid cell rabies vaccine [letter]. Lancet 1989;1:1334–1335.
73. Turner GS, Nicholson KG, Tyrrell DA, et al. Evaluation of a human diploid cell strain rabies vaccine: final report of a three year study of pre-exposure immunization. J Hyg (Lond) 1982;89:101–110.
74. Immunization Practices Advisory Committee. Rabies prevention: supplemental statement on the pre-exposure use of human diploid cell vaccine by the intradermal route. MMWR 1986;35:767–769.
75. Rosanoff E, Tint H. Responses to human diploid cell rabies vaccine: neutralizing antibody responses of vaccinees receiving booster doses of human diploid cell rabies vaccine. Am J Epidemiol 1979;110:322–327.
76. Bernard KW, Mallonee J, Wright JC, et al. Preexposure immunization with intradermal human diploid cell rabies vaccine: risks and benefits of primary and booster vaccination. JAMA 1987;257:1059–1063.
77. Berlin BS. Rabies vaccine adsorbed: neutralizing antibody titers after three-dose pre-exposure vaccination. Am J Public Health 1990;80:476–478.
78. Briggs DJ, Schwenke JR. Longevity of rabies antibody titre in recipients of human diploid cell rabies vaccine. Vaccine 1992;10:125–129.
79. Centers for Disease Control. Human rabies—Kenya. MMWR 1983;32:494–495.
80. Dreesen DW, Bernard KW, Parker RA, et al. Immune complex disease in 23 persons following a booster dose of rabies human diploid cell vaccine. Vaccine 1986;4:45–49.
81. Fishbein DB, Yenne KM, Dreesen DW, et al. Risk factors for systemic hypersensitivity reactions after booster vaccinations with human diploid cell rabies vaccine: a nationwide prospective study. Vaccine 1993;11:1390–1394.
82. Fishbein DB, Dreesen DW, Holmes DF, et al. Human diploid rabies vaccine purified by zonal centrifugation: a controlled study of antibody response and side effects following primary and booster pre-exposure immunizations. Vaccine 1989;7:437–442.
83. Sutter RW, Cochi SL, Brink EW, Sirotkin BI. Assessment of vital statistics and surveillance data for monitoring tetanus mortality, United States, 1979–1984. Am J Epidemiol 1990;131:132–142.
84. Centers for Disease Control. Tetanus surveillance—United States, 1989–1990. MMWR 1992;41(SS-8):1–9.
85. Gergen PJ, McQuillan GM, Kiely M, et al. A population-based serologic survey of immunity to tetanus in the United States. N Engl J Med 1995;332:761–766.
86. Sachs A. Modern views on the prevention of tetanus in wounded. Proc R Soc Med 1952;45:641–652.
87. Bruce D. Tetanus: analysis of 1458 cases which occurred in home military hospitals during the years 1914–1918. J Hyg (Lond) 1920;19:1–32.
88. Edsall G. Specific prophylaxis of tetanus. JAMA 1959;171:417–427.
89. Looney JM, Edsall G, Ipsen J, et al. Persistence of antitoxin levels after tetanus-toxoid inoculation in adults and effect of a booster dose after various intervals. N Engl J Med 1956;254:6–12.
90. Wolters KL, Dehmel H. Abschliessende Untersuchungen uber die Tetanusprophylaxe durch aktive Immunisierung. Z Hyg Infecktionskr 1942;124:326–332.
91. Passen EL, Andersen BR. Clinical tetanus despite a 'protective' level of toxin-neutralizing antibody. JAMA 1986;255:1171–1173.
92. Berger SA, Cherubin CE, Nelson S, Levine L. Tetanus despite preexisting antitetanus antibodies. JAMA 1978;240:769–770.
93. Goulon M, Girard O, Grosbuis S, et al. Les anticorps antitétaniques: titrage avant séro-anatoxinothérapie chez 64 tétaniques. Press Med 1972;1:3049–3050.
94. Levine L, McComb JA, Dwyer RC, et al. Active-passive tetanus immunization: choice of toxoid, dose of tetanus immune globulin and timing of injections. N Engl J Med 1966;274:186–190.
95. Rubbo SD, Suri JC. Combined active-passive immunization against tetanus with human immune globulin. Med J Aust 1965;2:109–113.
96. McComb JA, Dwyer RC. Passive-active immunization with tetanus immune globulin (human). N Engl J Med 1963; 268:857–862.

97. Tasman A, Huygen FJ. Immunization against tetanus of patients given injections of antitetanus serum. Bull WHO 1962;26:397–407.
98. Smolens J, Vogt AB, Crawford MN, et al. The persistence in the human circulation of horse and human tetanus antitoxin. J Pediatr 1961;59:899–902.
99. Simonsen O, Bentzon MW, Kjeldsen K, et al. Evaluation of vaccination requirements to secure continuous antitoxin immunity to tetanus. Vaccine 1987;5:115–122.
100. Simonsen O, Badsberg JH, Kjeldsen K, et al. The fall-off in serum concentrations of tetanus antitoxin after primary and booster vaccination. Acta Pathol Microbiol Scand 1986;94:77–82.
101. Simonsen O, Kjeldsen K, Heron I. Immunity against tetanus and effect of revaccination 25–30 years after primary vaccination. Lancet 1984;2:1240–1242.
102. Simonsen O, Klærke M, Jensen JE, et al. Revaccination against tetanus 17–20 years after primary vaccination: kinetics of antibody response. J Trauma 1987;27:1358–1361.
103. Ipsen J. Changes in immunity and antitoxin level immediately after secondary stimulus with tetanus toxoid in rabbits. J Immunol 1961;86:50–55.
104. Wassilak SG, Walter AO. Tetanus. In: Plotkin SA, Mortimer EA, eds. Vaccines. Philadelphia: WB Saunders, 1988:45–73.
105. Reinstein L. Peripheral neuropathy after multiple tetanus toxoid boosters. Arch Phys Med Rehabil 1982;63:332–334.
106. Edsall G, Elliot MW, Peebles TG, et al. Excessive use of tetanus toxoid boosters. JAMA 1967; 202:111–113.
107. Immunization Practices Advisory Committee. Update: prevention of *Haemophilus influenzae* type b disease. MMWR 1986;35:170–180.
108. Immunization Practices Advisory Committee. Meningococcal vaccines. MMWR 1985;34:255–259.
109. Immunization Practices Advisory Committee. Diphtheria, tetanus and pertussis; recommendations for vaccine use and other preventive measures. MMWR 1991;40(RR-10):1–2, 20–25.
110. American College of Physicians Task Force on Adult Immunization and Infectious Diseases Society of America. Guide for adult immunization. 3rd ed. Philadelphia: American College of Physicians, 1994.
111. American College of Obstetricians and Gynecologists. Immunization during pregnancy. Technical Bulletin no. 160. Washington, DC: American College of Obstetricians and Gynecologists, 1991.