

section three

IMMUNIZATIONS AND CHEMOPROPHYLAXIS

65. Childhood Immunizations

RECOMMENDATION

All children without established contraindications should receive diphtheria-tetanus-pertussis (DTP), oral poliovirus (OPV), measles-mumps-rubella (MMR), conjugate *Haemophilus influenzae* type b, hepatitis B, and varicella vaccines, in accordance with recommended schedules (see *Clinical Intervention*). Hepatitis A vaccine is recommended for children and adolescents at high risk for hepatitis A virus (HAV) infection. Pneumococcal vaccine and annual influenza vaccine are recommended for children and adolescents at high risk (see *Clinical Intervention* and Chapter 66). See Chapter 67 for recommendations on postexposure prophylaxis against selected infectious diseases, and Chapter 25 for recommendations regarding the Bacille Calmette-Guérin (BCG) vaccine.

Burden of Suffering

A number of infectious diseases are preventable through routine childhood immunizations. Largely as a result of widespread childhood vaccination over the past several decades, diphtheria, pertussis, tetanus, poliomyelitis, measles, mumps, rubella, and congenital rubella syndrome have become remarkably less common in the U.S. than in prevaccination years, and the numbers of cases reported are at or near the lowest levels ever.¹ Comparisons of the total numbers of reported cases in the U.S. in 1994 and in the years preceding vaccination reveal an impressive decrease in reported cases of diphtheria (from 9,493 [1948] to 2 cases), tetanus (from 601 [1948] to 51 cases), paralytic poliomyelitis (from 18,308 [1954] to 0 cases due to endemic wild virus), measles (from 481,530 [1962] to 963 cases), mumps (from 152,209 [1968] to 1,537 cases), rubella (from 57,686 [1969] to 227 cases), and congenital rubella syndrome (from 77 [1970] to 7 cases).^{2,2a} Before the introduction of poliovirus vaccine in 1955, polio occurred in epidemic waves of increasing magnitude, reaching a peak incidence of more than 20,000 paralytic cases in 1952.³ The last outbreak, in 1979, totaled only 10 paralytic cases. Although the number of pertussis cases has also declined markedly since the prevaccination years (from 74,715 [1948] to 4,617 cases), long-term trends suggest an overall increase in the reported incidence of pertussis since 1976, rising from 0.5/100,000 to 2.6/100,000 in 1993 and 1.8/100,000 in 1994.^{4,4a} Many of these cases occurred in unvaccinated or inadequately vaccinated infants and children.

Newer childhood vaccines include *H. influenzae* type b (Hib), hepatitis B, hepatitis A, and varicella vaccines. Systemic illness from Hib disease, including meningitis, pneumonia, arthritis, and epiglottitis, previously occurred before age 5 in about 1 of every 200 children born in the U.S.⁵ The highest rates of Hib disease in the U.S. have been reported in Alaska Native and certain Native American populations. The incidence of invasive Hib disease in children <5 years old declined by an estimated 95% (from 41 to 2/100,000) between 1987, when the first Hib vaccine was licensed, and 1994.^{6,6a}

Children less than 5 years old account for only 1% of reported cases of hepatitis B and 1–3% of the 200,000 to 300,000 hepatitis B virus (HBV) infections estimated to occur annually in the U.S., but 20–30% of chronic infections.⁷ The likelihood of developing chronic infection has been estimated to be 80–90% in perinatally infected neonates, decreasing to 25% for those infected at age 5, and to <10% for infected adults.⁸ Chronic infection can lead to severe complications including chronic active hepatitis, cirrhosis, and hepatocellular carcinoma.^{9–11}

Nearly 27,000 cases of hepatitis A were reported in the U.S. in 1994 (10.3/100,000),^{2a} although the actual number of cases is estimated to be several times higher.⁹ Children aged 5–14 years have the highest rate of reported hepatitis A (about 15 cases per 100,000 in 1993).² About half of reported cases of hepatitis in the U.S. are attributable to hepatitis A.⁹ High-risk groups include travelers to countries with intermediate or high hepatitis A endemicity,¹² some religious communities, and Alaska Native, Pacific Islander, and Native American populations; persons institutionalized for custodial care may also have an increased risk. Day care centers may be an important source of epidemic HAV infection.¹³

Because chickenpox, caused by infection with varicella-zoster virus (VZV), infects nearly everyone by adulthood, its annual incidence approximates the birth cohort (4 million in 1993).^{14,15} At least 90% of cases occur in children less than 15 years old.¹⁴ Most adults are immune.¹⁶ Although generally mild in healthy children, chickenpox often results in missed school days for the child, missed work days for their parents, and visits to health care providers, and it occasionally leads to serious complications (e.g., encephalitis, pneumonia, bacterial superinfection), hospitalizations, and, rarely, death.^{14,17–20} Complication rates per case of varicella and case-fatality rates are substantially higher for older adolescents and adults than for children.^{14,17} Infants are also at high risk of complications.

Efficacy of Vaccines

DTP Vaccine. The efficacy of the DTP vaccine is established on the basis of clinical studies and decades of experience with universal childhood im-

munization.^{21–24} Substantial declines in diphtheria, tetanus, and pertussis disease followed the introduction of whole-cell pertussis vaccine combined with diphtheria and tetanus toxoids in the late 1940s.^{24,25} The diphtheria and tetanus toxoids are generally safe and are most commonly associated with self-limited local reactions,²⁶ although case reports have described allergic or Arthus-like reactions and peripheral neuropathy following frequent tetanus boosters. Anaphylaxis occurs in rare instances.^{27–29}

Increased attention has focused in recent years on the efficacy and safety of the pertussis component of the vaccine.^{30–32} In a national surveillance study of households with laboratory-confirmed pertussis, the efficacy of currently used whole-cell pertussis vaccines in fully vaccinated (three or more doses) children 1 through 4 years of age was estimated to be 59–89% for prolonged cough, 78% for typical paroxysmal cough, and 96–97% for severe clinical illness.²² In another national surveillance study, vaccine efficacy in preventing pertussis, defined as either any culture-proven cough illness or typical pertussis illness, was 64% for three doses and 82% for four or more doses.^{4a} The whole-cell preparation commonly produces local redness, swelling, and pain, and systemic events such as fever, fretfulness, and protracted, inconsolable crying.³³ DTP has also been associated with more serious adverse events such as febrile seizures in about 57/100,000 doses and hypotonic/hyporesponsive episodes in 3.5–291/100,000 doses.³³ The risk of seizures may be higher in certain children, such as those with a personal or family history of seizures.^{34,35} Limited follow-up of such cases, however, suggests that most, if not all, are associated with benign outcomes.^{36,37} The National Childhood Encephalopathy Study (NCES), a large British case-control study, reported that pertussis-containing vaccines were associated with more severe neurologic illnesses at a rate of 6.8 per million doses (95% CI, 2.1–15.9 per million), including acute encephalopathy in 2.7 (0–10.5) per million doses.³⁸ A 10-year follow-up study reported an association between death or permanent neurologic dysfunction and DTP vaccine only among children who had developed a serious acute neurologic illness within 7 days of receiving DTP.³⁹ The NCES has been criticized for possible bias and error in case ascertainment and other methodologic problems.³³ Detailed analysis of this and other controlled and uncontrolled observational studies led the Institute of Medicine to conclude that evidence was consistent with (but did not establish) a causal relationship between DTP vaccine and acute encephalopathy, with a range of excess risk between 0 and 10.5 per million doses,³³ and between DTP and chronic neurologic dysfunction in those rare children who experienced a serious acute neurologic illness within 7 days after receiving DTP.⁴⁰ The incidence of serious neurologic disorders following DTP administration is substantially less than that following pertussis disease.³⁸ Nevertheless, the high rate of adverse local and mild systemic reactions, as

well as the possibility of rare adverse neurologic sequelae, has stimulated interest in development of less reactogenic vaccines.⁴¹

Acellular forms of pertussis vaccine induce fewer local and systemic side effects than does the whole cell vaccine when administered to infants and children up to 6 years old.⁴²⁻⁴⁸ In a randomized placebo-controlled trial of 3,801 Swedish children aged 5-11 months, the efficacy of two acellular pertussis vaccines was 79-80% in preventing severe culture-proven pertussis and 54-69% for preventing culture-proven cases with any cough.⁴⁹⁻⁵¹ Four-year follow-up indicates persistent efficacy ranging from 69% to 95%, depending on case definition.⁵² Household exposure studies in Japan have reported efficacy >90% against typical pertussis among children receiving acellular vaccines at age 2 years.^{53-55a} In a prospective institutional exposure study, children vaccinated with acellular pertussis-component DTP (DTaP) beginning at a median age of 5 months (range, 3-26) were significantly less likely to develop typical pertussis symptoms compared with unvaccinated children.⁵⁶ None of these studies directly compared the acellular vaccine to the whole-cell vaccine. Immunogenicity appears comparable to the whole cell vaccine for the antigens present in the acellular vaccines.^{44,57} Preliminary results from two European randomized, double-blind trials indicate that DTaP at 2, 4, and 6 months of age was at least as efficacious as DTP with significantly fewer side effects; DTaP is likely to be licensed for use in infancy in the near future (personal communication, John R. La Montagne, PhD, National Institutes of Health (NIH), Bethesda, Aug. 15, 1995). DTaP is currently licensed in the U.S. for use in children 15 months of age as the fourth and/or fifth doses of the recommended DTP series.^{58,59}

OPV Vaccine. Three doses of live oral poliovirus (OPV) vaccine offers protection against all three poliovirus types in 95-100% of children. As a result, disease caused by indigenous wild poliovirus has been eliminated in the U.S.⁶⁰ An estimated 1 out of every 2.5 million vaccine doses results in paralytic poliomyelitis, however, and all cases of endemic paralytic poliomyelitis in the U.S. since 1980 (about eight cases per year) have been associated with the vaccine.⁶⁰ The vaccine has also resulted in several cases of fatal vaccine-strain poliovirus infections, primarily in immunocompromised patients.²⁹ The licensing of enhanced-potency inactivated poliovirus vaccine (IPV), which has no documented serious adverse effects and appears to have comparable immunogenicity,^{61,62} has led some to propose replacement of the live vaccine with this product.⁶³ IPV may be less effective, however, in limiting transmission of wild poliovirus among susceptible members of the population.⁶⁴ OPV has few significant adverse effects other than the risk of paralytic poliomyelitis.²⁹ The rare occurrence of Guillain-Barré syndrome (GBS) was associated with a one-time OPV mass

vaccination program in controlled studies in Finland, where IPV had been used routinely.²⁹ A retrospective epidemiologic survey of GBS in southern California, however, found no correlation between the usual age of OPV immunization and the incidence of GBS.⁶⁵ Because it requires injection, IPV is associated with greater discomfort and possibly greater administrative costs than is OPV. Combining IPV with other infant vaccines^{66,67} would alleviate this problem.

MMR Vaccine. A single dose of MMR is highly protective against measles, mumps, and rubella and its widespread use has resulted in substantial declines in the incidence of all three diseases.^{2,68} It is generally associated with only mild adverse effects in healthy individuals.^{68,69} MMR vaccine rarely causes thrombocytopenia (2.5–3.3/100,000 vaccinated persons), urticaria (0.6/100,000), and anaphylaxis (estimated at 0.1–5/100,000).^{29,70} Several deaths from vaccine-strain viral infection have been reported, all in severely immunocompromised children; none has been reported in children infected with human immunodeficiency virus (HIV).²⁹ The efficacy and adverse effects of rubella vaccine are described in detail in Chapter 32.

Despite the efficacy and safety of the vaccine, measles remains an important public health problem in the U.S. due to failure to immunize and to immunization failure. Between 1989 and 1994, 27–64% of measles cases occurred among unvaccinated but vaccine-eligible persons and 19–22% among persons who had received one vaccine after 12 months of age (immunization failure).^{71–72a} Most immunization failures appear to occur in children who fail to respond to the vaccine (primary immunization failure), an estimated 5% of children immunized after 15 months of age.^{73,74} In the past, the rate of primary immunization failure has been higher among children vaccinated before 15 months of age, presumably because maternal antibody interfered with response.⁷⁵ More recent studies indicate excellent serologic response and similar clinical efficacy in children vaccinated at 12–14 months, perhaps because maternal antibody levels achieved in a vaccinated cohort of mothers decline earlier than levels achieved by natural infection.^{76–82} Antibody response remains lower than when the vaccine is given at 15 months, however. Current evidence indicates that revaccination of primary immunization failures results in seroconversion rates comparable to that of never vaccinated persons⁸³ and prevents measles outbreaks.⁸⁴

Although some evidence suggests that waning immunity (secondary immunization failure) may also be a factor in immunization failure,^{85–91} seropositivity rates generally remain high at least 10–15 years following vaccination,^{92–94} anamnestic antibody responses occur in vaccinated persons who apparently lack antibody,^{83,93} and cohorts of known seroconverters followed through time in Great Britain and Japan have shown little evidence

of increasing disease incidence with time since immunization.⁹³ In 27-year follow-up of a British vaccine trial, there was no significant decline in vaccine efficacy with time (although the number of cases was quite small).⁹⁵

Because of immunization failures, a two-dose vaccination protocol against measles appears necessary to eliminate transmission of this highly communicable disease.^{88,96-98} Indirect evidence in support of a two-dose regimen comes from studies showing that attack rates during outbreaks are lower among populations of individuals who have had two doses of vaccine,^{82,88-91,99} and from the rarity of reported measles cases among persons who had received two doses of vaccine.^{72,72a} In Finland, a two-dose vaccination program administered at 14-18 months and at 6 years (with >95% coverage), along with "catch-up" vaccination for children 11-13 years and for individuals at occupational risk, has essentially eliminated indigenous measles, mumps, and rubella.⁷⁰ Adverse reactions to a second dose of vaccine seem to be no more common than to the first.

Hib Vaccine. The efficacy of a capsular polysaccharide (polyribosyl-ribitol phosphate [PRP]) vaccine in preventing infection with Hib in children over age 2 was first demonstrated in Finland in 1984.¹⁰⁰ Newer vaccines with substantially improved immunogenicity were subsequently developed by covalently conjugating PRP with protein antigens and were licensed for use in children 15-18 months of age in the late 1980s. Postlicensure studies have indicated vaccine efficacy of 74-88% for children 18-59 months of age.¹⁰¹⁻¹⁰³ Licensure of Hib conjugate vaccines for infants under 6 months of age followed demonstration of 93% efficacy of two doses of PRP-OMP conjugate vaccine in a randomized trial, and 100% efficacy of three doses of Hib oligosaccharide conjugate (HbOC) in a quasi-randomized trial.¹⁰⁴⁻¹⁰⁶ A postlicensure case-control study reported protective efficacies of 71%, 89%, and 94% after one, two, and three doses, respectively, of HbOC.¹⁰⁷ Although U.S. controlled trials of a third vaccine (PRP-T) were terminated after the licensure of other Hib conjugate vaccines for use in infancy, no cases of invasive Hib disease were reported among more than 6,200 vaccine recipients at the time of termination,¹⁰⁸ and protective efficacy has been reported from a British trial in which infants were given this vaccine at 2, 3, and 4 months,¹⁰⁹ and from a Finnish immunization program using historical controls.¹¹⁰ A combined DTP-HbOC vaccine and use of PRP-T vaccine reconstituted with DTP (from a single manufacturer) have been licensed based on immunogenicity similar to that of the individual vaccines, although no clinical efficacy information is available.^{111,112} These combined vaccines allow a reduced number of injections when both vaccines are indicated. Other combination vaccines are currently being evaluated.¹¹³ Declines in antibody levels occur with all vaccines after administration of the primary series, but booster vaccination at 12 months of age elicits a good antibody response.¹¹⁴⁻¹¹⁶ Surveillance in a number of dif-

ferent populations indicates a 55–95% decline in the incidence of Hib disease with widespread use of Hib conjugate vaccines.^{6,117–122} A substantial decline in the incidence of Hib disease among unvaccinated children¹²⁰ and in persons 5 years⁶ may be due to reduced carriage and transmission of the bacteria from vaccinated children.^{123,124} In randomized controlled trials, serial combinations of different vaccines (PRP-OMP, HbOC, or PRP-T) were as safe and at least as immunogenic as single conjugate vaccine series, supporting the interchangeability of these vaccines.^{125–127} Adverse effects of the Hib vaccine are generally mild (local tenderness, redness and swelling, irritability, fever, malaise, etc.).¹²⁸

Hepatitis B Vaccine. In the U.S., infants born to hepatitis B surface antigen-positive (HBsAg+) mothers are at high risk of becoming infected with HBV, but most other infants have little risk of infection before adolescence. Controlled trials,^{129–135a} cohort studies,^{136,137} and a time series study,¹³⁸ have demonstrated that hepatitis B vaccine given alone to infants of HBsAg+ mothers is 62–92% effective (depending on dosage, interval, vaccine, and maternal antigen status) in preventing the development of the HBV chronic carrier state during the first 1–5 years of life. The protective efficacy of vaccine combined with hepatitis B immune globulin (HBIG) is somewhat higher (85–95%) than for vaccine alone in these infants (see Chapter 24).

Because universal vaccination of low-risk infants has only been introduced recently in the U.S., its ability to protect these infants later in life must be inferred from studies in other populations. From controlled trials^{139–141} and time series studies^{142–147} conducted in populations where horizontal HBV transmission is common, universal vaccination of infants, children, and/or adolescents with a three- or four-dose regimen is estimated to be >84% effective in preventing HBV infection and >80% effective in preventing the development of chronic HBV carriage. Mass vaccination of children in New Zealand¹⁴² and infants in Taiwan,¹⁴⁸ American Samoa,¹⁴⁹ and Alaska Native communities¹⁵⁰ has led to substantial reductions in acute HBV events and the prevalence of chronic infection in both vaccinated and unvaccinated populations. Controlled trials and time series indicate protection against HBV infection and chronic carriage lasting from 3 to as long as 11–12 years in vaccinated infants, children, and adolescents, despite declines in antibody levels.^{130,142,143, 146,151–155} Breakthrough infections appear to be associated more with low initial antibody response than with declining antibody levels.^{139,146,156} The recombinant vaccines currently in use in the U.S. induce antibody responses and short-term (up to 5 years) efficacy in children similar to those of the plasma-derived vaccine.^{131,133,138,142,147,157–163} Mild reactions—including local soreness and induration, low-grade fever, irritability, and poor feeding—are reported by the parents of up to 13% of vaccinated children and 4–7%

of vaccinated infants.^{161,162,164} There have been several case reports of nonfatal anaphylaxis from recombinant hepatitis B vaccine.²⁹

Hepatitis A Vaccine. Inactivated hepatitis A vaccine, delivered in two doses 1 month apart, protected against hepatitis A for at least 1 year in a double-blind randomized controlled trial in more than 30,000 Thai children aged 1–16 years.¹⁶⁵ Protective efficacy was 94% at 12 months, and 100% at 17.5 months after a booster dose at 12 months. After the trial ended, all controls received two doses of the vaccine and were followed for an additional 10 months. The subsequent attack rate was 6 cases per 100,000, compared to 114 cases per 100,000 in this control group during the same interval while the trial was ongoing, and to 52–101 cases per 100,000 in historical controls. In a smaller U.S. trial of healthy children aged 2–16 years, a single dose of a different inactivated vaccine was 100% efficacious (lower bound 87%) in preventing hepatitis A at mean 103-day follow-up.¹⁶⁶ In other high-risk populations, seroconversion rates of 82–95% after one dose and 100% after two to three doses of inactivated hepatitis A vaccine have been reported in children ranging in age from 1 to 15 years.^{167–169} Although the duration of clinical immunity has not been established, protective levels of antibody have been shown to persist at least four years after administration of three doses of vaccine.^{170–173} Estimates derived from models of antibody decline after vaccination predict that protective levels of antibody could last for at least 20 years.¹⁷⁰ Vaccine efficacy is low in the first week after vaccination, rising to 77–90% at 2 weeks and 90–100% at 3–4 weeks.^{166,174–176,179} To provide immediate protection for those at high risk of exposure (e.g., travelers to endemic areas), administration of immune globulin (IG) with the first vaccine dose may be necessary. Although several studies have reported lower mean antibody titers when the vaccine is administered concomitantly with IG, vaccine seroconversion rates appear to be comparable.^{177,179} In direct comparisons with IG, traditionally used as preexposure prophylaxis against hepatitis A for high-risk persons such as international travelers (see Chapter 67), the vaccine led to higher and longer-lasting antibody titers.^{178–184} The reported 94–100% protective efficacy of hepatitis A vaccine is higher than that reported for IG (80–90%) (see Chapter 67), but the clinical efficacies of the two interventions have not been directly compared in clinical trials.

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.^{165–167,169} Serious allergic reactions, without long-term consequences, have been reported rarely in temporal association with hepatitis A vaccination.¹²

Varicella Vaccine. The efficacy of a live attenuated Oka strain varicella-zoster vaccine was 98% in preventing chickenpox through two varicella

seasons in a randomized, double-blind, placebo-controlled trial in healthy children and adolescents aged 1–14 years.^{185,186} Other studies in children and adolescents have compared the attack rate after household or other close exposure to that of historical controls and estimated vaccine efficacy at 86–98%.^{186–190} Breakthrough infections occur at a rate of about 1–2% per year, but illness is attenuated, with fewer lesions and a reduced incidence of fever compared to natural infections.^{186,191,192} Protective efficacy and antibody levels have been shown to persist for at least 7–10 years.^{186,193} In a 17–20-year follow-up study, only 2 of 96 adults who received vaccine in childhood (age 10 months to 13 years) developed breakthrough infections (both mild cases), despite 100 documented episodes of contact with persons infected with VZV.¹⁹⁴ Antibody levels were higher than those observed 10 years earlier. It is unclear what effect immune boosting caused by reinfection with wild-type VZV had on the level or duration of protection against disease.

The vaccine has been less well studied in older adolescents and adults than in children. Adolescents 13 years and adults have a poorer immune response to the varicella vaccine, and two doses are required to achieve optimal seroconversion rates.^{187,190,195} A hospital and household exposure study, conducted in health care workers and parents of young children, reported a protective efficacy of only 50%, but all breakthrough infections were mild.¹⁹⁶

Adverse effects of the vaccine have included injection site reactions and, less commonly, varicella-like rashes and fever.^{185,187,190} Experience with substantially greater numbers of vaccine recipients would be required to rule out rare, serious adverse reactions. Mild herpes zoster has been reported in several healthy children after varicella vaccine, but it appears to occur at a reduced rate compared to that associated with natural varicella,¹⁹⁷ as has been demonstrated for vaccinated children with leukemia.^{198,199} Herpes zoster has been reported in one adult recipient of the vaccine.²⁰⁰ The most important potential adverse consequence of universal preschool varicella vaccination is a shift of the age distribution of cases into adulthood, when the disease is more severe.^{14,17} Such a shift would occur if immunity from childhood vaccination wanes in adulthood, or if a large number of older children enter adolescence and adulthood without having been vaccinated and without having acquired natural immunity to VZV because of reduced circulation of wild virus. An age-structured theoretical transmission model suggests, however, that over a plausible range of values for vaccine efficacy, duration of immunity, and levels of coverage, routine immunization of preschool children would greatly reduce the number of primary varicella cases and would therefore reduce overall morbidity (as measured by hospitalizations) despite a shift in the age distribution of cases.²⁰¹ This model also suggests that “catch-up” immunization of 12-year-olds for the first 11 years of the vaccination pro-

gram would reduce the likelihood that a large pool of susceptible adolescents and adults would be created by universal preschool vaccination.

Recommendations of Other Groups

Recommendations on the administration of childhood vaccines are issued regularly by the Advisory Committee on Immunization Practices (ACIP),^{202,203} the American Academy of Pediatrics (AAP),¹³ and the American Academy of Family Physicians (AAFP).²⁰⁴ These three groups, working with federal agencies, have approved a unified childhood immunization schedule.²⁰⁵ The recommendations for the vaccines in the synthesized schedule are generally similar to those recommended by the Task Force (see *Clinical Intervention*), except: giving a second dose of MMR at either age 4–6 or 11–12 years is considered equally acceptable in this schedule, whereas the Task Force recommends 4–6 years as the preferred age (see Discussion); and routine hepatitis B vaccine was recommended only in infancy in the unified schedule, whereas the Task Force also recommends its routine use in all children and adolescents not previously immunized. ACIP and AAP have subsequently revised their recommendations for hepatitis B vaccine to include all children aged 11–12 years who have not previously been vaccinated; ACIP also recommends vaccinating unimmunized children under 11 years who are Pacific Islanders or who reside in households of first-generation immigrants from countries with high or intermediate HBV endemicity.^{206,216} ACIP and AAP recommend one dose of varicella vaccine for all healthy children age 12 months to the 13th birthday who have not been previously immunized and who lack a reliable history of varicella, with a target age of 12–18 months for routine vaccination; two doses of vaccine 4–8 weeks apart are recommended for susceptible adolescents aged 13 years.^{207,207a} AAP recommends optional serologic testing in healthy adolescents older than 18 years who lack a history of varicella.²⁰⁷ Recommendations for the use of varicella vaccine are being developed by AAFP and other organizations. The Food and Drug Administration has approved inactivated hepatitis A vaccine for use in selected groups including travelers, military personnel, and laboratory workers.²⁰⁸ Recommendations for the use of hepatitis A vaccine in children are being developed by ACIP, AAP, AAFP, and other groups. ACIP has issued recommendations for the use of inactivated hepatitis A vaccine for susceptible persons aged 2 years traveling to or working in countries with intermediate or high HAV endemicity.^{208a}

Discussion

All of the vaccines licensed for routine use in children have been proved efficacious in controlled studies or multiple time series. Those that have been in widespread use for some years (diphtheria, pertussis, tetanus, polio,

measles, mumps, rubella, Hib) have already demonstrated a dramatic effect on the incidence of childhood disease. In the case of polio, more than a decade has passed since the last documented transmission of wild poliovirus in the U.S., and more recently poliomyelitis has been eradicated in the entire Western hemisphere.²⁰⁹ Global eradication efforts are now concentrated on interrupting transmission in Asia and sub-Saharan Africa. All cases of endemic paralytic poliomyelitis in the U.S. are now caused by vaccine-strain poliovirus infections, indicating that there may be a benefit from replacing OPV with enhanced-potency IPV. The use of combination vaccines that include IPV may reduce the costs and adverse effects associated with adding another injection to the infant vaccine schedule. Such combination vaccines are not yet available in the U.S.

Whether universal hepatitis B and varicella vaccination will lead to benefits similar to those attributable to previously approved vaccines is unknown. Their appropriateness for routine use in healthy children is a policy decision that must take into account other issues in addition to vaccine efficacy, including cost-effectiveness, available resources, and competing priorities. Routine infant vaccination against hepatitis B in the U.S. has been recommended primarily as a way to prevent HBV infection in adolescents and adults, but this benefit has not yet been documented. Universal vaccination in early adolescence (e.g., age 11–12) would be effective in preventing adolescent HBV infection, but it would not prevent transmission in early childhood, when the risk of developing chronic carriage is highest and which continued to occur in the U.S. despite selective vaccination of infants born to HBsAg+ mothers. One cost-effectiveness analysis reported an incremental cost of universal newborn vaccination relative to screening pregnant women and selective vaccination of high-risk newborns to be \$30,347 per discounted life-year gained, which is comparable to that of other health care strategies commonly used in North America, such as treatment for mild hypertension.²¹⁰ Another cost-effectiveness analysis²¹¹ reported that screening all pregnant women and giving vaccine plus HBIG to neonates of HBsAg+ mothers (as currently recommended in Chapter 24), combined with universal vaccination of children at age 10 with a booster at age 20, was more cost-effective than universal vaccination of newborns (with boosters at age 10 and 20) or universal vaccination of adolescents at age 10 (with a booster at age 20) without screening in pregnancy. This analysis did not account, however, for the consequences of horizontal transmission and consequent chronic infection during childhood. A cost-effectiveness analysis has evaluated prevaccination testing for hepatitis B in adolescents or preadolescents; this strategy was not effective in terms of cost or rate of completed vaccination unless the seroprevalence of antibodies to HBsAg was at least 40% (also see Chapter 24).^{211a}

For varicella vaccine, there are few data regarding protective efficacy

beyond about 10 years after vaccination. The likely change in VZV epidemiology as a result of universal childhood immunization, i.e., that chickenpox would occur primarily in adulthood when it tends to be more severe, remains an important concern. While the previously cited model²⁰¹ found that the overall effect of universal preschool vaccination would be beneficial, longer experience will be necessary to demonstrate this. Cost effectiveness analysis suggests that routine vaccination for preschool-age children results in cost savings when the analysis includes both direct medical costs and indirect costs (i.e., current work-loss of parents and of infected adults, and future work-loss of those who die or who are permanently disabled from encephalitis).²¹² Vaccination before age 13 is preferable because two doses 4–8 weeks apart are required to achieve optimal seroconversion rates when the vaccine is given after age 12. The use of combined vaccines (e.g., MMRV,^{213,214} which is not currently available in the U.S.) would reduce the number of injections needed, reducing the adverse effects associated with multiple needlesticks and potentially reducing costs. Vaccinating all adolescents and adults with a negative or uncertain history of chickenpox is likely to be more effective in preventing chickenpox than serologic testing followed by immunization of test-negative adolescents and adults, because with the latter strategy, loss to follow-up and false-positive test results will reduce the proportion protected. Serologic testing prior to vaccination may be more cost-effective, however, because many adolescents and most adults with negative or uncertain histories of chickenpox are in fact immune, and because the need for two doses to be given at two separate visits increases the costs of vaccination.²¹⁵

Recommendations have been made to give a second MMR dose at either 4–6 years or 11–12 years.²⁰⁵ Giving the second dose at 4–6 years has two apparent advantages: primary immunization failures are corrected sooner and the health care and school systems are poised to capture the most individuals for immunization at the time of school entry. The advantage of a dose at 11–12 years is that it should have a more immediate impact on outbreaks involving middle, junior high, and high schools, and colleges. Studies directly comparing different two-dose schedules are under way. The weight of the currently available evidence would not appear to favor delaying the second dose into late childhood with the intent of preventing secondary immunization failure. Efforts should be made, however, to vaccinate all children aged 11–12 years who have not previously received a second dose of MMR.

CLINICAL INTERVENTION

All children without established contraindications should receive diphtheria-tetanus-pertussis (DTP), oral poliovirus (OPV), measles-mumps-rubella

(MMR), conjugate H. influenzae type b (Hib), hepatitis B, and varicella vaccines ("A" recommendation).

The recommended childhood immunization schedule includes DTP vaccine at ages 2 months, 4 months, and 6 months; DTP at 12–18 months or DTaP at 15–18 months; and DTP or DTaP between ages 4 and 6 years, just prior to school entry. A combined tetanus-diphtheria (Td) booster should be administered at age 11–12 years (14–16 years is an acceptable alternative) and periodically in adulthood (see Chapter 66). OPV vaccine is recommended at ages 2 months, 4 months, 6–18 months, and 4–6 years.

MMR vaccine should be administered at age 12–15 months and again at 4–6 years of age; 11–12 years is an acceptable alternative for the second dose. Giving the first dose at 15 months may be preferable when compliance with a visit at this age is assured, because efficacy and immunogenicity are slightly higher than at 12 months. Children over 6 years of age who present for care and have not yet received two doses of measles vaccine should be vaccinated with MMR, with the goal that all children will have had two doses of measles or MMR vaccine by 11–12 years of age.

Hib conjugate vaccine should be given at 2, 4, and 6 months (HbOC or PRP-T) or 2 and 4 months (PRP-OMP), with a booster dose at 12–15 months of age using any of the conjugate vaccines. While giving a single conjugate Hib vaccine for the primary series is preferred because of proven clinical efficacy, there is good evidence for the safety and immunogenicity of heterogeneous Hib conjugate vaccine series. Therefore, immunization at the recommended intervals (2, 4, 6, and 12–15 months) should not be delayed by efforts to determine the type of vaccine previously received. When this information is unavailable, any of the conjugate vaccines approved for use in infants may be given to complete the series. Licensed combined vaccines (e.g., DTP-HbOC [Tetramune®]*) may be substituted for the relevant individual vaccines in cases where both vaccines would normally be given in order to reduce the total number of injections given.

Hepatitis B vaccine is recommended for all infants, and for all children and adolescents not previously immunized, particularly those in high-risk populations (see Chapters 24 and 66). For infants, the first dose is recommended at 0–2 months (preferably prior to hospital discharge), the second dose 1–2 months after the first, and the third dose at 6–18 months (preferably at least 4 months after the second dose). Giving hepatitis B vaccine at 0, 1, 2, and 12 months of age is also acceptable. After infancy, the vaccine schedule is at the current visit and 1 and 6 months later. Clinicians may wish to inform parents that booster doses may be required in the future to maintain immunity through adolescence and adulthood.

* Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

Varicella vaccine administered subcutaneously in one 0.5-mL dose, is recommended for routine use in healthy children 12–18 months of age, and in children under age 13 with no reliable history of varicella infection or previous immunization. Clinicians should inform parents that varicella disease in adulthood is associated with increased risk of serious complications, the duration of immunity provided by varicella vaccine has not been established, and booster doses of the vaccine may be required to maintain protection throughout adulthood. Two doses of vaccine delivered 4–8 weeks apart are recommended for healthy adolescents 13 years of age with no reliable history of varicella infection or previous vaccination. Given the relatively high prevalence of immunity in adolescents with no history of chickenpox and the results of cost-effectiveness analysis, clinicians may wish to offer serologic testing for varicella susceptibility to history-negative adolescents 13 years who are likely to comply with return visits.

Clinicians may wish to conduct an assessment of immunization status for all children at age 11–12, in particular to determine whether the patient needs Td, MMR, varicella, or hepatitis B vaccines. Clinicians are referred to published guidelines for details on vaccine contraindications, instructions for immunizing children with medical disorders (including human immunodeficiency virus infection), and modified protocols recommended during community outbreaks or epidemics or for children with delayed immunization.^{13,202}

Hepatitis A vaccine is recommended for all high-risk children aged 2 years and all high-risk adolescents (“A” recommendation). High-risk groups include persons living in, traveling to, or working in areas where the disease is endemic and periodic outbreaks occur (e.g., countries with high or intermediate endemicity, Alaska Native, Pacific Islander, and Native American communities, certain religious communities) (see Chapter 66 for additional high-risk groups and recommendations for adult immunization). Hepatitis A vaccination may also be considered for institutionalized persons (e.g., those living in chronic care facilities). 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).^{*} Three doses (360 ELISA units/dose), administered intramuscularly, are recommended for persons aged 2–18 years; the second and third doses are given 1 and 6–12 months after the first dose. The need for periodic booster doses 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), IG (0.02 mL/kg) should be given simultaneously with the first

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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 the two regimens have not been directly compared in clinical trials. Other factors to consider in choosing between the two interventions are patient preference, the likely frequency and duration of exposure, the need for immediate protection, and cost.

Annual influenza vaccines are recommended for adolescents and children 6 months of age who are residents of chronic care facilities or have chronic cardiopulmonary disorders, metabolic diseases (including diabetes mellitus), hemoglobinopathies, immunosuppression, or renal dysfunction (“B” recommendation) (see Chapter 66 for the review of evidence regarding influenza vaccine). Split-virus vaccine is recommended for children 12 years; the recommended vaccine dose is 0.25 mL for children 6–35 months of age and 0.5 mL for children 3 years of age.¹³ Amantadine and rimantadine prophylaxis against influenza A is discussed in Chapter 66.

Pneumococcal vaccines are recommended for immunocompetent adolescents and children (2 years of age) with chronic cardiac or pulmonary disease, diabetes mellitus, and anatomic asplenia (excluding sickle cell disease), and those living in special environments or social settings with an identified increased risk of pneumococcal disease (e.g., certain Native American and Alaska Native populations) (“B” recommendation) (see Chapter 66 for the review of evidence regarding pneumococcal vaccine). Routine revaccination is not recommended, but it may be appropriate to consider periodic revaccination in immunocompetent individuals at highest risk for morbidity and mortality from pneumococcal disease (e.g., those with severe chronic disease) who were vaccinated more than 5 years previously. There is insufficient evidence to recommend for or against pneumococcal vaccine as an efficacious vaccine for immunocompromised children 2 years of age, but recommendations for vaccinating these persons may be made on other grounds, including high incidence and mortality rates of pneumococcal disease and minimal adverse effects from vaccine (“C” recommendation). Examples of immunocompromised conditions associated with high risk for pneumococcal disease include acquired or congenital immunodeficiency (including HIV infection), sickle cell disease, nephrotic syndrome, chronic renal failure, metastatic or hematologic malignancy, and other conditions associated with immune suppression, such as organ transplant. It may be appropriate to consider periodic revaccination in these patients, who are likely to have poor initial antibody response and rapid decline of antibodies after vaccination.

See Chapter 25 (screening for tuberculous infection) for recommendations regarding the BCG vaccine. Recommendations on postexposure prophylaxis against selected infectious diseases, including tetanus, hepatitis A, hepatitis B, and Hib, are given in Chapter 67.

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