66. Adult Immunizations—*Including Chemoprophylaxis Against Influenza A*

RECOMMENDATION

Annual influenza vaccine is recommended for all persons aged 65 and older and persons in selected high-risk groups (see ***Clinical Intervention***). Pneumococcal vaccine is recommended for all immunocompetent individuals who are age 65 years and older or otherwise at increased risk for pneumococcal disease (see ***Clinical Intervention***). There is insufficient evidence to recommend for or against pneumococcal vaccine for high-risk immunocompromised individuals, but recommendations for vaccinating these persons may be made on other grounds. The series of combined tetanus-diphtheria toxoids (Td) should be completed for adults who have not received the primary series, and all adults should receive periodic Td boosters. Vaccination against measles and mumps should be provided to all adults born after 1956 who lack evidence of immunity. A second measles vaccination is recommended for adolescents and young adults in settings where such individuals congregate (e.g., high schools and colleges). See Chapter 32 for recommendations for rubella vaccine. Hepatitis B vaccine is recommended for all young adults not previously immunized and for all persons at high risk for infection (see ***Clinical Intervention***). Hepatitis A vaccine is recommended for persons at high risk for hepatitis A virus (HAV) infection (see ***Clinical Intervention***). Varicella vaccine is recommended for susceptible adults (see also Chapter 65). See Chapter 25 for recommendations regarding the Bacille Calmette-Guérin (BCG) vaccine. Recommendations for postexposure prophylaxis against selected infectious diseases are in Chapter 67; see also Chapter 24, Screening for Hepatitis B Virus Infection.

INFLUENZA

Burden of Suffering

Influenza, which frequently causes incapacitating malaise for several days, is responsible for significant morbidity and decreased productivity during epidemics. Twenty thousand or more excess deaths have been reported during each of 10 different epidemics from 1972–1973 to 1990–1991; more than 40,000 excess deaths occurred in each of three of these epi-

demics.[1] During severe pandemics (e.g., 1957 and 1968), there are often high attack rates across all age groups, and mortality usually is markedly increased. Elderly persons and persons of all ages with certain chronic medical disorders (see *Clinical Intervention*) are at increased risk for complications from influenza infections. More than 90% of the deaths attributed to pneumonia and influenza in these epidemics occurred among persons aged 65 and older.[1] Influenza has been estimated to cause a yearly average of 4.1–4.4 million excess respiratory illnesses and 16.6–17.9 million excess bed and restricted activity days in persons over 20 years of age.[2] Excess rates of hospitalization have also been documented for children with influenza who have chronic conditions such as severe asthma, cystic fibrosis, and diabetes.[3]

Efficacy of Vaccine

Inactivated (killed-virus) influenza vaccine containing antigens identical or similar to currently circulating influenza A and B viruses has been shown in controlled trials to be 70–80% effective in preventing influenza illness or reducing severity of influenza illness in healthy children, adolescents, and adults under age 65.[4–8] The vaccine has also been reported to reduce clinical symptoms in health care workers,[9] which may translate into a reduction in transmission to high-risk patients.

Only one randomized placebo-controlled trial has studied vaccine efficacy in high-risk persons for whom the vaccine is generally recommended. This trial enrolled 1,838 persons aged 60 years and older, three fourths of whom had no risk factors other than age.[10] During the influenza season, the vaccine significantly reduced the proportion with influenza-like illness (from 3% to 2%) and with serologically diagnosed infections (from 9% to 4%). In stratified analyses, protective efficacy was similar in healthy older adults and those with chronic disease but was reduced in subjects ≥70 years of age. In a poorly reported randomized controlled trial comparing different types and dosages of influenza vaccine in elderly persons living in the community,[11] one of the vaccines reduced clinical illness rates by 50–70% compared with other vaccine types and dosages. Illness rates were also substantially reduced compared to an unvaccinated cohort not enrolled in the trial. In a large serial cohort study of community-dwelling elderly persons, influenza vaccination reduced hospitalization rates by 48–57% for pneumonia and influenza and by 27–39% for all acute and chronic respiratory conditions, after adjustment for covariates.[12] Case-control studies in persons who are 65 years or older have reported that during epidemic periods when there was a good antigenic match between vaccine and virus, influenza vaccination prevented 31–45% of hospitalizations for pneumonia and influenza[13–15] and 43–49% of deaths due to all respiratory

conditions.[13] In a separate analysis using vital statistics data, influenza vaccination reduced total mortality by 27–30% among individuals aged 45 years or older.[13]

Adequately designed and performed observational studies conducted during influenza outbreaks also generally support the efficacy of influenza vaccine in preventing illness, hospitalization, and mortality in the institutionalized elderly population and in community-dwelling elderly persons with high-risk chronic conditions, although efficacy estimates vary widely (e.g., 24–58% efficacy against pneumonia).[16–22] Vaccination of nursing home residents also may prevent institutional outbreaks.[23] Randomized controlled trials in nursing homes have suggested that greater protection may be offered by other, as yet unlicensed, vaccine formulations or combinations (e.g., diphtheria toxoid conjugate vaccine or addition of live intranasal vaccine).[24,25] Data are more limited for younger high-risk persons. One cohort study in children with moderate to severe asthma demonstrated 49% vaccine efficacy against clinical illness despite a poor antigenic match with the epidemic influenza A virus, but no effect was seen on hospitalizations or asthma attack rates or severity.[26]

Because of frequent seasonal variation in the hemagglutinin and neuraminidase antigens of circulating viruses ("antigenic drift"), it is necessary to administer the vaccine annually each fall, prior to the epidemic season. This schedule allows the annually reformulated influenza vaccine to include antigens detected from recent global viral surveillance, which are likely to be circulating during the subsequent season. Although allergic reactions have been described, principally in patients with hypersensitivity to eggs, serious adverse effects from influenza vaccine are quite uncommon.[1] Randomized placebo-controlled trials of influenza vaccine have reported no difference in systemic reactions, but mild local side effects were more common after vaccine and occurred in up to 20% of patients.[27,28]

Amantadine and rimantadine are 70–90% effective in preventing illness caused by outbreaks of naturally occurring strains of influenza A viruses when used prophylactically in healthy community-living or institutionalized persons.[29–34] Several trials have shown much lower protection rates,[35,36] however, possibly due to late initiation of chemoprophylaxis or inadequate compliance. No controlled trials of these medications have been conducted in nursing home populations, but observational studies support the efficacy of chemoprophylaxis as an adjunct to vaccination during influenza A outbreaks in these institutions.[21,37,38] Neither drug is effective as prophylaxis against influenza A for household members of simultaneously treated index cases,[39,40] although amantadine has been proven efficacious in preventing influenza A disease when the index case is not treated.[41] Transmission of resistant viruses from treated patients may

reduce the efficacy of chemoprophylaxis in household or institutional contacts.[22,39] Neither drug prevents influenza B infection, so they are appropriate only in presumed influenza A epidemics.

Amantadine and rimantadine produce transient insomnia, anxiety, nausea, dizziness, and impaired concentration in 5–25% of patients.[42–47] The risk of adverse central nervous system effects has been shown to be significantly lower with rimantadine.[33] Adverse effects occur more frequently and with greater severity in older persons and have been associated with increased risk of falls.[48,49] Toxic levels resulting from reduced drug clearance have been identified in elderly persons.[42,49]

PNEUMOCOCCAL DISEASE

Burden of Suffering

Pneumococcal disease is a significant cause of morbidity and mortality in the U.S. Although pneumococcal infection is not a reportable disease, population-based surveillance studies have reported annual invasive pneumococcal disease rates of at least 15–19/100,000 population and pneumococcal meningitis rates of 0.3–1.2/100,000.[50–54] Significantly higher incidence rates are reported for persons less than 5 years of age or over age 65; blacks, Native Americans, and Alaska Natives; nursing home residents; alcoholics; and those with underlying chronic medical or immunodeficient conditions.[50–57] Pneumococcal disease accounts for about 15% of severe community-acquired pneumonia, which has a case-fatality rate (proportion of cases resulting in death) of 9–26%.[58–63] Pneumococcal bacteremia and meningitis are also associated with high case-fatality rates.[50–54,63,64] The highest case-fatality rates from invasive pneumococcal infection occur in elderly persons (30–43%) and patients with co-morbid conditions (25–27%), and the lowest occur in healthy children (0–3%).[50–53,63] In recent years, drug-resistant strains of *Streptococcus pneumoniae* have emerged; recent estimates suggest that in some locales 15% or more of pneumococcal isolates are drug resistant.[50,65,65a] The emergence of drug-resistant strains underscores the importance of preventing pneumococcal disease by vaccination.

Efficacy of Vaccine

The 14-valent polysaccharide pneumococcal vaccine, which was licensed in 1977, was replaced in 1983 by a 23-valent polysaccharide vaccine.[66] The latter contains purified capsular materials from 88% of the strains of *S. pneumoniae* causing bacteremic pneumococcal disease reported in the U.S.[67] In randomized controlled trials, 4- to 13-valent pneumococcal vaccines were 76–92% efficacious in preventing pneumococcal pneumonia in healthy young adult populations living in epidemic conditions.[68–70] A 14-valent

vaccine was also efficacious in reducing respiratory mortality in a population from a developing country.[71] The efficacy of pneumococcal vaccine in the general U.S. population has not been determined with certainty. Controlled trials in the U.S. involving low-risk middle-aged and older adults failed to demonstrate protective efficacy,[72] although the relatively low incidence of pneumococcal infection in healthy U.S. adults makes efficacy difficult to establish in a prospective clinical trial. A meta-analysis combining the most recent trials (follow-up periods of 16–36 months) in low-risk populations in the U.S. and elsewhere reported significant reductions in definitive and presumptive pneumococcal pneumonia with vaccination.[73] Vaccinated individuals had 11 fewer episodes of definitive pneumococcal pneumonia and 25 fewer episodes of presumptive pneumococcal pneumonia per 1,000 subjects. Results were similar for definitive and presumptive pneumonia due to vaccine types only. Small reductions in mortality were not statistically significant.

Trials in relatively healthy institutionalized elderly (≥50–55 years of age) have demonstrated significant reductions in the incidence of pneumonia, and in mortality in one study, with 3- and 14-valent vaccines, although these trials were limited by flaws in design and conduct.[74,75] Other trials of 14- to 17-valent vaccines in high-risk populations, all adequately designed and conducted, have been unable to detect significant reductions in pneumococcal or all-cause pneumonia or mortality.[76–79] A meta-analysis combining five trials in high-risk populations also reported no effects of vaccine on pneumococcal pneumonia, all-cause pneumonia, or mortality.[73] The sample sizes were much smaller than for the analyses in low-risk populations, but effect estimates for most outcomes did not suggest important benefits.

One possible explanation for the lack of vaccine efficacy in trials in high-risk populations is that the trials may have included subsets of individuals for whom the vaccine has little benefit. Case-control studies and indirect cohort studies (comparing the distribution of pneumococcal serotypes in the blood of vaccinated and unvaccinated persons) have been much more feasible to perform than controlled trials, although such observational studies may be more prone to bias. These studies support the protective value of pneumococcal vaccine in immunocompetent recipients, with vaccine efficacy estimates of 60–75% reported but not in severely or relatively immunocompromised individuals, including those with alcoholism, chronic renal failure, immunoglobulin deficiency, nephrotic syndrome, sickle cell disease, multiple myeloma, metastatic or hematologic malignancies, or systemic lupus erythematosus.[80–86] For some of these disorders, efficacy point estimates suggest a benefit, but confidence intervals are wide and include the possibility of no benefit. Additional research is needed to obtain more definitive data on the efficacy of pneumococcal vaccine and to develop vaccines that have better efficacy in both immuno-

competent and immunocompromised individuals, as well as in high-risk children under 2 years of age.

The total duration of antibody protection from pneumococcal vaccination is unknown; elevated titers appear to persist in adults for at least 5 years after immunization, but in some persons, they may fall to prevaccination levels within 10 years.[66] A case-control study reported a statistically significant decline in protective efficacy with increasing time since vaccination (e.g., from 88% within 3 years to 75% if ≥5 years since vaccination in persons aged 55–64).[81] On the other hand, an indirect cohort study reported that clinical efficacy persisted at least 7–10 years.[84]

There is little evidence of serious adverse effects from this vaccine, although erythema, induration, or pain at the injection site occur in about one third to one half of patients. Fever, myalgia, and severe reactions occur in no more than 1% of patients.[66,72] Most evidence indicates little difference in adverse reactions to revaccination compared to initial vaccination.[66]

TETANUS AND DIPHTHERIA

Burden of Suffering

Largely as a result of routine immunization, tetanus and diphtheria have become uncommon diseases in the U.S.: 51 cases of tetanus (0.02/100,000) and 2 cases of diphtheria were reported in 1994.[86a] In 1948, before tetanus and diphtheria toxoids were widely introduced, there were over 600 cases of tetanus and about 9,500 cases of diphtheria in the U.S.[87] The prevalence of immunity to tetanus in the U.S. population, as measured by serum antibodies, declines with age beginning at age 40 and is only 28% among persons ages 70 or older.[88] Adults ages 50 and older account for the majority of cases of tetanus.[87,88] Tetanus remains a serious infection, with death occurring in 19–24% of cases.[88,89] Reports may underrepresent tetanus mortality by as much as 60%.[90] The tetanus case-fatality rate increases with age and is 26% for persons ages 70 and older.[88] The case-fatality rate is also high in neonates, indicating the need to adequately immunize women of childbearing age against tetanus. Diphtheria is a potentially severe illness, with a case-fatality rate of 5–10% in unvaccinated individuals. The disease is rare in the U.S., but large outbreaks have occurred in other developed countries despite relatively high rates of childhood immunization.[91–94]

Efficacy of Vaccine

The efficacy of the tetanus and diphtheria toxoids is established on the basis of clinical studies and decades of experience with universal childhood immunization.[95,96] A primary series of three doses of Td, followed by

a booster dose, is highly effective in producing protective antibody titers lasting as long as 15–25 years and results in anamnestic responses with booster immunization as much as 20–30 years later.[97–104] In Sweden, a five-dose regimen (primary series plus boosters at age 8–10 and 18 years) resulted in greater than 90% of subjects having protective tetanus antitoxin levels at age 50 years, slightly fewer than at age 30.[105] Tetanus is unlikely in Americans who have received a primary vaccination series,[89,90,106] although clinical immunity may wane somewhat after 10–20 years.[89] Td often produces mild local inflammation, occasionally Arthus-type reactions and peripheral neuropathy (following frequent boosters), and rarely, anaphylaxis.[107–110]

MEASLES, MUMPS, AND RUBELLA

Burden of Suffering

Measles, a childhood illness, was reported in 232 (0.1/100,000) American adults (aged 20 or older) in 1994, a substantial decline from the recent peak of 6,210 cases (3.9/100,000) reported in 1990.[87,111] Adults accounted for nearly one fourth of all cases with known age reported in 1994.[111] About one third of adult infections occur among persons ages 20–24,[87] often in places where young adults congregate, such as schools or college campuses.[111] Hospitalization for measles and complications such as pneumonia and encephalitis are more common in adults than in school-aged children. Mumps infection was reported in 319 persons ≥20 years of age in 1993 (0.2/100,000), accounting for 20% of reported cases with known age.[87] Mumps outbreaks continue to occur periodically in schools and similar settings; in several recent outbreaks, most of those infected had previously been vaccinated against mumps.[111a] Rubella infection is discussed in Chapter 32.

Efficacy of Vaccine

A single dose of measles vaccine is 95% effective in producing long-term immunity.[112,113] Seropositivity rates remain high at least 10–15 years following vaccination,[114,115] and cohorts of known seroconverters have shown little evidence of increasing disease incidence with time since immunization.[115] Adult infections occur primarily in persons who have not been naturally infected or appropriately vaccinated in the past,[111] as well as those who were vaccinated before age 15 months.[116,117] Persons born before 1957 are likely to have been naturally infected and need not be considered susceptible.[118] Based on the age distribution and location of recent measles outbreaks,[111,117] revaccination of young adults in settings such as colleges and the workplace is likely to be most effective in reducing inci-

dence in adults. Measles outbreaks are less common at colleges where two doses of vaccine are required prior to matriculation.[119] When outbreaks do occur in these settings, attack rates are lower among persons who have had two doses of vaccine.[117,120,122–124] Measles has been virtually eliminated among military recruits by revaccinating those whose screening sera suggest they are susceptible despite a history of vaccination.[125]

Since the introduction of mumps vaccine in the United States in 1967, there has been a 99% decline in the incidence of mumps, supporting the efficacy of this vaccine.[111a] The incidence of mumps in adults declined 50% between 1988–1990 and 1991–1993.[111a] Recommendations issued in 1989 for a two-dose measles vaccination schedule, with MMR recommended as the preferred vaccine, may have contributed to this recent decline. The age distribution and location of recent mumps outbreaks also suggests that revaccinating young adults in settings such as schools and colleges may be effective in reducing the incidence in adults. As with measles, persons born before 1957 can generally be considered immune to mumps and need not be vaccinated. Rubella screening and immunization are discussed in Chapter 32.

Adverse effects of measles or combined measles-mumps-rubella (MMR) vaccine in adults are usually mild and self-limited.[118,126] Administration of MMR vaccine is not associated with adverse effects in persons already immune to these diseases, and thus the combined MMR vaccine is preferable to individual vaccines such as measles vaccine, since many recipients may be susceptible to more than one of the three diseases MMR prevents.

HEPATITIS B

Burden of Suffering

An estimated 200,000–300,000 persons become infected with hepatitis B virus (HBV) in the U.S. each year and more than 10,000 require hospitalization.[127,128,188] The risk of developing a chronic HBV infection (i.e., carrier state) after acute infection is about 6–10% in adults.[127,130,131] Some 1–1.25 million persons in the U.S. are chronic HBV carriers.[188] About one quarter of carriers develop chronic active hepatitis, which can progress to cirrhosis; carriers are also at risk for developing hepatocellular carcinoma.[128,132,133] Some 5,000 hepatitis B-related deaths occur each year as a result of cirrhosis and liver cancer.[128] Persons with acute or chronic HBV infection are also at risk for infection with hepatitis delta virus (HDV), which can itself cause acute, possibly fulminant, hepatitis or chronic hepatitis that may progress to cirrhosis.[128] Since HDV cannot be transmitted in the absence of HBV infection, measures to prevent HBV infection will also prevent the complications of HDV infection.

Efficacy of Vaccine

Plasma-derived hepatitis B vaccine, which became available in 1982, has 85–95% protective efficacy when administered in three intramuscular doses to immunocompetent patients.[134–138] Controlled trials and time series in adult responders to plasma-derived vaccine indicate persistent protection against clinical HBV infection and chronic carriage lasting at least 7–9 years despite declines in protective antibody levels.[139–141,147] The recombinant vaccines licensed in 1986 and currently in use in the U.S. induce antibody responses and short-term efficacy (up to 5 years) similar to those of the plasma-derived vaccine.[142–145] Information on longer-term efficacy is not yet available for recombinant vaccines. The possible need for booster doses after longer intervals will be assessed as additional data become available.

Compared to healthy young persons, older adults, overweight persons, smokers, chronic hemodialysis patients, injection drug users, and human immunodeficiency virus (HIV)-infected patients are significantly less likely to have an adequate antibody response to the vaccine; those who do respond have a more rapid decline in antibody levels.[142,146–155] A repeat vaccination series in persons who fail to respond to the first series results in moderate antibody response in up to 50%.[156] Injection into the buttocks has been associated with a suboptimal immune response, and therefore the deltoid muscle is the preferred injection site.[128,146] Local soreness at the injection site is a common side effect.[145] There have been several case reports of nonfatal anaphylaxis from recombinant hepatitis B vaccine.[157]

HEPATITIS A

Burden of Suffering

Almost 27,000 cases of hepatitis A were reported in the U.S. in 1994 (10.3/100,000),[86a] although the actual number of cases is estimated to be several times higher.[128] Adults aged 20–39 years account for 43% of reported cases.[87] About half of reported hepatitis cases in the U.S. are attributable to hepatitis A.[128] The case-fatality rate and clinical severity of hepatitis A increase with increasing age.[128,158] Groups at high risk for hepatitis A include certain Alaska Native, Pacific Islander, and Native American populations, institutionalized persons and workers in these institutions, men who have sex with men, users of injection or street drugs (depending on local epidemiology), certain laboratory workers, some religious communities, and travelers to countries where hepatitis A has intermediate or high endemicity.[128,159,160] For susceptible travelers visiting developing countries, the incidence rate of hepatitis A has been estimated

at 300 cases per 100,000 persons per month and the mortality rate at 3 deaths per 100,000 per month.[160]

Efficacy of Vaccine

Inactivated hepatitis A vaccine, now licensed in the U.S., has been proven efficacious against hepatitis A in randomized controlled trials in children (see Chapter 65).[161,162] Although trials evaluating clinical outcomes have not been performed in adults, hepatitis A vaccine produces seroconversion rates of 90–100% after one dose and 99–100% after two doses in healthy adult volunteers, including Alaska Natives.[163–169] The duration of immunity has not been established, but in adults, protective levels of antibody have been shown to persist at least 4 years after administration of three doses of vaccine.[164,168,170,170a] Estimates from models of antibody decline after vaccination predict that protective levels could last at least 20 years.[164] Vaccine efficacy is low in the first week after vaccination, rising to 77–90% at 2 weeks and 90–100% at 3–4 weeks.[162,165,171,172,176]

To provide immediate protection for those at high risk of exposure (e.g., travelers to endemic areas), giving immune globulin (IG) with the first vaccine dose may be necessary (see Chapter 67). Although several studies have reported lower mean antibody titers when the vaccine is administered concomitantly with IG, vaccine seroconversion rates appear to be comparable.[173,176,181] Seroconversion rates do not appear to be adversely affected when hepatitis A vaccine is given with hepatitis B vaccine.[174]

In direct comparisons with IG, traditionally used as preexposure prophylaxis against hepatitis A for high-risk persons (see Chapter 67), the vaccine led to higher and longer-lasting antibody titers.[175–181] The reported protective efficacy of hepatitis A vaccine is higher than that reported for IG (see Chapters 65 and 67), but the clinical efficacies of the two interventions have not been directly compared.

Adverse effects of the vaccine, including mild local reactions (pain, tenderness, redness, and swelling) and minor systemic symptoms such as fever, headache, and malaise, occur in 10–30% of recipients and are more common after the second and third doses.[161,162,169,170,182,183] Serious allergic reactions without long-term consequences have been reported rarely in temporal association with hepatitis A vaccine.[160]

Recommendations of Other Groups

Guidelines on adolescent and adult immunizations have been published by the American College of Physicians (ACP) and the Infectious Diseases Society of America (IDSA),[184] the American Academy of Family Physicians,[185] the American Academy of Pediatrics,[3] the Canadian Task Force on the Periodic Health Examination,[186] the American College of Obstetri-

cians and Gynecologists (ACOG),[186a] and the Advisory Committee on Immunization Practices (ACIP).[187] ACIP has also issued specific recommendations on the use of Td;[96] pneumococcal,[66] influenza,[1] hepatitis B,[128,170a,188] rubella,[189] measles,[118] varicella,[189a] and hepatitis A[189b] vaccines; and the use of vaccines in persons with altered immunocompetence.[190] ACOG has issued detailed guidelines on the use of vaccines during pregnancy.[191]

A few of these recommendations differ from those made in this chapter. The Canadian Task Force recommends against pneumococcal vaccine in immunocompromised individuals and found insufficient evidence to recommend for or against routine pneumococcal vaccination for healthy community-living elderly persons.[186] ACP[184] recommends that a single Td booster at age 50 for those who have completed the full five-dose pediatric series is an equally acceptable alternative strategy to decennial Td boosters.[96] ACIP and AAP recommend catch-up immunization with hepatitis B vaccine for adolescents aged 11–12 who have not been vaccinated previously, but they do not recommend routine hepatitis B vaccination for low-risk persons over 12 years, primarily because of cost and implementation considerations.[3,188,188a] ACIP recommends two doses of live measles vaccine or evidence of measles immunity for two groups in addition to those entering schools or colleges: persons who travel abroad and medical personnel at the time they begin employment.[118] ACOG recommends routine influenza vaccine beginning at age 55 rather than 65 and hepatitis B vaccine only for high-risk groups.[186a]

Antiviral chemoprophylaxis against influenza A, using either rimantadine hydrochloride or amantadine hydrochloride, has been recommended by the ACP, IDSA, and ACIP for high-risk persons and their caretakers who cannot be or have very recently been vaccinated (i.e., within 2 weeks for adults; within 2 weeks of the second dose for children), immunodeficient individuals as a supplement to vaccine, and residents and unvaccinated staff during outbreaks in institutions.[184,192]

Discussion

Most adults have not been immunized in accordance with existing immunization guidelines.[193] Perceptions that adult vaccine-preventable infections are not important health problems and that available vaccines are not safe and efficacious[193] can be readily refuted by the evidence already described. The cost of vaccines is another possible barrier to widespread immunization, but studies have shown that the prevention of morbidity and mortality from infectious diseases makes immunization cost-effective. For example, analyses of routine influenza and pneumococcal vaccination of persons aged 65 and older suggest that their cost-effectiveness is com-

parable to that of other widely recommended preventive services such as mammography or screening for hypertension.[12,15,194,195] Hepatitis B vaccination of high-risk groups (those with HBV incidence >5%), with or without prior screening for susceptibility, has been shown to be cost-effective, even cost-saving in some analyses.[196–198]

Cost-effectiveness analysis may also provide guidance on appropriate vaccination strategies. Vaccination of high-risk newborns and adults against hepatitis B has been ineffective in eliminating the disease. One cost-effectiveness analysis reported that vaccinating all adolescents against hepatitis B, in addition to the current strategy of screening pregnant women and vaccinating high-risk newborns, would cost only $3,695 per year of life saved.[198] While Td booster vaccination every 10 years is efficacious in preventing disease, antibody studies suggest that an interval of 15–30 years between boosters is likely to be adequate, especially given the small absolute risk of either disease in the U.S. A recent cost-effectiveness analysis reported that a decennial-booster strategy added a 2-minute survival advantage compared with a single booster at age 65 years, at a cost of $281,748 per year of additional life saved,[199] although potential costs related to diphtheria were not incorporated into the analysis.[200]

Compared to IG, hepatitis A vaccine appears to have greater and longer-lasting efficacy against infection with fewer adverse effects, but it is unclear whether the benefits outweigh the costs of the vaccine. One cost-effectiveness analysis reported that for all age groups, use of IG for post-exposure prophylaxis or for preexposure short-term (≤6 months) prophylaxis is less expensive than vaccination.[201] Testing for hepatitis A antibodies in groups with a high prevalence of immunity (e.g., frequent travelers, military personnel, older persons) reduces vaccination costs, however. An analysis for British soldiers calculated a more favorable cost-benefit ratio for the vaccine than for IG if there were at least two exposures to areas endemic for hepatitis A in 4 years.[202]

CLINICAL INTERVENTION

Influenza vaccine should be administered annually to all persons ages 65 and older and to persons 6 months of age or older who are residents of chronic care facilities or suffer from chronic cardiopulmonary disorders, metabolic diseases (including diabetes mellitus), hemoglobinopathies, immunosuppression, or renal dysfunction ("B" recommendation). Influenza vaccine is also recommended for health care providers for high-risk patients ("B" recommendation). In persons at high risk for influenza A (e.g., during institutional outbreaks), *amantadine* or *rimantadine prophylaxis* (200 mg/day orally) may be started at the time of vaccination and continued for 2 weeks ("B" recommendation). A lower dose (≤100 mg/day) of amanta-

dine is recommended for persons with reduced creatinine clearance and those 65 years of age and older. A reduced dosage (100 mg/day) of rimantadine is indicated for those with reduced renal or hepatic function and for elderly nursing home residents and may also be necessary in healthy persons 65 years and older who experience side effects. Amantadine and rimantadine are most useful as short-term prophylaxis for high-risk persons who have not yet received the vaccine or are vaccinated after influenza A activity in the community has already begun; when the vaccine may be ineffective due to major antigenic changes in the virus; for unimmunized persons who provide care for high-risk persons; to supplement protection provided by vaccine in persons who are expected to have a poor antibody response; and for high-risk persons in whom the vaccine is contraindicated (i.e., those with anaphylactic hypersensitivity to egg protein). If vaccine is contraindicated, amantadine or rimantadine should be started at the beginning of the influenza season and continued daily for the duration of influenza activity in the community.

Pneumococcal vaccine is recommended for all immunocompetent individuals who are aged 65 years and older or otherwise at increased risk for pneumococcal disease ("B" recommendation). High-risk groups include institutionalized persons ≥50 years of age, persons ≥2 years of age with certain medical conditions, including chronic cardiac or pulmonary disease, diabetes mellitus, and anatomic asplenia (excluding sickle cell disease), and persons ≥2 years of age who live in special environments or social settings with an identified increased risk of pneumococcal disease (e.g., certain Native American and Alaska Native populations). Routine revaccination is not recommended, but it may be appropriate to consider revaccination in immunocompetent individuals at highest risk for morbidity and mortality from pneumococcal disease (e.g., persons ≥75 years of age or with severe chronic disease) who were vaccinated more than 5 years previously. Revaccination with the 23-valent vaccine may be appropriate for high-risk persons who previously received the 14-valent vaccine. There is insufficient evidence to recommend for or against pneumococcal vaccine as an efficacious vaccine for immunocompromised individuals, but recommendations for vaccinating these persons may be made on other grounds, including high incidence and case-fatality rates of pneumococcal disease and minimal adverse effects from the vaccine ("C" recommendation). Immunocompromised conditions associated with high risk for pneumococcal disease include alcoholism, cirrhosis, chronic renal failure, ne-phrotic syndrome, sickle cell disease, multiple myeloma, metastatic or hematologic malignancy, acquired or congenital immunodeficiency (including HIV infection), and other conditions associated with immunosuppression, such as organ transplant. It may be appropriate to consider periodic revaccination in these high-risk immunocompromised patients,

who are likely to have poor initial antibody response and rapid decline of antibodies after vaccination.

The *Td vaccine series* should be completed for patients who have not received the primary series, and all adults should receive periodic Td boosters ("A" recommendation). For persons not previously immunized, the recommended schedule for the primary Td series is 0, 2, and 8–14 months. The optimal interval for booster doses is not established. The standard regimen is to provide a Td booster at least once every 10 years, but in the U.S., intervals of 15–30 years between boosters are likely to be adequate in persons who received a complete five-dose series in childhood (see Chapter 65). For international travelers, an interval of 10 years between boosters is recommended.

MMR vaccine should be administered to all persons born after 1956 who lack evidence of immunity to measles (receipt of live vaccine on or after the first birthday, laboratory evidence of immunity, or a history of physician-diagnosed measles) ("A" recommendation). A second measles vaccination is recommended for adolescents and young adults in settings where such individuals congregate (e.g., high schools, technical schools, and colleges), if they have not previously received a second dose (see Chapter 65) ("B" recommendation). The combined MMR vaccine is preferable to monovalent measles vaccine, since many recipients may also be susceptible to mumps or rubella due to inadequate vaccination or primary vaccine failure. Susceptible individuals should be vaccinated against mumps ("B" recommendation). Administration of the MMR or measles vaccine during pregnancy is not recommended. See Chapter 32 for recommendations on rubella screening and vaccination.

Hepatitis B vaccine is recommended for all young adults not previously immunized ("A" recommendation). Hepatitis B vaccine is also recommended for susceptible adults in high-risk groups, including men who have sex with men, injection drug users and their sex partners, persons who have a history of sexual activity with multiple partners in the previous 6 months or have recently acquired another sexually transmitted disease, international travelers to countries where HBV is of high or intermediate endemicity, recipients of certain blood products (including hemodialysis patients), and persons in health-related jobs with frequent exposure to blood or blood products ("A" recommendation). The recommended regimen for the recombinant hepatitis B vaccine is to administer 10 or 20 μg (depending on vaccine product) intramuscularly in the deltoid muscle at the current visit and at 1 and 6 months later. Clinicians should consider testing antibody response to the vaccine in individuals at very high risk from hepatitis B who are likely to have an inadequate antibody response (i.e., chronic renal dialysis patients, injection drug users, HIV-infected patients). Recommendations on screening for HBV infection and prevention

of perinatal transmission are in Chapter 24. Recommendations for persons with possible percutaneous or sexual exposure to individuals infected with hepatitis B virus are in Chapter 67.

Hepatitis A vaccine is recommended for all high-risk adults ("B" recommendation). High-risk groups include persons living in, traveling to, or working in areas where the disease is endemic and periodic hepatitis A outbreaks occur (e.g., Alaska Native, Pacific Islander, and Native American communities, certain religious communities, countries with high or intermediate endemicity), men who have sex with men, users of injection or street drugs (depending on local epidemiology), military personnel, and certain hospital and laboratory workers. Hepatitis A vaccine may also be considered for institutionalized persons (e.g., in prisons and institutions for the developmentally disabled) and workers in these institutions and in day care centers. Where tracking or identification of high-risk patients is not practical or cost-effective, universal vaccination may be a reasonable policy given the minimal adverse consequences of the vaccine. At this writing, the only licensed hepatitis A vaccine is Havrix® (SmithKline Beecham Pharmaceuticals).* Two doses (1,440 ELISA units/dose) at 0 and 6–12 months are recommended for persons over age 18 years. The need for periodic booster doses of the vaccine has not been established. For persons requiring immediate protection against hepatitis A (e.g., travelers to high-risk areas who have not previously been vaccinated), clinicians may wish to consider giving IG simultaneously with the first dose of hepatitis A vaccine, although the clinical efficacy of this approach has not been established. IG can also be recommended as an efficacious intervention for short-term (≤5–6 months) preexposure prophylaxis against hepatitis A (see Chapter 67). While some evidence suggests that the vaccine may be more efficacious than IG, the clinical efficacies of these two interventions have not been directly compared. Other factors to consider in choosing between these two interventions include patient preference, the likely duration of exposure, the need for immediate vs. long-term protection, and cost.

Two doses of *varicella vaccine* delivered 4–8 weeks apart are recommended for healthy adults with no history of varicella infection or previous vaccination ("B" recommendation) (see Chapter 65 for the review of evidence regarding varicella vaccine). Vaccination efforts should be targeted to susceptible health care workers and family contacts of immunocompromised individuals, and may also be targeted to susceptible adults who live or work in environments with a high likelihood of varicella transmission (e.g., day care centers, residential institutions, colleges, military bases). Given the high prevalence of immunity in adults with no history of

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chickenpox and the results of cost-effectiveness analysis (see Chapter 65), clinicians may wish to offer serologic testing for varicella susceptibility to history-negative adults who are likely to comply with return visits.

See Chapter 25 for recommendations regarding the Bacille Calmette-Guérin (BCG) vaccine. Recommendations on postexposure prophylaxis against selected infectious diseases, including tetanus, hepatitis A, and hepatitis B, are given in Chapter 67.

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