# Active Immunization in the United States: Developments over the Past Decade

**PENELOPE H. DENNEHY**

Division of Pediatric Infectious Diseases, Rhode Island Hospital, Providence, Rhode Island

---

## INTRODUCTION

872

## DISEASES FOR WHICH NEW VACCINES BECAME AVAILABLE

- Hepatitis A
  - 873
- Japanese Encephalitis Virus Infection
  - 874
- Lyme Disease
  - 875
- Rotavirus Infection
  - 876
- Varicella
  - 877

## DISEASES FOR WHICH IMPROVED VACCINES BECAME AVAILABLE

- Haemophilus influenzae Type b
  - 880
- Pertussis
  - 881
- Pneumococcal Disease
  - 882
- Rabies
  - 883
- Typhoid
  - 884

## DISEASES FOR WHICH THE IMMUNIZATION STRATEGY HAS CHANGED

- Hepatitis B
  - 885
- Measles
  - 887
- Meningococcal Disease
  - 888
- Poliomyelitis
  - 888

## DISEASES FOR WHICH COMBINATION VACCINES ARE AVAILABLE

- Diphtheria-Tetanus-Pertussis-Haemophilus influenzae Type b Conjugate Combination Vaccines
  - 890
- Diphtheria-Tetanus-Pertussis-Hepatitis B Combination Vaccines
  - 890
- Inactivated Poliovirus Combination Vaccines
  - 890
- Haemophilus influenzae Type b Conjugate-Hepatitis B Combination Vaccines
  - 890
- Hepatitis A-Hepatitis B Combination Vaccines
  - 891
- Measles-Mumps-Rubella-Varicella Combination Vaccines
  - 891
- Other Combination Vaccines
  - 891

## DISEASES FOR WHICH IMPROVED VACCINES ARE UNDER DEVELOPMENT

- Cholera
  - 891
- Influenza
  - 892
- Meningococcal Disease
  - 892

## DISEASES FOR WHICH INVESTIGATIONAL VACCINES HAVE BEEN DEVELOPED

- Enteral Pathogens
  - 893
- Enterotoxigenic *Escherichia coli*
  - 893
- *Shigella*
  - 894
- Herpesviruses
  - 894
- Herpes simplex virus
  - 895
- Cytomegalovirus
  - 895
- Epstein-Barr virus
  - 896
- Human Immunodeficiency Virus
  - 896
- Respiratory Viruses
  - 897
- Respiratory syncytial virus
  - 898
- Parainfluenza viruses
  - 898

## VACCINE SAFETY

- Hib Vaccine and Diabetes
  - 899
- Measles Vaccine and Autism
  - 899
- Hepatitis B Vaccine and Multiple Sclerosis
  - 900

## CONCLUSION

- 900

## REFERENCES

- 900

* Mailing address: Division of Pediatric Infectious Diseases, Rhode Island Hospital, 593 Eddy St., Providence, RI 02903. Phone: (401) 444-4298. Fax: (401) 444-5650. E-mail: pdennehy@lifespan.org.
INTRODUCTION

The development of vaccines for prevention of infectious diseases has revolutionized our approach to public health. In many countries people enjoy better health because of effective immunization programs which have diminished the morbidity and mortality of once common infectious diseases (Table 1). In a recent compilation of the most important public health advances of the 20th century by the Centers for Disease Control and Prevention (CDC), immunizations were ranked first (107). The success of immunizations is illustrated by the 1977 eradication of smallpox after a 10-year effort directed by the World Health Organization (WHO) and the extraordinary progress toward the global elimination of poliomyelitis in the 1990s (99, 375).

To achieve this progress in public health, scientists and physicians have combined efforts to understand the biology of infectious agents. They have worked to purify the agents and, in some cases, their components; to develop and test vaccines; and to manufacture and administer these vaccines to appropriate segments of the population. In addition, government and physician advisory groups have developed appropriate recommendations and schedules for immunization.

The purpose of this article is to review the changes that have taken place in active immunization in the United States over the past decade. Since 1990, new and improved vaccines have become available for ten diseases and four new combination vaccines are under development for three additional diseases. In addition, immunization strategies for four diseases have changed and investigational vaccines have been developed for a broad array of infections.

DISEASES FOR WHICH NEW VACCINES BECAME AVAILABLE

Hepatitis A

Hepatitis A virus (HAV) infection is most prevalent in developing countries, reflecting the primary route of transmission of fecal-oral, person-to-person spread. HAV also remains the most frequent cause of acute viral hepatitis in the United States and has led to substantial morbidity and associated costs (93, 237). The incidence of disease varies considerably among different populations in the United States (93, 237, 340). Community-wide outbreaks recurring every 3 to 10 years in high-risk communities account for much of disease occurrence and are a primary target for control by vaccination. Rates of infection are highest among Alaskan Natives and American Indians. Other groups at increased risk include travelers to developing countries, homosexual and bisexual men, and users of illicit drugs. However, 45% of reported cases have no identifiable risk factor indicating that selective immunization is unlikely to have a major impact on the control of HAV.

Outbreaks among children attending day care centers and their staff are common and have been associated with community outbreaks (197). However, the prevalence of HAV infection in day care center staff and among children and adolescents who previously attended day care is not increased, suggesting that infections within day care settings most commonly reflect transmission within the community (93, 214).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Peak incidence</th>
<th>No. of cases</th>
<th>% Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(yr)</td>
<td>in 1999</td>
<td></td>
</tr>
<tr>
<td>Diptheria</td>
<td>206,939 (1921)</td>
<td>1</td>
<td>99.9</td>
</tr>
<tr>
<td>Pertussis</td>
<td>265,269 (1934)</td>
<td>7,288</td>
<td>97.2</td>
</tr>
<tr>
<td>Tetanus</td>
<td>1,314 (1922–1926)</td>
<td>40</td>
<td>96.9</td>
</tr>
<tr>
<td>Poliomyelitis, paralytic</td>
<td>21,269 (1952)</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Measles</td>
<td>894,134 (1941)</td>
<td>100</td>
<td>99.9</td>
</tr>
<tr>
<td>Mumps</td>
<td>152,209 (1968)</td>
<td>387</td>
<td>99.7</td>
</tr>
<tr>
<td>Rubella</td>
<td>57,868 (1969)</td>
<td>267</td>
<td>99.5</td>
</tr>
<tr>
<td>Congenital rubella syndrome</td>
<td>20,000 (1964–5)</td>
<td>9</td>
<td>99.9</td>
</tr>
<tr>
<td>Hib</td>
<td>20,000 (before 1987)</td>
<td>261</td>
<td>98.7</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>21,102 (1990)</td>
<td>7,694</td>
<td>63.5</td>
</tr>
<tr>
<td>Varicella</td>
<td>158,364 (1992)</td>
<td>46,016</td>
<td>70.9</td>
</tr>
</tbody>
</table>

* Data from Centers for Disease Control and Prevention, Summary of Notifiable Diseases, United States, 1999 (105a).

Disease in the United States is most common in children aged 5 to 14 years of age (93). Infection rates are appreciable in younger children in whom infection is usually asymptomatic and who serve as a silent reservoir. Children and infants can shed HAV for longer periods than adults, up to several months after onset of clinical illness. Because children frequently have asymptomatic infections and may shed virus for prolonged periods, they play an important role in HAV transmission. In one study in adults without an identified source of infection, 52% of their households included a child younger than 6 years (94). Thus, control of HAV by active immunization will likely necessitate universal childhood immunization.

Both inactivated and attenuated HAV vaccines have been developed (157). However, only inactivated vaccines have been licensed in the United States. Inactivated HAV vaccine is prepared by methods similar to those used for inactivated poliomyelitis vaccine. Virus is propagated in human diploid fibroblast cell cultures, formalin inactivated, and adsorbed to aluminum hydroxide adjuvant (18, 93). Two such products have been licensed in the United States, HAVRIX (SmithKline Beecham Biologicals) in 1995 and VAQTA (Merck & Co.) in 1996. Each vaccine has two formulations, an adult and a pediatric product of different antigen content. The pediatric formulation is indicated for persons 2 to 18 years of age. The vaccines can be used interchangeably (57).

Inactivated HAV vaccine is highly immunogenic. After a single dose, 95% of children and nearly all adults seroconvert within 1 month (18, 93). Following a second dose in children, seroconversion approaches 100%.

Concurrent administration of immune globulin and vaccine inhibits the peak serum antibody concentration achieved but not the rate of seroconversion (363). Since the antibody concentrations are well above the protective concentration, this inhibition is not considered to be clinically significant and supports passive-active immunoprophylaxis when indicated.

In two large clinical trials of inactivated HAV vaccine in children older than 2 years, protective efficacy has been greater than 90% (207, 371). In a double-blind, placebo-controlled, randomized study in Thailand involving approximately 34,000 vaccinees, the protective efficacy against clinical hepatitis A was 94% following two doses given 1 month apart; it was 100%...
rotavirus live virus 1998
lyme disease bacterial components 1998
dtap toxoids and inactivated bacterial components 1991
varicella live virus 1995
hepatitis a inactivated virus 1995
hib conjugate and hepatitis b (combination) hib conjugate and hepatitis b (inactivated virus) 1996
rabies (pcec) inactivated virus 1997
japanese encephalitis inactivated virus 1992
hib conjugate and dtap (combination) hib conjugate and dtap (toxoids and inactivated whole bacteria) 1993
hib conjugate (prp-t) polysaccharide-protein conjugate 1993
hepatitis a inactivated virus 1995
varicella live virus 1995
typhoid, parenteral capsular polysaccharide 1994
hib conjugate (prp-t) polysaccharide-protein conjugate 1993
hib conjugate and dtp (combination) hib conjugate and dtp (toxoids and inactivated whole bacteria) 1993
hib conjugate and dtap toxoids and inactivated bacterial components 1991

following a subsequent 12-month booster dose (207). Some early studies suggested that passively acquired maternal hav antibody might interfere with vaccine immunogenicity in infants. Subsequent studies have been conflicting (223, 296). Until this issue is fully resolved, the use of hav vaccine in children younger than 2 years is not recommended.

 Vaccination is also effective in controlling outbreaks in communities with a high rate of disease (93). For example, in a New York state community in which hepatitis A is highly endemic in children, a single dose of vaccine was 100% effective beginning 3 weeks after immunization in preventing symptomatic disease. (371).

 Data are not available to determine if and when booster doses would be indicated. However, the duration of protection following vaccination is likely to be prolonged. While the data on persistence of serum antibody and protection against infection are limited to approximately 5 years of experience, adults have been demonstrated to maintain protective antibody concentrations for at least 6 years and kinetic models of antibody decline indicate possible antibody persistence for 20 years (360).

 Except for rare reports of anaphylaxis and anaphylactoid reaction in adults in Europe and Asia, serious reactions to inactivated hav vaccine have not been reported (93). Pain, tenderness, and induration at the injection site can occur (207).

HAV vaccine is currently recommended only for persons 2 years of age or older who are at increased risk of infection (18, 94). The indications are as follows: persons traveling to or working in a country with high or intermediate incidence of HAV infection; persons with clotting factor disorders; sexually active homosexual and bisexual males; illicit drug users; and persons working with infected primates or with HAV in a laboratory. Routine vaccination of persons with chronic liver disease including other forms of infectious hepatitis is recommended since they may be at increased risk of fulminant hepatitis if they become infected with HAV. Children living in areas where rates of hepatitis A are at least twice the national average should be routinely vaccinated. In addition, children living in areas where rates of hepatitis A are at least greater than the national average but lower than twice the national average should be considered for routine vaccination (94). Although the CDC Advisory Committee on Immunization Practices (ACIP) guidelines do not recommend routine vaccination of food handlers, consideration may be given to vaccination of these workers in areas where state and local health authorities or private employers determine that vaccine is cost-effective (94).

 Vaccination should also be considered for control of hepatitis A outbreaks in communities in which the rate of infection is increased. Production of a highly immune population reduces the incidence of hepatitis A and decreases transmission by preventing fecal shedding of HAV (94). However, since effectiveness of vaccination has not been demonstrated in localized outbreaks occurring in institutions for the developmentally disabled, day care centers, schools and prisons, intramuscular immune globulin currently is recommended for close contacts of infected persons in these circumstances. At present, HAV vaccine is not routinely indicated for day care center attendees and staff or for food handlers.

 To control the significant public health burden of hepatitis A in the future, licensure of HAV vaccine for infants and development of combination products containing HAV and other vaccine antigens may lead to inclusion of HAV vaccine in the routine childhood immunization program.

Japanese Encephalitis Virus Infection

Japanese encephalitis virus, the most important cause of epidemic arbovirus encephalitis in Asia, has a wide clinical spectrum ranging from asymptomatic infection to severe infection with permanent neurologic sequelae and a high case fatality rate of 30 to 70% (272, 358). Despite the high fatality rate, vaccine has not been available in the United States until recently. In December 1992, a je virus vaccine was licensed in the United States for use in persons living in or traveling to Asia.

JE vaccine is a formalin-inactivated virus derived from purified infected mouse brain (80). Immunogenicity studies in the United States indicate that three doses are needed to provide protective concentrations of antibody in more than 80% of vaccinees (305). The longevity of neutralizing antibody after the primary vaccination series is not known. In one Japanese study, protective antibody titers persisted for 3 years after a booster dose (236).

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Type of vaccine</th>
<th>Date of first licensure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A and Hepatitis B (combination)</td>
<td>Inactivated virus</td>
<td>2001</td>
</tr>
<tr>
<td>Heptavalent pneumococcal conjugate (PCV7-CRM197)</td>
<td>Polysaccharide-protein conjugate</td>
<td>2000</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Bacterial components</td>
<td>1998</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Live virus</td>
<td>1998</td>
</tr>
<tr>
<td>Rabies (PCEC)</td>
<td>Inactivated virus</td>
<td>1997</td>
</tr>
<tr>
<td>Hib conjugate and DtaP (combination)</td>
<td>See Hib conjugates and DtaP</td>
<td>1996</td>
</tr>
<tr>
<td>Hib conjugate and Hepatitis B (combination)</td>
<td>Hib conjugates and hepatitis B (inactivated virus)</td>
<td>1996</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Inactivated virus</td>
<td>1995</td>
</tr>
<tr>
<td>Varicella</td>
<td>Live virus</td>
<td>1995</td>
</tr>
<tr>
<td>Typhoid, parenteral</td>
<td>Capsular polysaccharide</td>
<td>1994</td>
</tr>
<tr>
<td>Hib conjugate (PRP-T)</td>
<td>Polysaccharide-protein conjugate</td>
<td>1993</td>
</tr>
<tr>
<td>Hib conjugate and DTP (combination)</td>
<td>Hib conjugate and DTP (toxoids and inactivated whole bacteria)</td>
<td>1993</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Inactivated virus</td>
<td>1992</td>
</tr>
<tr>
<td>DTP</td>
<td>Toxoids and inactivated bacterial components</td>
<td>1991</td>
</tr>
</tbody>
</table>
A field trial of the currently licensed JE vaccine which was conducted in Thai children demonstrated an efficacy of 91% compared with placebo (203). Efficacy was 80% for a single year for a prototype of the currently licensed vaccine field tested in Taiwanese children (205).

Local reactions to JE vaccine occur in about 20% of vaccinees, while approximately 10% have reported systemic side effects such as fever, headache, malaise, or rash (80). Hypersensitivity type reactions characterized by urticaria and/or angioedema of the extremities, face, and oropharynx have been reported. The median interval between the first dose of vaccine and onset of symptoms is 12 h. After a second dose the interval is generally longer, with a median of 3 days; it may be as long as 2 weeks. Reactions have occurred after a second or third dose when preceding doses did not cause symptoms. The reaction rates are similar after both first and second doses and are approximately 15 to 62 per 10,000 immunizations among U.S. citizens. Neurologic adverse reactions, including acute disseminated encephalomyelitis have also been reported. In Denmark, acute disseminated encephalomyelitis has been estimated to occur in 1 in 50,000 to 75,000 vaccinees. However, a recent review of postmarketing data in the United States from 1993 to 1999 found no serious neurologic events after JE immunization (349).

The JE vaccine is recommended for persons who will be residing in areas where JE is endemic or epidemic (80). The risk for acquiring JE is highly variable within regions of endemic infection. Therefore, the incidence of JE in the area of residence, conditions of housing, nature of activities, and the possibility of unexpected travel to high-risk areas are factors that should be considered in the decision to vaccinate. JE vaccine is not recommended for all travelers to Asia. The vaccine should be offered to persons spending 1 month or longer in areas of endemic infection during the transmission season, especially if travel will include rural areas. The yellow book, Health Information for International Travel, updated regularly by the CDC, provides a useful table that lists affected areas by country and also notes the transmission season.

The recommended primary immunization series is three doses administered on days 0, 7, and 30. An abbreviated schedule of days 0, 7, and 14 can be used when a longer schedule is impractical because of time constraints. Although two doses administered 1 week apart will confer short-term immunity in 80% of vaccinees, this schedule should be used only under unusual circumstances. The last dose should be administered at least 10 days before travel begins to ensure an adequate immune response and access to care if a delayed adverse reaction occurs (80). No data are available on vaccine safety and efficacy in infants (4). The duration of protection is unknown, and definitive recommendations cannot be given on the timing of booster doses. Booster doses may be administered after 2 years.

Since generalized urticaria and angioedema can occur within minutes to as long as 2 weeks after vaccination, medications including epinephrine and equipment to treat anaphylaxis should be available. Vaccinees should be observed for 30 min following vaccination and should be warned about the possibility of delayed urticaria and angioedema. Vaccinees should be advised to remain in areas with ready access to medical care for 10 days after receiving a dose of JE vaccine.
are administered by intramuscular injection. The initial dose is followed by a second dose 1 month later and a third dose 12 months after the first. Vaccine administration should be timed so that the second dose and the third dose are given several weeks before the beginning of the *B. burgdorferi* transmission season, which usually begins in April (100). The duration of immunity following the three-dose vaccination series is unknown, and the need for booster doses has not been determined. Accelerated schedules of administration and use of vaccine in persons younger than 15 years are under study.

Local reactions at the site of injection were reported by significantly more vaccinees (24%) than placebo recipients (7.6%) (339). Reports of myalgia, influenza-like illness, fever, and chills within 30 days after a dose were significantly more common among vaccinees than placebo recipients, but none of these were reported by greater than 5% of either group (339). Reports of arthritis were not significantly different between vaccinees and placebo recipients, but vaccine recipients reported significantly more transient arthralgia and myalgia following each dose of vaccine (339). There is a serious theoretical concern that OspA vaccine might induce chronic inflammatory arthritis in genetically susceptible individuals through molecular mimicry of a human lymphocyte surface antigen, lymphocyte function antigen 1 (hLFA-1) (192). Ongoing postmarketing surveillance has not demonstrated any cause for concern thus far.

Recommendations for use of Lyme disease vaccine developed by ACIP were issued in June 1999 (100). Lyme disease vaccine should be targeted to persons at risk for exposure to infected ticks. This risk can be assessed by considering whether a person resides in an area where Lyme disease is highly endemic and the extent to which a person’s activities place him or her in contact with ticks (154). Vaccine should not be administered to individuals with treatment-resistant Lyme arthritis.

Vaccination of persons with frequent or prolonged exposure to ticks in areas where Lyme disease is endemic is likely to be an important preventive strategy. For persons with only brief or intermittent exposure to tick habitats in areas where Lyme disease is endemic, the public health benefits of vaccination, compared with early diagnosis and treatment of Lyme disease, are not clear. Vaccination should not be considered a substitute for other preventive measures, such as avoiding tick habitats, wearing protective clothing, using repellents to avoid tick attachment, and promptly removing attached ticks, since the vaccine is less than 100% efficacious and does not provide protection against other tick-borne illnesses.

**Rotavirus Infection**

Rotavirus is the most common cause of severe gastroenteritis in the United States and worldwide and affects virtually all children during the first 5 years of life in both developed and developing countries. In the United States, rotavirus is a common cause of hospitalizations, emergency room visits, and outpatient clinic visits. Because of this large burden of disease, several rotavirus vaccines have been developed. One of these vaccines was found to be safe and efficacious in clinical trials among children in North America, South America, and Europe. On the basis of these studies, this vaccine was licensed for use in the United States in 1998.

The licensed vaccine, RRV-TV (RotaShield [Wyeth-Lederle Vaccines and Pediatrics]), is a live, oral vaccine incorporating four strains of rotavirus, a rhesus rotavirus strain with human serotype G3 specificity and three single-gene human-rhesus reassortants for human serotypes G1, G2, and G4. G serotypes are determined by the VP7 protein found in the outer capsid of the virus. Fourteen G serotypes have been identified, but only five are important in humans. Serotype G1 is most common, followed by serotype G3, and serotypes will vary from year to year in any geographic location. In RRV-TV the three human-rhesus reassortants have been modified from the parent rhesus strain by single-gene reassortment so that each strain contains 10 genes from the parent rhesus strain along with a single gene encoding the VP7 protein from human rotavirus strain G1, G2, or G4. Each dose of vaccine contains $10^5$ PFU of each component rotavirus strain. RRV-TV is lyophilized and requires reconstitution with diluent containing citrate-bicarbonate.

Serological correlates of immunity against rotavirus infection have not been established. As a result, field studies have been necessary to demonstrate the efficacy of rotavirus vaccines. The efficacy of RRV-TV was evaluated in four field trials, two in the United States (311, 323) and one each in Venezuela (294) and Finland (219). The findings of all four studies were similar; the vaccine demonstrated efficacies of 48 to 68% against any rotavirus diarrhea, 38 to 91% against moderate disease, and 70 to 100% against severe diarrhea. The studies demonstrated a 50 to 100% efficacy in preventing doctor visits for evaluation and treatment of rotavirus diarrhea. The vaccine was also effective in reducing the duration of rotavirus diarrhea. The trial in Finland was large enough to examine the efficacy of the vaccine in preventing rotavirus hospitalizations: protection was 100% (219). In this study, vaccinated children were also protected from nosocomially acquired rotavirus diarrhea. Extended follow-up in the study in Finland demonstrated that protection against severe disease persisted through three rotavirus seasons (220). No data are available on the efficacy of administration of fewer than three doses of RRV-TV.

Because infections with serotype G1 viruses have predominated in most studies, the efficacy of RRV-TV against this serotype is well established. In studies conducted in the United States and Finland, RRV-TV was also effective in preventing nonserotype G1 disease (219, 311, 323).

In the clinical trials, RRV-TV was administered to almost 7,000 infants aged 6 to 28 weeks. Following the first dose, there was a statistically significant excess of both low-grade fever ($>38^\circ$C) and high fever ($>39^\circ$C) compared with placebo recipients. FEVERS generally occurred 3 to 5 days after administration of vaccine, were low grade, and were seen in fewer than 25% of recipients. Decreased appetite, irritability, and decreased activity also were reported following the first dose of vaccine in some trials; these symptoms were highly associated with the presence of fever (221). A statistically significant excess of fever of $>38^\circ$C was also noted after the second dose of RRV-TV; no increase in any symptoms was noted after the third dose of RRV-TV. In the efficacy study in Finland (221), vaccinated children had a significantly increased rate of diarrhea after the first dose of vaccine compared with placebo recipients; diarrhea was also associated with the presence of...
fever (221). No significant differences in vomiting were demonstrated between vaccinees and placebo recipients.

In clinical trials, intussusception was noted among 5 of approximately 10,000 vaccine recipients. This number was not significantly higher than among placebo recipients in the studies (312). However, the ACIP, in its recommendation for routine rotavirus vaccination of infants, indicated that postlicensure surveillance was needed for intussusception and any other rare adverse events that might occur following receipt of the vaccine.

Routine immunization with three doses of RRV-TV was recommended for infants at ages 2, 4, and 6 months (21, 105). An estimated 1.5 million doses of rotavirus vaccine were administered to infants from September 1998 until July 1999. In July 1999, the CDC recommended that health care providers and parents postpone use of RRV-TV for infants based on reports to the Vaccine Adverse Event Reporting System (VAERS) of intussusception in 15 infants who received rotavirus vaccine (81). Also at that time, the manufacturer, in consultation with the Food and Drug Administration (FDA), voluntarily ceased further distribution of the vaccine.

In response to the VAERS reports, a preliminary analysis of data from an ongoing post licensure study at Northern California Kaiser Permanente (NCKP) was performed (81). The rate of intussusception among never-vaccinated children was 45 per 100,000 infant-years, and the rate among children who had received RRV-TV was 125 per 100,000 infant-years. The rate was increased among children who had received RRV-TV during the preceding 3 weeks (219 per 100,000 infant-years) and among children who had received RRV-TV during the previous week (314 per 100,000 infant-years). In addition, preliminary data on intussusception from Minnesota were analyzed (81). The observed rate of intussusception within 1 week of receipt of RRV-TV was 292 per 100,000 infant-years. The preliminary data from Minnesota and from NCKP both suggested an increased risk for intussusception following receipt of RRV-TV. However, the number of cases of intussusception among vaccinated children was small both at NCKP and in Minnesota, and neither study had adequate power to establish a statistically significant difference in the incidence of intussusception among vaccinated and unvaccinated children.

Several studies were undertaken to further define and quantify the association. A multistate case-control study of cases of intussusception occurring between 1 November 1998 and 30, June 1999 in the 19 states with the highest reported vaccine distribution was begun in June 1999. Results of this case-control study show a significantly elevated risk during the 3 to 14 days following vaccination, with an estimated attributable risk of 1 case of intussusception for every 4,670 to 9,474 infants vaccinated (277). A managed-care organization cohort study in 10 health maintenance organizations with automated databases for case finding and vaccine status found that the incidence rate of intussusception was 25/100,000 person-years among unexposed infants and 540/100,000 person-years 3 to 7 days postvaccination. The attributable risk was one case of intussusception per 11,073 children vaccinated (239).

On 22, October 1999, the ACIP, after a review of scientific data from several sources, including preliminary data from both the managed-care cohort and the multistate case-control studies, concluded that intussusception occurs with significantly increased frequency in the first 1 to 2 weeks after vaccination with RRV-TV, particularly following the first dose (116). The ACIP and the American Academy of Pediatrics (AAP) withdrew their recommendations for vaccination of infants in the United States with RRV-TV. The manufacturer has subsequently ceased marketing the vaccine.

The relation between intussusception and RRV-TV is not understood and merits further research. The findings could impact directly on the use of this and other rotavirus vaccines. In addition, the worldwide burden of rotavirus disease remains substantial. Thus, the ACIP decision may not be applicable to other settings, where the burden of disease is substantially higher and where the risks and benefits of rotavirus vaccination could be different.

Varicella

Varicella is currently the most common childhood infectious disease in the United States. Before the availability of varicella vaccine, varicella infection was responsible for an estimated 4 million cases, 11,000 hospitalizations, and 100 deaths each year in the United States (97). Approximately 90% of cases occurred in children, with the highest incidence among children aged 1 to 6 years. In recent years, severe infections with group A beta-hemolytic streptococci have complicated varicella, leading to considerable morbidity and mortality in otherwise healthy individuals (115).

Varicella vaccine was licensed in the United States in 1995. The licensed vaccine is a preparation of the Oka strain of varicella virus obtained from the vesicle fluid of a healthy child with varicella that has been attenuated by serial propagation in human embryo lung fibroblasts, guinea pig embryonic cells, and human diploid cell cultures. Varicella vaccine is labile and must be stored at 4°C for less than 72 h or frozen at −15°C or colder until reconstituted.

Varicella vaccine is highly immunogenic in susceptible children. Seroconversion has occurred in more than 96% of children 12 months to 12 years of age after one dose of vaccine (372). Preexisting antibody, if present at 12 months of age, does not appear to interfere with antibody response. As with other viral vaccines, the antibody response after immunization is lower than that from natural disease. Adolescents and adults have age-related decreases in the ability to develop a primary response to varicella virus (186). Seroconversion rates of 78 to 82% after one dose and 99% after two doses have been reported in those older than 12 years (186, 372).

In ongoing studies in the United States and Japan, serum antibodies to varicella have been detected for as long as 10 to 20 years after immunization in more than 95% of immunized children (34, 222). Antibody concentrations have persisted for at least 1 year in 97% of adults and adolescents who were given two doses of vaccine 4 to 8 weeks apart (186). Cell-mediated immunity to varicella-zoster virus (VZV) has been detected in 87% of children and 94% of adults at 5 years postvaccination (377).

Varicella vaccine is highly effective in preventing varicella in children and in reducing the severity of infection if they do become infected. In prelicensure controlled clinical trials, varicella vaccine was 70 to 90% effective in preventing varicella and more than 95% effective in preventing severe disease (242,
Several postlicensure studies have shown similar results, with vaccine effectiveness ranging from 83 to 100% in preventing varicella and 87 to 100% in preventing severe disease (129, 212, 362). In follow-up studies, about 1 to 4% of vaccinated children per year have developed chickenpox following exposure to wild-type varicella virus, a rate that does not seem to increase with length of time after immunization (128). These vaccine failure-related cases are mild, with fewer skin lesions, lower rates of fever, and more rapid recovery (47, 367).

In adults and adolescents who have seroconverted, varicella vaccine provides protective efficacy rates of approximately 70% after household exposure. The remaining 30% develop attenuated disease with fewer skin lesions and little or no systemic toxicity, as in children (186).

The use of varicella vaccine has an impact on the epidemiology of disease. Active surveillance for varicella has been conducted at sites in Pennsylvania, Texas, and California since 1995 as part of a CDC-sponsored study (J. Seward, J., C. Peterson, L. Mascola, et al., Abstr. Pediatr. Acad. Soc. Am. Acad. Pediatr. Joint Meet., abstr. 1629, 2000). During the period from 1995 to 1999, vaccine coverage in 1- to 2-year old children rose to 70% while overall cases of varicella declined by 70 to 90%. The greatest decline was in children 1 to 4 years of age, but cases also declined in all other age groups, including infants younger than 1 year and adults, suggesting herd immunity. Decreasing rates of varicella have also been associated with increasing use of varicella vaccine in a day care center population (127).

Current estimates of vaccine efficacy and antibody persistence in vaccinees are based on observations when natural varicella infection has been highly prevalent. The extent to which boosting from exposure to natural varicella has impacted on the efficacy of vaccine or duration of immunity is not known. In prelicensure clinical studies, mean serum anti-VZV levels among vaccinees continued to increase with time after vaccination. This has been attributed to immunologic boosting caused by exposure to wild-type VZV in the community. A recent study analyzed serum antibody levels and infection rates over 4 years of follow-up in 4,631 children immunized with varicella vaccine (240). Anti-VZV titers decreased over time in high-responder subjects but rose in vaccinees with low titers. Among subjects with low anti-VZV titers, the frequency of clinical infection and immunological boosting substantially exceeded the 13%-per-year rate of exposure to wild-type VZV. These findings suggest that vaccine strain VZV persisted in vivo and reactivated as serum antibody titers decreased after vaccination.

Varicella vaccine produces relatively few adverse reactions (331, 374). Local reactions, rashes, and low-grade fevers occur in as many as 10% of vaccine recipients (32), but rates of rash and fever have been similar in placebo groups in several studies (169, 368). In postlicensure studies, the most frequently reported adverse event is a mild vesicular rash that occurs in approximately 5% of vaccinees (97, 185). Vesicular rashes that occurred within 2 weeks of vaccination were more likely to be due to wild-type VZV, while rashes that occurred more than 2 weeks postvaccination were more likely to be due to the Oka vaccine strain (331). There has been one report of rash and pneumonia as the result of vaccination of a 15-month-old child infected with human immunodeficiency virus (HIV). The child’s HIV status was not known at the time of vaccination (374).

A major concern has been whether vaccination would increase the risk of zoster. Based on reports to VAERS, the rate of herpes zoster after varicella vaccination is 2.6/100,000 vaccine doses distributed (97). The incidence of herpes zoster after natural varicella infection among healthy persons younger than 20 years is 68/100,000 person-years (194) and, for all ages, 215/100,000 person year (160). However, these rates should be compared cautiously because the latter rates are based on populations monitored for longer periods than were the vaccinees. Cases of herpes zoster have been confirmed by PCR to be caused by both vaccine virus and wild-type virus, suggesting that some herpes zoster cases in vaccinees might result from antecedent natural varicella infection (97, 199).

Transmission of the vaccine virus is rare and occurs most often from immunocompromised vaccinees. Of the 15 million doses of varicella vaccine distributed, on only three occasions has transmission from immunocompetent persons been documented by PCR analysis (244, 321). All three cases resulted in mild disease without complications. In one case, a child aged 12 months transmitted the vaccine virus to his pregnant mother (254, 321). The mother elected to terminate the pregnancy, and fetal tissue tested by PCR was negative for varicella vaccine virus. The two other documented cases involved transmission from healthy children aged 1 year to a healthy sibling aged 4½ months and a healthy father, respectively (97). Transmission has also occurred from patients with zoster due to vaccine strain virus (56). Transmission has not been documented in the absence of a vesicular rash postvaccination. No evidence indicates reversion to virulence of the vaccine strain during transmission; siblings of leukemic vaccine recipients who acquired vaccine virus had mild rashes in 75% of cases and symptomless seroconversion in 25% (32).

Varicella vaccine is licensed for use in individuals 12 months of age or older who have not had varicella. One dose of varicella vaccine is recommended for immunization of susceptible healthy children from 12 to 18 months of age (23, 96). The vaccine may be given concurrently with measles-mumps-rubella vaccine (MMR) but at separate sites. In addition, one dose of vaccine is recommended for immunization of all children from age 19 months to the 13th birthday who lack a reliable history of varicella infection and who have not previously been vaccinated. Susceptible healthy adolescents who have reached their 13th birthday and adults should be immunized with two doses of varicella vaccine 4 to 8 weeks apart. If more than 8 weeks elapses following the first dose, the second dose can be administered without restarting the schedule. If the adolescent or young adult does not have a reliable history of varicella, serologic testing for immunity before vaccination is likely to be cost-effective since 71 to 93% of such individuals are actually immune (251).

In February 1999, the ACIP expanded its recommendations for varicella vaccine to promote wider use of the vaccine for susceptible children and adults (97). The updated recommendations include establishing child care and school entry requirements, use of the vaccine following exposure and for outbreak control, use of the vaccine for some children infected with HIV, and vaccination of adults and adolescents at high risk for exposure.
The ACIP recommends that all states require children entering child care facilities and elementary schools to have received varicella vaccine or to have other evidence of immunity to varicella. Other evidence of immunity should consist of a physician’s diagnosis of varicella, a reliable history of the disease, or serologic evidence of immunity. To prevent susceptible older children from entering adulthood without immunity to varicella, states should also consider implementing a policy that requires evidence of varicella vaccination or other evidence of immunity for children entering middle school or junior high school.

Data from both the United States and Japan indicate that varicella vaccine is effective in preventing illness or modifying varicella severity if used within 3 days, and possibly up to 5 days, of exposure (32, 35, 320, 366). The ACIP and the AAP now recommend the vaccine for use in susceptible persons following exposure to varicella (10, 97). If the exposure results in infection, no evidence indicates that administration of varicella vaccine during the presymptomatic or prodromal stage of illness increases the risk for vaccine-associated adverse events.

Varicella outbreaks in child care facilities, schools, and other institutions can last 3 to 6 months. Varicella vaccine has been used successfully by state and local health departments and by the military for outbreak prevention and control. Therefore, the ACIP recommends that state and local health departments consider using the vaccine for outbreak control either by either advising exposed susceptible persons to contact their health care providers for vaccination or offering vaccination through the health department (97).

The ACIP has strengthened its recommendations for susceptible persons aged 13 years or older at high risk for exposure or transmission, including designating adolescents and adults living in households with children as a new high-risk group (97). Varicella vaccine is recommended for susceptible persons in the following high-risk groups: (i) persons who live or work in environments where transmission of VZV is likely, (ii) persons who live and work in environments where transmission can occur, (iii) nonpregnant women of childbearing age, (iv) adolescents and adults living in households with children, and (v) international travelers. Vaccination is also routinely recommended for all susceptible health care workers (77).

Varicella vaccine is not licensed for use in persons who have blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems. The manufacturer makes free vaccine available to any physician through a research protocol for use in patients who have acute lymphoblastic leukemia and who meet certain eligibility criteria (96). The ACIP previously recommended that varicella vaccine not be administered to persons with primary or acquired immunodeficiency, including immunosuppression associated with AIDS or other clinical manifestations of HIV infections, cellular immunodeficiencies, hypogammaglobulinemia, and dysgammaglobulinemia (96). The ACIP maintains its recommendation that varicella vaccine not be administered to persons who have cellular immunodeficiencies, but persons with impaired humoral immunity may now be vaccinated (97).

In addition, some HIV-infected children may now be vaccinated (97). Varicella vaccine is contraindicated in persons with other conditions associated with impaired immunity or in persons receiving steroid therapy who have not changed. Varicella vaccine is contraindicated in persons with the following conditions: (i) pregnancy, (ii) severe febrile illness, and (iii) known history of anaphylactic reaction to vaccine components (23, 96). Administration of varicella vaccine should be avoided if the individual is receiving immunosuppressive doses of systemic corticosteroids. The effects of corticosteroids vary, but many clinicians consider a prednisone dose equivalent to either 2 mg/kg of body weight or 20 mg per day to be sufficiently immunosuppressive to raise concerns about the safety of vaccination with live-virus vaccines.

After cessation of immunosuppressive therapy, varicella vaccine is generally withheld for at least 1 month. Because the intensity and type of immunosuppressive therapy, radiation therapy, underlying disease, and other factors determine when immunologic responsiveness will be restored, however, a definitive recommendation for an interval after cessation of immunosuppressive therapy when varicella vaccine can be safely and effectively administered is often not possible.

Transmission of the live attenuated varicella virus vaccine used for immunization has been documented rarely. Therefore, contacts of immunocompromised patients should be vaccinated to prevent the spread of natural varicella to such patients. Vaccinees who develop a rash in the month after immunization should avoid direct contact with immunocompromised, susceptible individuals for the duration of the rash.

Receipt of antibody-containing blood products (whole blood, plasma, or parenteral immunoglobulin) may interfere with seroconversion to varicella vaccine. Varicella vaccine should not be given to persons with Reye’s syndrome has occurred in children infected with varicella who receive salicylates. Whether varicella vaccine might induce Reye’s syndrome is not known, but the vaccine manufacturer recommends that salicylates should not be given within at least 6 weeks after administration of varicella vaccine.
DISEASES FOR WHICH IMPROVED VACCINES BECAME AVAILABLE

Haemophilus influenzae Type b

Prior to the introduction of routine infant and childhood vaccination against Haemophilus influenzae type b (Hib), this pathogen was a major cause of invasive bacterial infections in young children in the United States. It was the most common cause of bacterial meningitis and epiglottitis and a significant cause of septic arthritis, occult febrile bacteremia, and pneumonia in children younger than 5 years, causing an estimated 12,000 cases of meningitis and 8,000 additional cases of invasive Hib disease annually (131). The cumulative risk of Hib disease was approximately 1 in every 200 American children in the first 5 years of life, with the peak incidence of Hib meningitis occurring between 6 and 12 months of age.

Because the majority of cases of Hib disease occurred in infancy, vaccines that induced protection by 6 months of age were necessary for effective control of Hib disease. Realization of this goal was made possible by the development of conjugate vaccines in which the capsular polysaccharide of Hib, its major virulence factor and the antigen against which protective antibodies are directed, is chemically linked to a protein carrier. Although the purified capsular polysaccharide, polyribosylribitol phosphate (PRP), is a poor immunogen in children younger than 18 months, PRP conjugated to a protein carrier has the antigenic properties of the protein carrier. As a result, PRP conjugate vaccine induces protective antibody in infants and young children and significantly greater concentrations of circulating anti-PRP at all ages than does the unconjugated polysaccharide (315, 370). This age-dependent immunogenic characteristic of purified PRP (and other polysaccharide antigens) is that of a T-cell-independent antigen to which humoral responses are mediated by B-cell lymphocytes alone without T-helper lymphocytes. In contrast, the polysaccharide-protein conjugate vaccines are T-cell-dependent antigens in which T-helper lymphocyte activation as well as B-cell mediation of the humoral antibody response occurs. T-cell-dependent antigens also elicit booster responses that are important to the effectiveness of polysaccharide vaccines.

Four conjugate vaccines have been licensed in the United States since 1987 (Table 3). Each conjugate vaccine is composed of PRP antigen conjugated to a protein carrier. The vaccines differ in the protein carrier, size of the saccharide component, and chemical linkage. The PRP-D conjugate vaccine is licensed only for infants 15 months of age or older. Three Hib vaccines are licensed for infant vaccination: HbOC, PRP-T, and PRP-OMP.

Placebo-controlled field trials of both HbOC and PRP-OMP in infants in the United States demonstrated nearly 100% protection and provided the basis for the initial approval of these vaccines for use in this country. In a study in northern California of HbOC, vaccine efficacy was 100% for infants receiving the three-dose schedule at 2, 4, and 6 months of age (50). In a Navajo population of infants at high risk of Hib disease who were vaccinated at 2 and 4 months of age with either PRP-OMP or placebo, vaccine efficacy was 100% at 1 year of age and 93% in total (324). Randomized, placebo-controlled trials of PRP-T were terminated before completion, when the FDA approved HbOC and PRP-OMP for use in infants (183). Licensure of PRP-T was based on the comparable immunogenicity in a three-dose schedule to that of the other two products. In addition, an efficacy trial in Great Britain and the lack of cases in the terminated trials indicate comparable efficacy of PRP-T to that of HbOC and PRP-OMP (52, 359).

Hib conjugate vaccines are well tolerated. Local reactions occur in approximately 25% of recipients but typically are mild and last less than 24 h (152, 370). Systemic reactions such as fever and irritability are infrequent. While an increased risk of invasive Hib disease in the early postvaccination period exists with unconjugated PRP vaccine, the risk of disease immediately after conjugate vaccination is not increased (209). Other serious adverse events, such as anaphylaxis, have not been reported with Hib conjugate vaccines.

Since 1991, routine vaccination against Hib disease has been recommended for all children beginning at approximately 2 months of age (13, 59, 101). HbOC, PRP-T, and PRP-OMP are now considered interchangeable for primary as well as booster vaccination. Excellent immune responses have been

---

**TABLE 3. Hib conjugate vaccines**

<table>
<thead>
<tr>
<th>Vaccine manufacturer</th>
<th>Abbreviation for vaccine (trade name)</th>
<th>Carrier protein</th>
<th>Polysaccharide size</th>
<th>Spacer</th>
<th>Licensure in the United States</th>
<th>Date of licensure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aventis Pasteur</td>
<td>PRP-D (ProHIBit)</td>
<td>Diphtheria toxoid CRM197 (a nontoxic mutant diphtheria toxin)</td>
<td>Medium</td>
<td>6 carbon</td>
<td>For children ≥15 mo</td>
<td>1987</td>
</tr>
<tr>
<td>Wyeth-Lederle Vaccines &amp; Pediatrics</td>
<td>HBcOC (HiBTITER)</td>
<td></td>
<td></td>
<td>None</td>
<td>For infants and children ≥2 mo</td>
<td>1988</td>
</tr>
<tr>
<td>Merck &amp; Company</td>
<td>PRP-OMP</td>
<td>An OMP complex of N. meningitidis Tetanus toxoid</td>
<td>Large</td>
<td>Complex, involving a thioether 6 carbon</td>
<td>For infants and children ≥2 mo</td>
<td>1989</td>
</tr>
<tr>
<td>Aventis Pasteur</td>
<td>PRP-T (ActHIBa, OmiHIBb)</td>
<td></td>
<td></td>
<td></td>
<td>For infants and children ≥2 mo</td>
<td>1993</td>
</tr>
</tbody>
</table>

---

* Distributed in the United States by Aventis Pasteur.
* Distributed in the United States by Glaxo SmithKline.
achieved when vaccines from different manufacturers have been interchanged in the primary series (29, 48, 190). If PRP-OMP is administered in a series with one of the other two products licensed for infants, the recommended number of doses to complete the series is determined by the other product (and not by PRP-OMP). For example, if PRP-OMP is administered for the first dose at age 2 months and another vaccine is administered at age 4 months, a third dose of any of the three licensed Hib vaccines is recommended at age 6 months to complete the primary series. A final dose of any product, irrespective of the prior vaccines received, is acceptable at 12 to 15 months of age for completion of the Hib immunization schedule.

For children in whom Hib immunization has not been initiated by 7 months of age, recommended schedules differ according to the child’s age and choice of conjugate vaccine (see references 13 and 59 for further information). Previously unimmunized children aged 15 months or older should be immunized with a single dose of any licensed conjugate Haemophilus vaccine. For previously unimmunized children 5 years or older, immunization is indicated only if they have an underlying condition predisposing to Hib disease, such as asplenia or HIV infection.

Introduction of Hib conjugate vaccines in the United States, first in children 18 months and older and later as a routine infant immunization, has dramatically decreased the incidence of disease. By 1995, Hib disease levels had declined by more than 95% below preimmunization levels (98, 369). The remarkably rapid reduction in disease incidence was partly because of the ability of the vaccine to reduce nasopharyngeal carriage of the organism, leading to reduced rates of exposure and infection even in those not immunized (39).

### Pertussis

Pertussis (whooping cough) continues to cause significant morbidity and mortality among young children worldwide (275). The WHO has estimated that in the absence of vaccination, approximately $10^6$ deaths would have occurred from the disease and its complications. In the United States, the number of cases has been reduced by approximately 95% during the vaccine era. Nevertheless, approximately 4,000 reported cases of pertussis still occur each year (86) and large outbreaks of 100 or more cases also have occurred recently (122, 177).

Effective prevention programs necessitate immunization of young infants, beginning at 2 months of age, because the morbidity and mortality of pertussis is greatest in infants, especially those younger than 6 months (86, 120). Approximately 35% of reported cases in the United States occur in infants younger than 6 months. In this age group, the case-fatality rate from 1992 to 1994 was 0.6%; 71% of the infants were hospitalized; and complications such as pneumonia, seizures, and encephalopathy were frequent (86). High rates of immunization in children beyond infancy may further reduce the risk of infection in infants by decreasing the incidence of infection in older family members and the transmission of Bordetella pertussis within the household.

Whole-cell pertussis vaccine, which has been in use for many years, is a suspension of inactivated B. pertussis, and is combined with diphtheria and tetanus toxoids (DTP). This vaccine has a high incidence of local and systemic reactions. To reduce the incidence of reactions, acellular vaccines composed of one or more purified components of B. pertussis have been developed and combined with diphtheria and tetanus toxoids (DTaP). Multiple acellular vaccines have been formulated from different components of B. pertussis and have been tested in children. All vaccines contain a detoxified pertussis toxin, pertussis toxoid (151). In addition, most vaccines have one or more of the following B. pertussis antigens: filamentous hemagglutinin, pertactin, and fimbrial proteins. In the early 1990s, two acellular vaccines were approved for use in children 15 months of age and older in the United States. Approval for infant immunization followed in 1996. Four acellular vaccines are approved for the primary vaccination series during infancy (Table 4). Two of these vaccines, ACEL-IMUNE and Certira, were withdrawn from the market in 2001. Of the available acellular pertussis vaccines, Triedia is currently licensed for the five-dose DTaP vaccination series while Infanrix is licensed for the first four doses of the vaccination series. The ACIP recommends that whenever feasible, the same brand of DTaP vaccine should be used for all doses of the vaccination series. If the vaccine provider does not know or does not have available the type of DTaP previously administered, any of the available licensed DTaP vaccines may be used to complete the vaccination series (114).

For both whole-cell and acellular vaccines, serological correlates of immunogenicity have not been established for assessing efficacy. As a result, field and other epidemiological studies are necessary to demonstrate efficacy. Studies of household contacts exposed to pertussis in the United States indicate that the efficacy of whole-cell vaccine is 80% or greater (86, 120, 286). The efficacy of eight acellular pertussis vaccines in infants has been evaluated (302). Rates of prevention of pertussis with these vaccines have ranged from 58 to 93%. Comparison of efficacy between the different products, however, often is not possible because of differences in study design.

<table>
<thead>
<tr>
<th>Vaccine manufacturer</th>
<th>Trade name</th>
<th>No. of pertussis antigens</th>
<th>Antigenic content*</th>
<th>Date of licensure</th>
<th>Dose series approved</th>
<th>Currently marketed in the United State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aventis Pasteur</td>
<td>Tripedia</td>
<td>2</td>
<td>PT, FHA</td>
<td>1996</td>
<td>5</td>
<td>Yes</td>
</tr>
<tr>
<td>Lederle Laboratories</td>
<td>ACEL-IMMUNE</td>
<td>3</td>
<td>PE, FHA, FIM</td>
<td>1996</td>
<td>5</td>
<td>No</td>
</tr>
<tr>
<td>Glaxo SmithKline</td>
<td>Infanrix</td>
<td>3</td>
<td>PT, FHA, PE</td>
<td>1997</td>
<td>4</td>
<td>Yes</td>
</tr>
<tr>
<td>Baxter-Hyland Immuno</td>
<td>Certiva</td>
<td>1</td>
<td>PT</td>
<td>1998</td>
<td>4</td>
<td>No</td>
</tr>
</tbody>
</table>

* PT, pertussis toxin; FHA, filamentous hemagglutinin; PE, pertactin; FIM, fimbriae.
vaccine schedule (specifically, number of doses and age of administration), case definitions for pertussis, and other confounding variables. In general, these acellular vaccines appear to be similar in efficacy to most whole-cell vaccines.

Local and febrile reactions to whole-cell vaccines are common, occurring in more than half of DTP recipients (132). These manifestations usually develop within the first 24 h and are of brief duration. The incidence of these febrile reactions following administration of acellular vaccine is significantly lower (151, 302). Comparison of the rates with different acellular vaccines have demonstrated similar safety profiles for each of these vaccines (123, 329). Rates of local reactions increase with each subsequent dose of DTaP vaccine (298, 356). Booster doses of acellular pertussis vaccine may be associated with extensive local swelling, especially with vaccines containing high diphtheria vaccine content (309). Severe reactions to acellular vaccines are rare (123, 151, 302, 329).

Vaccination against pertussis is routinely recommended for children at 2, 4, and 6 months of age, followed by a fourth dose at 12 to 18 months of age and a fifth dose at 4 to 6 years of age (8, 11, 87, 88). As of January 2000, the AAP and ACIP recommend exclusive use of acellular pertussis vaccines for all doses of the pertussis vaccine series (85, 114). DTP is not an acceptable alternative because of its higher rates of local reactions, fever, and other common systemic reactions.

Contraindications and precautions for pertussis vaccine are based on adverse reactions associated with whole-cell vaccine. While reactions following DTaP are much less common than those associated with DTP, the contraindications and precautions for DTaP are currently the same (8, 11, 87, 88).

Pneumococcal Disease

*Streptococcus pneumoniae* is the most common cause of invasive bacterial infection in children. In addition, the organism is responsible for 30 to 50% of cases of acute otitis media (AOM). Most cases of invasive disease occur in children younger than 2 years and adults 65 years of age and older (95).

To date, at least 90 serotypes of *S. pneumoniae* have been identified. The 23-valent polysaccharide pneumococcal vaccine, licensed in 1983, contains purified capsular polysaccharide antigen of 23 serotypes. These serotypes are responsible for 85 to 90% of adult infections and nearly 100% of cases of invasive disease and 85% of cases of otitis media in children. Efficacy rates for prevention of bacteremia and meningitis caused by vaccine serotypes for the polysaccharide vaccine are 61 to 75% in immunocompetent adults (58, 330) and 57% in children younger than 5 years (58).

The polysaccharide vaccine has been effective in reducing severe disease in the adult population (58) but has had little impact in young children because the vaccine is not immunogenic in children younger than 2 years of age (9). In addition, the polysaccharide vaccine has not been effective in preventing otitis media caused by *S. pneumoniae* (9).

Recommendations by the ACIP and the AAP do not include routine use of the currently licensed polysaccharide vaccine except for those older than 2 years with a medical condition which puts them at high risk of severe pneumococcal infection, such as sickle cell disease, functional or anatomic asplenia, nephrotic syndrome or chronic renal failure, immunodeficiency, cerebrospinal fluid leak, or HIV infection, and adults older than 65 years (9, 95).

Several factors have made the development of new preventative strategies for pneumococcal disease a high priority (137). Resistance of *S. pneumoniae* to multiple antibiotics has increased rapidly in the United States and even more rapidly in other parts of the world (224). Children younger than 2 years have the highest rate of invasive pneumococcal infection but do not develop an effective antibody response to polysaccharide vaccine. In addition, children up to 5 years of age may have poor responses to serotypes 6B, 14, 19F, and 23F, common causes of pediatric infections and the most prevalent penicillin-resistant serotypes.

These factors have prompted the development of conjugated polysaccharide-protein vaccines. These new vaccines are similar in design to the licensed Hib conjugate vaccines. Pneumococcal conjugate vaccines under development differ in the carrier protein, the molecular size of the polysaccharide, and the method of conjugating the polysaccharide to the protein (170). To date, the candidate carrier proteins have been the same as those used in Hib conjugate vaccines. Because of the large number of serotypes of *S. pneumoniae* which cause disease, development of these vaccines has been more difficult than development of similar vaccines for Hib. Each pneumococcal antigen must be coupled to a protein carrier, and the vaccine must be prepared to ensure that enough antigen is present to induce an immune response but not enough to elicit an adverse reaction.

Conjugate vaccines that contain polysaccharides of 5, 7, 9, or 11 pneumococcal serotypes conjugated to either tetanus toxoid, diphtheria toxoid, meningococcal outer membrane complex, or a mutant diphtheria toxin (CRM<sub>197</sub>) have been developed (170). Pneumococcal conjugate vaccines appear to be safe. The most commonly reported reactions have been local reactions at the injection site, but these occur at a lower frequency than do local reactions with other childhood vaccines such as DTP (310).

Currently, five pneumococcal vaccine candidates with different carrier proteins are under development (170). All appear to be comparable in their ability to induce primary immunity and immunologic memory. The immunogenicity of the vaccine appears to determined by the pneumococcal polysaccharide serotype rather than the carrier protein. Some serotypes (14, 18C, and 19F) are excellent immunogens, eliciting antibody protection after a single dose, while others (6B and 23F) require three doses of vaccine (170). All conjugate vaccines appear to elicit immunologic memory (170). Antibody concentrations achieved after the initial series of three doses are usually sustained only for a few months and then decline to near preimmunization levels. A dose of pneumococcal vaccine, either polysaccharide or conjugate, given in the second year of life elicits an amnestic-type response.

Heptavalent vaccine containing serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F conjugated to CRM<sub>197</sub> was studied in a large prospective placebo-controlled efficacy trial in Northern California that involved 38,000 children. The vaccine was 89% effective in prevention of invasive disease caused by any pneumococcal serotype and 97% effective against disease due to the seven vaccine serotypes (49). For noninvasive disease, there was a 7% decrease in cases of otitis media and a decrease of
The ability of the heptavalent vaccine to protect children against AOM was also evaluated in an efficacy trial conducted in Finland (171). Efficacy was estimated to be 34% for prevention of AOM caused by pneumococci of any serotype, while efficacy against AOM irrespective of etiology was 6%. Efficacy against AOM caused by vaccine-related serotypes was 57%, however, an increase of 33% in the rate of AOM episodes caused by nonvaccine serotypes occurred in the group receiving the heptavalent vaccine compared with controls. However, in spite of the increase in disease caused by nonvaccine serotypes, the net effect on pneumococcal AOM was a reduction of 34%.

The heptavalent vaccine (Prevnar [Wyeth-Lederle Vaccines]) was licensed in the United States in February 2000. Recommendations by the AAP and the ACIP for use of the licensed heptavalent pneumococcal conjugate vaccine (PCV7) have been issued (22, 90). The AAP and ACIP recommend universal use of PCV7 in children 23 months and younger. For children in whom pneumococcal immunization is initiated before 7 months of age, four doses of PCV7 are recommended at 2, 4, 6, and 12 to 15 months of age. For children beginning PCV7 immunization between 7 and 23 months of age, the recommended schedule differs according to the child’s age (see references 22 and 90 for further information). In addition, two doses of PCV7 are recommended for children 24 to 59 months of age who are at high risk of invasive pneumococcal infection and have not previously been immunized with PCV7. These children should also receive the 23-valent polysaccharide vaccine (PPV23) to expand serotype coverage. Routine immunization of low- and moderate-risk children 24 months of age or older is not recommended by the AAP at this time (22). The ACIP recommends that PCV7 be considered for all children aged 24 to 59 months, with priority given to those aged 24 to 35 months, of Alaskan Native, American Indian, or African American descent, and those who attend group day care centers (90). Children aged 24 to 59 months at high risk who have not previously received PCV7 but who have already received PPV23 should be vaccinated with two doses of PCV7 given ≥2 months apart (90). Current data do not support a recommendation to replace the 23-valent polysaccharide vaccine with PCV7 vaccine for older children and adults (90).

 Routine infant immunization using this newly developed conjugate vaccine could lead to significant reductions in S. pneumoniae disease. If use of the conjugate vaccine eliminates nasopharyngeal carriage of S. pneumoniae, as suggested by preliminary data suggests (146, 147), person-to-person transmission will be interrupted and the incidence of disease should decline markedly.

One potential problem with such vaccines is the need to immunize against many different serotypes of pneumococci. Because of local reactions to the protein component, conjugate vaccines which contain more than 12 serotypes may be difficult to produce. As a result, different formulations of conjugate pneumococcal vaccine may be developed that would contain different serotypes targeted for a specific group of patients. Vaccine containing types 4, 6B, 9V, 14, 18C, 19F, and 23F would be necessary for prevention of otitis media in the United States, while types 1, 2, and 5 would need to be added to prevent pneumonia in developing countries. In addition, the use of conjugate vaccines against limited serotypes may lead to the emergence of pneumococcal serotypes which are currently less common and require adjustment of the vaccine composition.

**Rabies**

Rabies is a viral infection transmitted in the saliva of infected mammals. The virus enters the central nervous system of the host, causing an encephalomyelitis that is almost always fatal. Postexposure prophylaxis is possible because of the long incubation period of this infection.

Rabies in animals is common, and rabies postexposure prophylaxis is frequently given. Carnivorous wild animals, especially skunks, foxes, coyotes, raccoons, and bats, are a continuing potential source of rabies, accounting for most cases of animal rabies and the few cases of human rabies in the United States. Wildlife rabies occurs throughout the continental United States; only Hawaii remains consistently rabies free. Domestic animals (dogs and cats) represent only a small proportion of proven rabid animals, but as the primary interface between the sylvan reservoir and humans, they account for most postexposure immunoprophylaxis against rabies.

While the likelihood of human exposure to a rabid domestic animal in the United States is small, international travelers to areas where canine rabies is still endemic have an increased risk of exposure to rabies. In most of Asia, Africa, and Latin America, dogs are the most common source of rabies among humans. Of the 36 human rabies deaths reported to the CDC from 1980 through 1997, 12 appear to have been related to rabid animals outside the United States (75, 283).

Four formulations of three inactivated rabies vaccines are currently licensed for preexposure and postexposure prophylaxis in the United States. Human diploid cell vaccine (HDCV), derived from the Pitman-Moore strain, has been licensed in the United States since 1980. It is supplied in two forms: for intramuscular (I.M.) administration or for intradermal administration (63). Rabies vaccine, adsorbed (RVA), derived from the Kissing strain of rabies virus cultured in fetal rhesus lung diploid cells, was licensed in the United States in 1988. It is formulated for I.M. administration only. A third rabies vaccine, purified chick embryo cell (PCEC) vaccine, became available in the United States in 1997 (161). It is prepared from the Flury LEP rabies virus strain grown in primary cultures of chicken fibroblasts and is formulated for I.M. administration only. Duck embryo rabies vaccine has not been available in the United States since 1981. Allergic reactions occurred frequently with this vaccine.

When used as indicated, all three types of rabies vaccines are considered equally safe and effective for both preexposure and postexposure prophylaxis (see the ACIP recommendations [74]). However, only the HDCV intradermal vaccine has been evaluated and approved by the FDA for the intradermal dose and route for preexposure vaccination (63). Therefore, the RVA and PCEC vaccines should not be used intradermally. Usually, an immunization series is initiated and completed...
with one vaccine product. No clinical studies have been conducted that document a change in efficacy or the frequency of adverse reactions when the series is completed with a second vaccine product.

For adults, the i.m. rabies vaccination should always be administered in the deltoid area. For children, the anterolateral aspect of the thigh is also acceptable. The gluteal area should never be used for HDCV, RVA, or PCEC injections because administration of HDCV in this area results in lower neutralizing antibody titers (D. B. Fishbein, L. A. Sawyer, F. L. Reid-Sanden, and E. H. Weir. Letter, N. Engl. J. Med. 318:124–125, 1988).

Reactions after vaccination with HDCV, RVA, and PCEC vaccines are less serious and less common than with previously available vaccines (74). Local reactions at the injection site occur in 30 to 74% of injections, and systemic reactions, such as headache, nausea, abdominal pain, muscle aches, and dizziness, occur in 5 to 40% of vaccine recipients. Approximately 6% of persons who received booster doses of HDCV developed an immune complex-like reaction 2 to 21 days after administration of the booster dose (65). This reaction occurred less frequently among persons receiving primary vaccination.

The reactions have been associated with the presence of betapropiolactone-altered human albumin in the HDCV and the development of immunoglobulin E (IgE) antibodies to this allergen (180).

The essential components of rabies postexposure prophylaxis are wound treatment and, for previously unvaccinated persons, the administration of both rabies immune globulin (RIG) and vaccine (74). Studies conducted in the United States by CDC have documented that a regimen of one dose of RIG and five doses of rabies vaccine over a 28-day period was safe and induced an excellent antibody response in all recipients (30). RIG provides a rapid, passive immunity that persists if anatomically feasible, the full dose of RIG should be thoroughly infiltrated in the area around and into the wounds. Any remaining volume should be injected intramuscularly at a site distant from vaccine administration. RIG is unnecessary and should not be administered to previously vaccinated persons because an amnestic response will follow the administration of a booster regardless of the antibody titer (74).

Once initiated, rabies prophylaxis should not be interrupted or discontinued because of local or mild systemic adverse reactions to rabies vaccine. Usually, such reactions can be successfully managed with anti-inflammatory and antipyretic agents, such as ibuprofen or acetaminophen. When a person with a history of serious hypersensitivity to rabies vaccine must be revaccinated, antihistamines can be administered. Epinephrine should be readily available to counteract anaphylactic reactions, and the person should be observed carefully immediately after vaccination.

Typhoid

Typhoid fever remains a serious public health problem throughout the world, with an estimated incidence of 33 million cases and 500,000 deaths annually. It also is a serious threat to travelers visiting areas of endemic infection. In the United States, only 375 cases were reported in 1998. In virtually all areas of endemic infection, the incidence of typhoid fever is highest in children aged 5 to 19 years.

Parenteral inactivated vaccines have been used for many years. In field trials of inactivated typhoid vaccine, vaccine efficacy has ranged from 51 to 76% (109). Protection has not been correlated with specific Salmonella enterica serovar Typhi antibodies. In addition, protection in experimental challenge studies in volunteers has varied with the challenge inoculum and can be overcome by a high inoculum of serovar Typhi (248). Following parental vaccination, febrile reactions, head- ache, and severe local pain and swelling are common; 13 to 24% of vaccinees have subsequently missed school or work (248). Booster doses are recommended for recipients of parenteral vaccines.

Two new typhoid vaccines that provide significant protection without causing adverse reactions have been licensed in many countries (248). One of these is Ty21a, a live attenuated oral vaccine, which was licensed in the United States in 1991. The other is a parenteral vaccine containing the purified Vi polysaccharide capsular antigen of serovar Typhi which was licensed in 1994.

The oral vaccine consists of a stable mutant of a pathogenic serovar Typhi strain, Ty21a, that lacks the enzyme UDP-galactose-4-epimerase and the Vi capsular polysaccharide. The efficacy of the oral Ty21a vaccine in clinical trials has ranged from 42 to 96% following the initial series of three doses, with the lower efficacies seen in trials from areas with highly endemic disease (248, 334). The mechanism of protection is not known. Reactions from the oral Ty21a vaccine have been mild and rare. In safety trials, adverse reactions occurred with equal frequency among groups receiving vaccine or placebo (248). Since data on safety and efficacy in young children are not available, the manufacturer currently recommends that Ty21a vaccine not be given to children younger than 6 years.

Recommendations for booster doses for those whose primary immunization was given with oral vaccines have not yet been determined. Primary immunization involves multiple doses and varies in schedule and dose according to the vaccine preparation. Since the oral vaccine is a live attenuated strain, it should not be given to immunocompromised persons, including those known to be infected with HIV (248). This vaccine is promising for the control of endemic typhoid fever because protection lasts for at least 5 years and mass immunization may result in herd immunity.

Purified Vi, a recognized virulence factor of serovar Typhi, has been used as a parenteral polysaccharide vaccine. Efficacy of the Vi vaccine in clinical trials is 72% at 17 months and 64% at 21 months following a single dose (248). Since additional doses of purified Vi vaccine fail to boost antibody titers, Robbins and Schness have conjugated the Vi polysaccharide to protein carriers such as Escherichia coli labile toxin to confer T-cell-dependent properties upon the antigen (315). A clinical trial of a conjugate of the Vi polysaccharide bound to nontoxic recombinant Pseudomonas aeruginosa exotoxin A in Vietnamese children aged 2 to 5 years found the vaccine to be safe and immunogenic (252). The efficacy of this conjugate vaccine was 91%.
DISEASES FOR WHICH THE IMMUNIZATION STRATEGY HAS CHANGED

In developing recommendations for immunization, multiple factors are considered, including vaccine characteristics, scientific knowledge about the principles of immunization, assessment of the benefits of the vaccine, risk of the disease and its complications, vaccine costs, and risks of adverse reactions. Changes in relative benefits and risks necessitate continued review of recommendations. In the United States, recommendations for immunization of infants and children are made by two different committees, the ACIP and the AAP Committee on Infectious Diseases. These committees work closely together, and in most circumstances their recommendations are similar. Since 1995, these two committees and the American Academy of Family Practice (AAFP) have issued a single vaccine schedule at least once a year (103).

Several major changes in immunization schedules and strategy have occurred in the 1990s. These changes have included the establishment of a routine preadolescent immunization visit at age 11 to 12 years of age to provide a visit for updating immunizations (14, 76). The first booster dose of adult tetanus-diphtheria (Td) vaccine should be given at this visit, rather than at 14 to 16 years of age as previously was the case. In addition, at this preadolescent visit, children not previously vaccinated with hepatitis B, varicella, and/or the second dose of measles-containing vaccine should be given necessary immunizations and scheduled for future visits to receive any vaccines not administered during this visit.

Changes in relative benefits and risks have necessitated continued evaluation of recommendations. As new vaccines and scientific knowledge become available, vaccine recommendations and schedules have been modified and changed. Examples of changes in this decade include universal infant and adolescent hepatitis B immunization, addition of a second dose of measles-containing vaccine, introduction of acellular pertussis vaccine for infants, and recommendations for the use of inactivated poliomyelitis vaccine to decrease the incidence of vaccine-associated paralytic poliomyelitis in the United States.

Hepatitis B

Hepatitis B virus (HBV) infection is a leading cause of acute hepatitis and a major public health problem of global importance. Its incidence is especially high in many Asian and African countries. Individuals who develop chronic infection are at risk for chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma. In the United States, approximately 300,000 persons are infected each year and 2 million persons are estimated to be chronically infected (196). Not only are these persons at increased risk for chronic and malignant liver disease, but also, as chronic carriers, they serve as the reservoir for HBV transmission.

The initial strategies for prevention of hepatitis B through vaccination reflect the varying epidemiology of HBV infection in different areas of the world (60). In the United States, for example, infection is of comparatively low endemicity and occurs primarily in adolescents and adults. The risk of infection, however, is much greater in certain populations. Examples include those born and living in areas or among groups in which HBV is highly endemic and those with life-styles predisposing to HBV acquisition, such as male homosexual activity, intravenous drug abuse, and promiscuous heterosexual activity (3). Consequently, the original strategy of hepatitis B prevention in this country was selective vaccination based on risk factors. In contrast, in geographic areas where HBV infection is highly endemic, infection is usually acquired at birth or during childhood, resulting in the recommendation for universal vaccination of infants.

In 1991, the ACIP recommended a comprehensive hepatitis B vaccination strategy to eliminate HBV transmission in the United States (60). Critical elements of this strategy included prevention of perinatal HBV transmission by identifying and providing immunoprophylaxis to infants of hepatitis B surface antigen-positive mothers and universal hepatitis B vaccination of infants to interrupt transmission and prevent future infection. The advantages of this approach included the existence of effective programs of routine childhood immunization, protection without the need to identity specific risk factors, and protection before significant exposure occurred. In addition, the positive effects of universal infant immunization had been observed in Taiwan, where the strategy of universal infant immunization was already employed. In Taiwan, the overall prevalence rate of HBV in children aged 1 to 10 years decreased from 9.8% in 1984 to 1.3% in 1994 (117). As a result of the implementation of this strategy in the United States, a substantial increase was seen in the percentage of children aged 19 to 35 months who had received three doses of hepatitis B vaccine, from less than 10% in 1991 to 84% in 1997 (106).

In 1994, the ACIP expanded the recommendations to include previously unvaccinated children aged 11 to 12 years (111). No nationwide vaccine coverage data are available to assess vaccine coverage among children aged 11 to 12 years; however, vaccine coverage in this group is expected to increase as states implement middle school entry requirements for hepatitis B vaccination (70).

In October 1997, the ACIP expanded its hepatitis B vaccination recommendations still further to include all unvaccinated children up to 18 years of age and made hepatitis B vaccine available through the Vaccines for Children program (VFC) for persons up to 18 years of age who are eligible for VFC (113). The other ACIP priorities for hepatitis B vaccination of children remained unchanged and included all infants; children in populations at high risk for HBV infection such as Alaska Natives, Pacific Islanders, and children who reside in households of first-generation immigrants from countries where HBV infection is moderately or highly endemic; previously unvaccinated children aged 11 to 12 years; and older adolescents and adults in defined risk groups (60, 111). The goal of the 1997 recommendations was to increase access to hepatitis B vaccine by encouraging the vaccination of previously unvaccinated children and adolescents up to 18 years of age whenever they are seen for routine medical visits (113). This expansion of the recommended age group for vaccination and for VFC eligibility simplifies previous recommendations and the eligibility criteria for VFC vaccine.

Universal vaccination of infants and children aged 11 to 12 years will result in a highly immune population and is expected to eliminate HBV transmission in the United States. However, high rates of HBV infection continue to occur among Alaskan Native and Pacific Islander children and among children re-
siding in households of first-generation immigrants from countries where HBV infection is endemic (206, 258). As a result, targeted programs are needed to achieve high vaccination coverage among these children. In addition, because most HBV infections in the United States occur among adults, vaccinating infants and adolescents aged 11 to 12 years alone will not substantially lower the disease incidence for several years. Most HBV infections in adults occur among persons who have defined risk factors for HBV infection, including persons with multiple sex partners (more than one partner during the preceding 6 months), men who have sexual intercourse with men, and injected-drug users (111). The primary means of preventing these infections is to identify settings where adolescents and adults with high-risk drug and sexual practices can be routinely accessed and vaccinated.

Hepatitis B vaccines consisting of inactivated small envelope viral particles derived from chronic hepatitis B plasma were first introduced in the early 1980s. In the late 1980s, two recombinant vaccines were licensed (Recombivax HB [Merck & Co.] and Engerix-B [SmithKline Beecham Biologicals]). The CDC and AAP recommend doses and schedules for the use of hepatitis B vaccines licensed in United States in infants and other age groups (see references 5, 25, 26, 60, 104, and 111 for more information). In August 1998, the Merck Vaccine Division discontinued production and distribution of the 2.5-μg/0.5-ml pediatric dose of Recombivax HB hepatitis B vaccine, which was licensed for infants of HBsAg-negative mothers and children younger than 11 years. The 5-μg/0.5-ml dose of Recombivax HB is now indicated for all vaccinees up to 19 years of age regardless of the mother’s HBsAg status. The change was made to simplify the dosing of Recombivax HB and eliminate potential confusion when determining the correct dose of hepatitis B vaccine. The standard adult dose for Recombivax HB remains 10 μg/1.0 ml. The standard doses for the other licensed hepatitis B vaccine (Engerix B) remain unchanged. For the purposes of completing the hepatitis B vaccine series and achieving complete vaccination for hepatitis B, the two licensed hepatitis B vaccines are interchangeable when administered in doses recommended by the manufacturers (104).

In September 1999, the FDA approved an optional two-dose schedule of Recombivax HB for vaccination of adolescents aged 11 to 15 years. The ACIP recommended that this schedule be included in the Vaccines for Children Program in February 2000 (84). Using the two-dose schedule, the adult dose of Recombivax HB is administered to adolescents aged 11 to 15 years, with a second dose given 4 to 6 months after the first dose. In immunogenicity studies among adolescents aged 11 to 15 years, antibody concentrations and seroprotection rates were similar with the two-dose schedule and the currently licensed three-dose schedule. Follow-up data indicate that the rate of decline in antibody levels over 2 years for the two-dose schedule was similar to that for the three-dose schedule. No data are available to assess long-term protection or immune memory following vaccination with the two-dose schedule, and it is not known whether booster doses of vaccine will be required. Children and adolescents who have begun vaccination with a dose of 5 μg of Recombivax HB should complete the three-dose series with this dose. If it is not clear which dose an adolescent was given at the start of a series, the series should be completed with the three-dose schedule.

Routine screening of pregnant women for HBsAg is still recommended because the schedule of the vaccine given to the infant and the use of hepatitis B immune globulin (HBIG) are based on the HBsAg status of the mother (5, 25, 26, 60, 111). In addition to receiving the hepatitis B vaccine series, infants born to HBsAg-positive mothers should receive 0.5 ml of HBIG at a separate injection site within 12 h of birth. Infants born to HBsAg-negative mothers or children who received one or two doses of the 2.5-μg/0.5-ml dose of Recombivax HB may complete the hepatitis B vaccination series with either the 2.5-μg/0.5-ml or the 5.0-μg/0.5-ml dose (104). Children who have completed the hepatitis B vaccination series with the 2.5-μg/0.5-ml dose do not require revaccination (104).

Special considerations apply in the selection of hepatitis B vaccine products for the dose administered at birth due to the concern about exposure of young infants to thimerosal-containing vaccines. Thimerosal is a mercury-containing preservative that has been used as an additive to biologics and vaccines since the 1930s because it is effective in preventing bacterial and fungal contamination, particularly in multidose containers. The FDA Modernization Act of 1997 required the review and assessment of the risk of all mercury-containing pharmaceuticals. When vaccines were assessed, it was recognized that some children could be exposed over the first 6 months of life to a cumulative level of mercury that exceeds one of the federal guidelines on methyl mercury. However, a significant safety margin is incorporated into all the acceptable mercury exposure limits, and there are no data or evidence of any harm caused by the level of exposure using the existing immunization schedules. In addition, the risk posed by exposure to thimerosal, which contains ethyl mercury, is significantly lower than the methyl mercury on which the federal guidelines were based, is unknown. However, to avoid any potential risk, the Public Health Service, the AAP, and vaccine manufacturers agreed in July 1999 that thimerosal-containing vaccines should be removed as soon as possible.

On 8 July, 1999, the AAP and the Public Health Service released a joint statement about thimerosal in vaccines and the AAFP released a comparable statement (http://www.aafp.org/policy/camp/20.html) (27, 108). Recommendations were issued to minimize the exposure of young infants to thimerosal-containing vaccines until vaccines without thimerosal could be produced (108). Clinicians were advised to postpone the first dose of hepatitis B vaccine from birth until 2 to 6 months of age for infants born to HBsAg-negative mothers and to immunize preterm infants born to HBsAg-negative mothers when they reached term gestational age and a weight of at least 5.5 lb (2.5 kg). Because of the substantial risk of disease, there was no change in the recommendations for infants of HBsAg-positive mothers or of mothers whose status is not known. In populations where HBsAg screening of pregnant women was not routinely performed, it was recommended that vaccination of all infants at birth should be continued, as currently recommended.

After the statements on thimerosal in vaccines were published, changes occurred in newborn hepatitis B vaccination policies and practices in some hospitals. Distribution of thimerosal-free hepatitis B vaccines began in the fall of 1999 (67). By mid-September 1999, when adequate supplies of thimerosal-free hepatitis B vaccine became available, the CDC advocated a return to the previous infant hepatitis B vaccina-
tion practices, including administering the first dose of hepatitis B vaccine to newborns in hospitals that had discontinued the practice (http://www.cdc.gov/nip/news/thimerosal-guidance.htm) (27, 108). As of March 2000, thimerosal is no longer used as a preservative in any of the pediatric hepatitis B vaccines licensed in the United States (112). In 2000, preliminary assessments of the impact of these policy changes on routine hepatitis B vaccination practices were conducted by public health officials in Wisconsin, Oklahoma, Oregon, and Michigan. These assessments revealed that many hospitals in Wisconsin had not reinstated policies to ensure routine administration of hepatitis B vaccine to newborns despite the availability of preservative-free vaccine, that the number of vaccine doses given to newborns in both Oregon and Oklahoma had declined, and that an unvaccinated infant in Michigan had died from fulminant hepatitis B (78). The CDC concluded that restoring routine newborn hepatitis B vaccination practices may require active advocacy by professional and government groups.

Measles

Since the introduction of both an inactivated and a live attenuated measles vaccine (Edmonston B strain) in the United States in 1963, the reported incidence of measles has decreased by more than 99%. Although the incidence of measles has declined in all age groups, the decline has been greatest in children aged 5 to 14 years.

Measles was targeted for elimination in the United States by 1982. The efforts to eliminate measles were not successful as a result of two factors. The first was vaccine failure. In the late 1980s, outbreaks occurred in older children in schools in which immunization rates were usually greater than 95% (195, 264, 282). Attack rates were 1% to 5%, reflecting the accumulation of measles-susceptible individuals resulting from vaccine failure. The recurrent measles outbreaks among vaccinated school age children in 1989 prompted both the ACIP and the AAP to recommend that all children receive two doses of measles-containing vaccine, preferably as MMR (15, 61). Although administration of the second dose was originally recommended either at entry to primary school (ACIP) or middle/secondary school (AAP), the ACIP, AAP, and AAFP now recommend that a child receive the second dose at age 4 to 6 years rather than delaying it until the child is aged 11 to 12 years (83). Evidence now indicates that the major benefit of administering the second dose is a reduction in the proportion of persons who remain susceptible because of primary vaccine failure. Waning immunity is not a major cause of vaccine failure and has little influence on measles transmission, and revaccination of children who have low levels of measles antibody produces only a transient rise in antibody levels (163, 261, 263, 265, 288, 365).

The second factor leading to the measles outbreaks was the failure to implement current immunization strategies, especially in the inner cities, where a high proportion of preschool children (older than 15 months) had not been vaccinated. From 1989 through 1991, the proportion of unvaccinated persons with measles increased, reflecting outbreaks among unvaccinated inner-city preschool age children. Multiple barriers to timely immunization of these children were identified during investigation of the 1989 to 1991 measles resurgence.

The use of a two-dose schedule, combined with a major effort to increase vaccine coverage in preschool children, reduced the number of cases to 508 in 1996 (106). In 1998, measles reached a provisional record low number of 100 cases, with no measles-associated deaths (71). The epidemiology of measles during 1998 suggests that measles is no longer an indigenous disease in the United States.

In 1994, the AAP and ACIP lowered the recommended age for routine vaccination with measles vaccine from 15 months to 12 months (73). The decision to lower the routine age for primary vaccination was based on the observation that most children are susceptible to measles by 12 months of age due to waning transplacental immunity (259, 262). Most mothers now have vaccine-induced immunity rather than immunity conferred by infection with wild virus. The antibody concentrations induced by measles vaccination are generally lower than those induced by natural measles. Therefore, measles-specific antibodies acquired transplacentally are lower in infants of vaccinated mothers, resulting in susceptibility of these infants at an earlier age.

In 1998 the ACIP issued revised recommendations for the use of measles vaccine (83). Changes from previous recommendations include: (i) changes in the recommended interval between administration of immune globulin and measles vaccination and (ii) updated information on adverse events and contraindications, particularly for persons with severe HIV infection, persons with a history of egg or gelatin allergy or thrombocytopenia, and persons receiving steroid therapy.

Recent evidence indicates that high doses of immune globulins can inhibit the immune response to measles vaccine for 3 months or more (24, 332). The duration of this interference with the immune response depends on the dose of immune globulin administered. Blood and other antibody-containing blood products can also reduce the immune response to measles vaccine. Therefore, measles vaccine should be administered to persons who have received an immune globulin preparation only after the recommended intervals have elapsed (see references 24 and 73 for further information).

Recommendations for the use of measles vaccine in HIV-infected individuals have been changed as concerns about safety of MMR in severely immunocompromised HIV-infected persons arose (28, 83). The need to protect HIV-infected persons who are at increased risk for severe complications if infected with measles has been balanced against the risk of adverse reactions. As a result, measles vaccine is no longer recommended for HIV-infected persons with evidence of severe immunosuppression, for several reasons: a case of progressive measles pneumonitis occurred in a person with AIDS and severe immunosuppression to whom MMR vaccine was administered (82); evidence indicates a diminished antibody response to measles vaccine among severely immunocompromised HIV-infected persons (33); morbidity related to measles vaccination has been reported among persons with severe immunosuppression unrelated to HIV infection (42, 266, 269, 271); and in the United States, the incidence of measles is presently very low. Among HIV-infected persons who did not have evidence of severe immunosuppression, no serious or unusual adverse events were found after measles vaccination (267, 285, 289, 337). Therefore, MMR vaccination is recommended for all asymptomatic HIV-infected persons who do
not have evidence of severe immunosuppression and for whom measles vaccination would otherwise be indicated (28).

In persons who are allergic to eggs, the risk for serious allergic reactions such as anaphylaxis following administration of measles vaccine is extremely low and skin testing with vaccine is not predictive of allergic reaction to vaccination (7, 216, 232). Therefore, skin testing is not required before administering MMR to persons who are allergic to eggs. Similarly, the administration of gradually increasing doses of vaccine is not required (83). Data indicate that most anaphylactic reactions to measles- and mumps-containing vaccines are associated with hypersensitivity not to egg antigens but to other components of the vaccines, such as the gelatin stabilizer (191, 202, 231, 245).

Children who have a history of thrombocytopenia or thrombocytopenic purpura may be at increased risk for developing clinically significant thrombocytopenia after MMR vaccination (210). The decision to vaccinate with MMR should depend on the benefits of immunity to measles, mumps, and rubella and the risks for recurrence or exacerbation of thrombocytopenia after vaccination or during natural infection with measles or rubella (83).

Systemically absorbed corticosteroids can suppress the immune system of an otherwise healthy person. However, neither the minimum dose nor the duration of therapy sufficient to cause immune suppression is well defined. Although the immunosuppressive effects of steroid treatment vary, many clinicians consider a steroid dose that is equivalent to or greater than a prednisone dose of 2 mg/kg of body weight per day or a total of 20 mg per day daily sufficiently immunosuppressive to raise concern about the safety of administration of live-virus vaccines. Persons who have received systemic corticosteroids in doses of 2 mg/kg of body weight or 20 mg daily or on alternate days for an at least 14 days should avoid vaccination with MMR and its component vaccines for at least 1 month after cessation of steroid therapy (83). Persons who have received prolonged or extensive topical, aerosolized, or other local corticosteroid therapy that causes clinical or laboratory evidence of systemic immunosuppression should also avoid vaccination with MMR for at least 1 month after cessation of therapy (83).

**Meningococcal Disease**

*Neisseria meningitidis* is the leading cause of bacterial meningitis and continues to be a major public health problem, not only in the United States but also worldwide. Although the disease has a more severe impact on children and young adults, all age groups are susceptible to infections. The disease is transmitted from person to person by close contact. In the United States there are an estimated 3,000 cases per year involving meningococcal serogroups B, C, and, recently, Y. In other parts of the world, the number of cases is much larger. For example, during the 1996 epidemics caused by serogroup A in sub-Saharan Africa, more than 200,000 cases were reported, with 20,000 deaths. A significant proportion of the children who survive infections caused by *N. meningitidis* have permanent sequelae such as deafness.

Routine immunization against meningococcal disease has not been recommended in the United States by the ACIP or AAP because the risk of acquiring meningococcal disease is usually low. Furthermore, no vaccine is currently available for serogroup B, which accounts for nearly half of the cases in the United States, and the group C vaccine is poorly immunogenic in children 2 years of age or younger, a group accounting for 46% of the cases in recent surveillance data (215).

The incidence of invasive meningococcal disease in adolescents and young adults of high school and college age has increased in the United States since 1992 (317). As a result of the increase in the number outbreaks on college campuses, the American College Health Association issued a statement in September 1997 recommending that college students consider meningococcal immunization (http://www.acha.org/special-prj/men.htm). At that time, the ACIP and AAP did not change their recommendations because the overall incidence of disease in college students did not justify a recommendation for national immunization. The actual rate of meningococcal disease among college students is unknown; however, surveillance data suggest that it could not be more than 1.3/100,000 (213). This incidence is similar to that in the general population of 18- to 22-year-old individuals. Recent studies, however, indicate that certain groups of college students are at increased risk (184). The incidence of disease was significantly higher in on-campus residents than in the off-campus residents in a Maryland study (201). These data led to the October 1999 ACIP recommendation that college freshman dormitory residents be provided with information about meningococcal infection and the benefits of vaccination (http://www.cdc.gov/ncidod/dbmd/diseaseinfo/ meningococcalcollege.htm) (200). In June 2000, the ACIP reviewed the new data regarding the risk for meningococcal disease in college students, which demonstrated a modestly increased risk of disease in freshmen living in dormitories (92). Based on these data, the ACIP reaffirmed its recommendation that college freshman dormitory residents be provided with information about meningococcal infection and the benefits of vaccination and that vaccine should be made available to students who wish to receive it (92). The AAP issued a statement in December 2000 supporting immunization of college students, especially those living in dormitories (16).

**Poliomyelitis**

The widespread implementation of poliovirus vaccine programs has resulted in a dramatic reduction in the incidence of paralytic poliomyelitis throughout the world. In contrast to the prevaccine era, when more than 18,000 cases of paralytic disease occurred in the United States annually, the last known case in this country due to indigenous wild-type virus occurred in 1979 (343). Other than rare imported cases, the only cases of paralytic poliomyelitis in the United States since then have been vaccine related.

The effectiveness of polio vaccination has led to major and successful initiatives by the WHO for global eradication of poliovirus infections. This effort has been successful, resulting in an 80% reduction in the number of reported cases worldwide since the mid-1980s. Three WHO regions have eliminated or are close to eliminating poliovirus—the Region of the Americas has been polio free since 1991, the Western Pacific Region has not detected poliovirus since March 1997, and poliovirus transmission in the European Region is confined to southeastern Turkey. Reaching the global polio eradication goal will require accelerated activities in the remaining major foci of poliovirus transmission in southern Asia and in Africa (99).
These accomplishments in the elimination of poliovirus infection have been achieved primarily through the use of oral poliovirus vaccine (OPV). This product had been the vaccine of choice for children in the United States since the early 1960s because it induced optimal intestinal immunity, was painless to administer, and secondarily immunized some contacts by fecal-oral spread of the vaccine virus, therefore contributing to the immunity of the population (62). For these same reasons, global eradication necessitates the continued use of OPV in many parts of the world (375). However, since inactivated poliovirus vaccine (IPV) is also highly effective and does not cause vaccine-associated paralytic poliomyelitis (VAPP), IPV has been used for routine immunization in several European countries which have controlled or eliminated poliomyelitis, including Finland, France, and the Netherlands. Recently in Canada, IPV has replaced OPV as the vaccine of choice (303). Denmark, Israel, and the province of Prince Edward Island in Canada have utilized sequential schedules of IPV followed by OPV to reduce the risk of VAPP and to maintain the benefits of OPV. Since 8 to 10 cases of VAPP occur annually in the United States and the risk of exposure to wild-type poliovirus has been markedly reduced or eliminated, expanded use of IPV was recommended by CDC beginning in 1997 (89).

In 1999, as a result of progress in the global eradication of poliomyelitis, the need for further reductions in the risk for acquiring VAPP, and the acceptance of IPV by parents and physicians (79), the ACIP, AAP, and AAFP recommended IPV for the first two doses of poliovirus vaccine for routine childhood vaccination (17, 104).

To completely eliminate the risk for VAPP, in January 2000 an all-IPV schedule was recommended for routine childhood vaccination in the United States (20, 85, 102). All children should receive four doses of IPV: at age 2 months, at age 4 months, between ages 6 and 18 months, and between ages 4 and 6 years. OPV, if available, may be used only for the following special circumstances: (i) mass vaccination campaigns to control outbreaks of paralytic polio; (ii) Unvaccinated or, more commonly, a decrease, in the immunogenicity of one or more components of the combination vaccine. An antigen may have chemical incompatibilities with other antigens or may cause interference with the immune response to those antigens when incorporated into a single vaccine. The unpredictability of the effect of combining different products in the same syringe can be the result of interference, antigenic competition, or carrier protein interference. Interference can occur because of chemical incompatibility between the vaccine antigens and the stabilizers, adjuvants, or preservatives. For example, thimerosal, a preservative in DTP vaccine used in the United States, decreases the potency of poliovirus antigens in IPV. Formulations of DTP-IPV in Europe and Canada avoid interference by using neomycin as a preservative.

Antigenic competition occurs when one or more vaccine strains in a combination vaccine replicate more rapidly than the other strains. For example, the concentration of the three vaccine strains in OPV had to be adjusted because type 2 vaccine virus replicates more rapidly than type 1 and 3 vaccine viruses do. The administration of several doses of the vaccine also helps to ensure an adequate response to all three vaccine strains.

Carrier protein interference was identified when multiple polysaccharide-protein conjugate vaccines using the same carrier protein were administered simultaneously with large doses of the carrier protein antigen. An example would be the simultaneous administration of a tetravalent pneumococcal vaccine conjugated with tetanus toxoid and a DTP-IPV-Hib-T vaccine (145). This problem should be preventable by using different carrier proteins in new combination conjugate vaccines.

Clinical studies in infants have demonstrated that using some combination vaccine products containing Hib vaccine may induce a suboptimal immune response to the Hib vaccine component. Because of the potential for a suboptimal immune response to the Hib component (164), the currently licensed

An increasing number of new and improved vaccines are being introduced. The incorporation of these vaccines into already complex childhood immunization schedules poses a challenge. In the 2001 Recommended Childhood Immunization Schedule—United States, a minimum of 19 separate injections are needed to immunize a child from birth to 6 years of age (103). At some visits the administration of three or four separate injections can be indicated.

Combination vaccines represent one solution to the problem of increased numbers of injections. These vaccines incorporate into a single product antigens that prevent several diseases. Combination vaccines available for many years include DTP and MMR. Combinations licensed in recent years in the United States include DTaP, DTP-Hib vaccine, Hib-hepatitis B vaccine (Hib-A-Hep B), a DTaP-Hib vaccine for use as a fourth dose in children 12 to 15 months of age, and hepatitis A-hepatitis B vaccine (Hep A-Hep B). In the future, combination vaccines may include hepatitis A, Neisseria meningitides, Streptococcus pneumoniae, IPV, and varicella.

The ACIP, AAP, and AAFP have indicated a preference for the use of licensed combination vaccines over separate injections of the equivalent component vaccines (12, 68). Separate vaccines should not be combined into the same syringe for administration together unless such mixing is indicated on the package insert approved by the FDA. The safety, immunogenicity, and efficacy of unlicensed combinations are unknown.

Mixing antigens in the same syringe can result in an increase or, more commonly, a decrease, in the immunogenicity of one or more components of the combination vaccine. An antigen may have chemical incompatibilities with other antigens or may cause interference with the immune response to those antigens when incorporated into a single vaccine. The unpredictability of the effect of combining different products in the same syringe can be the result of interference, antigenic competition, or carrier protein interference. Interference can occur because of chemical incompatibility between the vaccine antigens and the stabilizers, adjuvants, or preservatives. For example, thimerosal, a preservative in DTP vaccine used in the United States, decreases the potency of poliovirus antigens in IPV. Formulations of DTP-IPV in Europe and Canada avoid interference by using neomycin as a preservative.
DTaP-Hib combination product should not be used for primary vaccination in infants aged 2, 4, or 6 months (110).

In general, vaccines from different manufacturers that protect against the same disease are interchangeable. Data are not currently available on the interchangability of DTaP vaccines. Vaccines from the same manufacturer should be used throughout a series wherever feasible. Combination vaccines are usually licensed based on studies indicating that the product’s immunogenicity (or efficacy) and safety are similar to those of monovalent products licensed previously. A combination vaccine may be used interchangeably with monovalent formulations and other combination products with similar component antigens produced by the same manufacturer.

Because of the reduced frequency of adverse reactions and high efficacy, the ACIP now recommends DTaP for routine use for all doses of the pertussis vaccination series (104). All major vaccine manufacturers are currently working, either alone or through strategic alliances, toward developing more polyvalent vaccines by adding antigens such as conjugated Hib polysaccharide, hepatitis B surface antigen, and/or inactivated poliovirus to DTaP.

**Diphtheria-Tetanus-Pertussis-Haemophilus influenzae**

**Type b Conjugate Combination Vaccines**

DTP-Hib vaccine combinations are currently being used in many countries. While most studies find that the immunogenicity of the individual components is unaffected by combination, some studies have reported significant reductions in antibody titers to the Hib polysaccharide, PRP, in infants receiving the combination vaccines (150). The clinical significance of this reduction is unclear since children vaccinated with Hib combination vaccines exhibit rapid anamnestic-type immune responses to Hib conjugate or Hib polysaccharide boosters despite initial low antibody responses and waning antibody responses at 1 to 2 years of age.

Substantial reductions in antibody responses to Hib have also been found in studies of DTaP-Hib combination vaccines (165). Studies of a DTaP-PRP-T combination vaccine demonstrated that infants receiving this vaccine had lower PRP antibody responses after three doses and at 9 to 12 months after primary immunization. However, these infants had a marked booster response to a fourth dose of PRP-T vaccine, with >97% of infants achieving a PRP antibody titer of 1.0 μg/ml or more (41, 328).

In 1996 the first DTaP-Hib (PRP-T) combination vaccine for use in the primary vaccine series was licensed in Europe and was followed by a pentavalent DTaP-Hib(PRPT)-IPV combination in 1997. A hexavalent vaccine consisting of DTaP-Hib(PRPT)-IPV-HepB has been developed and is currently licensed in Europe.

In the United States, the first DTaP-Hib(PRPT) combination vaccine was licensed in 1996. This combination is made by reconstituting a Hib conjugate vaccine (ActHIB) with a DTaP vaccine (TriHIBit) and is sold under the trade name TriHIBit. This combination vaccine can be administered only as the fourth dose of the vaccination series at age 15 to 18 months following administration of either DTaP or DTP. Due to the concern about reduced immunogenicity of the Hib component, no DTaP-Hib combinations are licensed in the United States for use as the first three doses of the vaccination series.

**Diphtheria-Tetanus-Pertussis-Hepatitis B Combination Vaccines**

Combined DTP-HepB and DTaP-HepB vaccines are safe and immunogenic in infants and are currently licensed in Europe (165). DTaP-Hib (PRP-T)-HepB combination vaccines have also been developed and are being tested in clinical trials (297, 376). As with the DTaP-Hib vaccines, the combination DTaP-Hib-HepB vaccines gave significantly lower PRP antibody levels than did the conjugate Hib vaccines alone, but brisk responses to a booster dose of Hib conjugate vaccine suggests that the combination vaccines are effective primers of the immune response.

**Inactivated Poliovirus Combination Vaccines**

Some studies have shown a reduction in poliovirus antibody responses when IPV is given in combination with other vaccines, but other studies have not demonstrated this effect. Overall, combining IPV with DTaP has had no consistent effect on responses to any component. Including Hib in the combination does not alter the response to the DTaP or IPV components but, as was seen with other combination vaccines containing Hib, antibody titers to PRP are typically lower with the combination.

A pentavalent combination, DTaP-IPV-Hib (PRP-T), has been in use in Canada and Europe since 1997. In contrast to other combination vaccines containing Hib, antibody titers to PRP were similar in children receiving the combination vaccine (E. Mills, M. Russell, and L. Cuninig, Program Abstr. 37th Intersci. Conf. Antimicrob. Agents Chemother., abstr. G95, 1997). Because this vaccine is based on a DTaP that is not currently licensed by the FDA, it is not available in the United States.

A hexavalent combination vaccine containing DTaP-IPV-Hib (PRP-T)-HepB has recently been approved in Europe. As with the DTaP-Hib vaccines, the combination DTaP-IPV-Hib-HepB vaccine gave lower PRP antibody levels than did a pentavalent combination, DTaP-IPV-Hib (PRP-T). While titers to HBV were lower in the children receiving the hexavalent combination than in those receiving hepatitis B vaccine alone, poliovirus antibody titers were enhanced in children receiving the hexavalent combination. These differences in antibody titers were not significant, and the hexavalent vaccine was found to meet or surpass the predefined criteria for equivalence to the pentavalent vaccine widely used in Europe and to hepatitis B vaccine (260, 327).

**Haemophilus influenzae Type b Conjugate-Hepatitis B Combination Vaccines**

In 1996, the first combined Hib conjugate and hepatitis B (recombinant) vaccine (Comvax) for infants was licensed in the United States. Comvax is made of the antigenic components used in PRP-OMP (PedvaxHIB) and HBV vaccine (RECOMBIVAX HB) and is indicated for vaccination of infants born to HBsAg-negative women. Three doses of Comvax should be administered at ages 2, 4, and 12 to 15 months (72). The use of
Convax in infants born to women who are HBsAg-positive or women of unknown HBsAg status has not yet been studied.

**Hepatitis A-Hepatitis B Combination Vaccines**

A combined hepatitis A and B vaccine was licensed in Europe in 1996 and Canada a year later. This vaccine has been proven safe and immunogenic when given as a 3 dose schedule in children, adolescents and adults (158, 355). On 11 May 2001, the FDA licensed the combined hepatitis A and B vaccine (TWINRIX [SmithKline Beecham Biologicals]) for immunization of persons aged 18 years or older.

**Measles-Mumps-Rubella-Varicella Combination Vaccines**

Use of a vaccine that combines MMR and varicella vaccines into a single injection (MMRV) would be the most effective way to immunize all children against varicella. However, recent studies indicate that the combination vaccine induces lower concentrations of antibody against varicella than are desirable while the concentrations of antibody against the other three viruses are protective (313, 373). New formulations of a combined MMR and varicella vaccine containing a more immunogenic varicella component are currently in clinical trials.

**Other Combination Vaccines**

Clinical trials evaluating pneumococcal conjugate-meningococcal conjugate and pneumococcal conjugate-meningococcal conjugate-Hib combinations are under way (121).

**DISEASES FOR WHICH IMPROVED VACCINES ARE UNDER DEVELOPMENT**

**Cholera**

Although cholera remains a significant public health concern in developing countries, most travelers visiting an area where cholera occurs are at very low risk of acquiring infection. The estimated risk of cholera disease in European or North American travelers to areas of endemic infection is one to two cases per 10^6 trips (257).

Cholera is caused by *V. cholerae* O1. There are two biotypes, classic and El Tor, and two serotypes, Inaba and Ogawa. Each strain is identified by both its serotype and its biotype, resulting in four potential bioserotypes of *V. cholerae* O1. The ongoing seventh pandemic is caused by the El Tor biotype of *V. cholerae* O1. A new epidemic *V. cholerae* strain, designated serogroup O139 and coexisting with traditional *V. cholerae* O1, appeared in India in 1992 and spread rapidly in Asia. The recent spread of *V. cholerae* O139 may be the early part of an eighth pandemic. *V. cholerae* O139 mainly affected adults, and it appeared as if there was no, or only little, preexisting immunity in the population previously naturally exposed to *V. cholerae* O1.

The currently available vaccines are inactivated preparations of whole-cell suspensions of classic Inaba and Ogawa strains of *V. cholerae* and are used parenterally (318). In field trials conducted in regions of endemic cholera infection, these vaccines are only about 50% effective in reducing the incidence of clinical illness for 3 to 6 months after vaccination (64).

The search for a better cholera vaccine is prompted by the recovery from natural infection often is followed by solid, long-lasting immunity (249). Oral vaccines currently under development are of two types: killed *V. cholerae* bacteria that are combined with purified cholera toxin B subunit and strains of *V. cholerae* that are attenuated by virtue of specific gene deletions.

Inactivated oral cholera B subunit whole-cell vaccine is prepared from four strains of killed *V. cholerae* (one classic Inaba, two classic Ogawa, and one El Tor) combined with purified recombinant cholera toxin B subunit. This vaccine is immunogenic but requires multiple doses and periodic boosters to maintain high levels of protection. After three doses, a whole-cell B subunit vaccine tested in Bangladesh had a protective efficacy of 85% during the first 6 months postvaccination and approximately 60% protective efficacy after 3 years (125, 126). After 5 years follow-up, the protective efficacy was just below 50% (361). Protection was age dependent and waned within 1 year in persons younger than 5 years. Studies of inactivated whole-cell cholera vaccines without the cholera B subunit in Bangladesh, Vietnam, and Peru show similar long-term efficacy to that of the whole-cell B subunit vaccine, although the whole-cell B subunit vaccine induced a higher level of protection for the first 6 to 8 months following immunization in Bangladesh (40, 322, 357, 361). The whole-cell B subunit vaccine is licensed in Sweden. Studies are under way to evaluate the utility of whole-cell or whole-cell B subunit vaccine for those living in areas of endemic infection, refugees, and travelers.

The modest protective efficacy of the oral inactivated whole-cell vaccine and the need for two or more doses prompted the development of single-dose attenuated live vaccines. Several live-attenuated strains of *V. cholerae* with known genetic deletions have been constructed and tested in volunteers. A vaccine candidate, CVD 103 HgR, lacking the toxic A subunit but retaining the immunogenic B subunit of cholera toxin, has been derived from the classical Inaba strain of *V. cholerae*. Randomized controlled studies of CVD 103 HgR have been carried out with several thousand subjects in a number of areas of endemic cholera infection and areas without endemic infection and have demonstrated good safety and immunogenicity (143, 238, 250, 333, 344, 345). Adverse reactions, which were mild and of short duration, included nausea, abdominal cramps, and diarrhea. Seroconversion rates of greater than 90% were seen following a single oral dose of the vaccine. Seroconversion occurred as early as 8 days after administration of the vaccine and lasted for 6 months (348).

Protective efficacy of the CVD 103 HgR vaccine was tested in volunteers challenged with pathogenic *V. cholerae* of both biotypes and serotypes. Complete protection against the classical biotype was demonstrated in 82 to 100% of all subjects and in 62 to 67% of subjects exposed to the El Tor biotype (250). A large-scale efficacy trial, involving more than 60,000 individuals, is under way in Jakarta, Indonesia. CVD 103 HgR has been licensed in some European countries and Canada.

Two new live oral vaccines against the El Tor strain of *V. cholerae*, which is the predominant strain worldwide at present, have been tested in volunteers. Like CVD 103 HgR, vaccine candidates CVD 111 and Peru 15 have known genetic deletions and lack the toxic A subunit but retain the immunogenic B subunit of cholera toxin. CVD 111 has been in clinical trials...
in the United States, Panama, and Peru in combination with CVD 103 HgR (354). In these trials it was shown that the two strains could be coadministered and an immune response to both biotypes could be obtained. The addition of CVD 111 improved the overall seroconversion rate and doubled the serum Ogawa vibriocidal titers, suggesting that the combination of an El Tor and a classical cholera strain is desirable. While CVD 111 was found to be well tolerated in semi-immune Peruvians, adverse effects were observed in nonimmune American subjects, indicating that this strain requires further attenuation before it can be safely used (353). The second El Tor strain, Peru 15, lacks an additional virulence factor found in CVD 111 and has been immunogenic but less reactogenic in clinical trials (319). Further studies are needed for both vaccine candidates.

Live vaccines against the O139 serotype have been developed and evaluated in U.S. adult volunteers and appear promising (140, 347). Further studies are needed to determine the protective efficacy of these vaccines.

**Influenza**

Influenza virus infection continues to cause significant morbidity and mortality despite the availability of effective vaccines and antiviral therapy for prevention and treatment of influenza. Influenza viruses cause annual epidemics of acute respiratory disease that affect persons of all ages.

A major difficulty in the development and provision of satisfactory immunizing agents for the prevention of influenza is the antigenic variation in these viruses. Periodic minor antigenic changes in influenza A or B virus are the major factors in the continuing occurrence of yearly influenza disease. While outbreaks are generally limited in magnitude, the resulting morbidity and mortality remains discouragingly high. Major antigenic changes of influenza A virus, as occurred in 1957 to 1958 (Asian strain) and again in 1968 to 1969 (Hong Kong variant), account for pandemic spread of disease associated with greater overall morbidity and mortality, especially in high-risk populations.

Trivalent inactivated vaccines are the only currently available vaccines against influenza viruses in the United States (6, 91). The killed vaccine must be given yearly because antibody response is short-lived and because of the yearly antigenic variation in the circulating strains of influenza. The vaccine efficacy is variable, depending on the immune response to vaccination and on how closely the vaccine strain resembles the circulating strains of influenza. To improve the immunogenicity of inactivated influenza vaccine, several new approaches are under investigation. Most efforts have focused on the viral hemagglutinin as a vaccine candidate and the use of more potent adjuvants (235). Inactivated intranasal vaccines have also been developed and are undergoing clinical trials (55, 234).

Live attenuated influenza virus vaccines are also under development (256). The attenuated influenza virus vaccines are reassortants containing two RNA genes encoding the two surface glycoproteins, hemagglutinin and neuraminidase, that are derived from the currently circulating virus and include six genes encoding the internal viral proteins from an attenuated strain. The most promising attenuated viruses for vaccine use are cold-adapted influenza virus strains. Intranasally administered, cold-adapted, live, attenuated influenza virus vaccines are currently being used in Russia and have been under development in the United States since the 1960s (130, 233, 255, 276, 307).

Cold-adapted strains are produced by growing influenza A virus at progressively lower temperatures to produce a strain that grows well at 25 to 33°C but not at 37°C. This property allows the vaccine strain to replicate in the upper respiratory tract but restricts its replication in the lower respiratory tract. The cold-adapted vaccine presents an alternative vaccine approach that offers several advantages, including stimulation of a wider range of antibodies; induction of local, humoral, and cellular immunity; and the ability to administer the vaccine intranasally, at the site of infection.

Cold-adapted vaccine has been studied clinically as monovalent, bivalent, and trivalent formulations in a wide range of age and high-risk groups (130, 307). The vaccine is given intranasally by spray and induces mild upper respiratory tract symptoms in about 10 to 15% of persons (43, 141). Several studies have demonstrated the safety, immunogenicity, and efficacy of these vaccines in preventing influenza in young adults, in whom the efficacy has been about the same as that of inactivated influenza virus vaccines (141, 166, 276). In a recent study involving healthy working adults, vaccination with live attenuated virus led to reductions of 19 to 24% in the occurrence of illness, reductions of 8 to 28% in days of work lost, and reductions of 25 to 41% in visits to health care providers compared with the effects of placebo (281). In a recent study of children aged 15 to 71 months, an intranasally administered trivalent, cold-adapted vaccine was 93% effective in preventing culture-positive influenza A (H3N2) and B infections. The cold-adapted vaccine reduced febrile illnesses by 21%, otitis media by 30%, and otitis media with concomitant antibiotic use by 35% among vaccinated children (45). In a follow-up study during the 1997 to 1998 season, the trivalent cold-adapted vaccine was 86% effective in preventing culture-positive influenza in children, despite a poor match between the vaccine’s influenza A (H3N2) component and the predominant circulating influenza A (H3N2) virus (43).

**Meningococcal Disease**

Considerable efforts have been focused on meningococcal vaccine development. The currently licensed vaccines, based on purified capsular polysaccharides from four major serogroups (A, C, W135, and Y), are moderately immunogenic, but the immune response, in general, is of short duration and cannot be boosted on reimmunization. Furthermore, the polysaccharide vaccines generally do not elicit an immune response in children younger than 2 years (69). Interestingly, group A capsular polysaccharide vaccine is moderately immunogenic in this age group; the underlying mechanisms of this unique response are not clear.

A current attractive strategy in vaccine development is to use polysaccharide-protein conjugate vaccines similar in design to the licensed Hib vaccines to enhance the immunogenicity and to induce memory. Protein-conjugate vaccines have been developed for group A and C strains (293). While both conjugates induce good antibody responses in young infants, studies
have shown better boosting with the C conjugates (174, 246, 314). Currently five meningococcal C vaccine candidates containing different carrier proteins are under development. All appear to be comparable in the ability to induce primary immunity and immunologic memory. One or more of these vaccines are expected to be licensed in the United States in the next 2 to 4 years.

In late 1999, conjugate group C meningococcal vaccine was licensed in the United Kingdom, where rates of meningococcal disease are twofold higher than in the United States. A comprehensive public health program to vaccinate children from 2 months to 17 years of age and entering college students has been initiated. The conjugate group C vaccine has shown short-term efficacy of >90% for both teenagers and toddlers (308).

The development of vaccines against group B strains remains problematic (159, 293). Unlike the other meningococcal capsular polysaccharides, the group B polysaccharide is a poor immunogen in both infants and adults. Recent studies using X-ray crystallography suggest that the poor immunogenicity may be due, at least in part, to the fact that the conformational epitope of group B polysaccharide that is capable of inducing an immune response may not be stable under various physiologic and pathological conditions (291). Because group B strains continue to be a major cause of meningococcal disease in the United States and several other countries, the development of an effective group B capsular polysaccharide vaccine would represent a major advance in the prevention of meningococcal disease.

Two approaches have been taken in the development of group B vaccines (159). The first is to chemically alter the group B polysaccharide by substitution of n-proprionyl into the polysaccharide to make the molecule more immunogenic (306). However, there are important concerns that such a vaccine might induce immunopathology such as the formation of cross-reactive autoantibodies to specific oligosaccharides also found on mammalian cells. For example, anti-group B polysaccharide antibodies cross-react with the neural cellular adhesion molecule, a membrane glycoprotein involved in cell-cell adhesion. Therefore, it is possible that a polysaccharide-based vaccine may induce immunopathological side effects. In small clinical trials, chemically altered group B polysaccharide vaccine has been safe, with no evidence of cross-reactivity with neural cellular adhesion molecule, but has failed to produce protective immune responses.

An alternative approach to meningococcal outer membrane proteins as immunogens. Studies indicate that protection can be induced by outer membrane proteins. Protein-based vaccines have been used in clinical trials in Brazil, Chile, and Iceland, with efficacies ranging from 50 to 80% (53, 153, 295, 351). Unfortunately, these vaccines induced no protection in children and the immune response was of short duration.

DISEASES FOR WHICH INVESTIGATIONAL VACCINES HAVE BEEN DEVELOPED

Routine immunizations for children have virtually eliminated many infectious diseases from the United States. These successes have encouraged research to develop vaccines to prevent other serious viral and bacterial diseases affecting children. A 1985 report by the Institute of Medicine (IOM) of the National Academy of Sciences reviewed the benefits that would be associated with the development and use of new and improved vaccines in the United States (136). The report listed 14 diseases for which vaccines were possible. A 1999 study from the IOM notes that considerable progress has been made since the 1985 study (137). Of 14 vaccines listed in the 1985 study as domestic priorities for development, 7 are now licensed. These include an acellular pertussis vaccine and vaccines against hepatitis A and B, Hib, varicella-zoster virus, rotavirus and pneumococcus.

The 1999 IOM report employs a new quantitative model to compare the cost and health benefits of developing candidate vaccines (137). This model can be used to evaluate the potential impact of a new vaccine on public health. In the 1999 report, this model was used to evaluate diseases for which candidate vaccines were being developed. The report divided 26 candidate vaccines into four groups, from most to least favorable for development. The four vaccines in the top tier include a cytomegalovirus (CMV) vaccine given to adolescents; a universal influenza vaccine; a group B streptococcus vaccine for high-risk adults and pregnant women; and an S. pneumoniae vaccine for infants and seniors. Other diseases for which vaccines would be desirable include Chlamydia trachomatis, enterotoxigenic E. coli (ETEC), Epstein-Barr virus (EBV), Helicobacter pylori, hepatitis C virus, herpes simplex virus (HSV), human papillomavirus, Mycobacterium tuberculosis, Neisseria gonorrhoea, respiratory syncytial virus, parainfluenza virus, Shigella, and group A and B streptococcus.

The advances in biotechnology, the increasing understanding of virulence factors of infectious agents, and the knowledge of the host immune response have led to an explosion in the number of new approaches being used to develop vaccines (167). The three general categories of approaches include live vaccines; killed, inactivated, or subunit vaccines; and, most recently, DNA-based vaccines. In addition, there are new enabling technologies such as adjuvants or delivery systems and vectors which can be applied to these approaches. Vaccines are being developed by the application of these vaccine technologies for a number of infectious agents for which vaccines are not currently available. Candidate vaccines are in human trials for many of the pathogens listed in the 1999 IOM report.

Enteric Pathogens

Diarrheal diseases are a major cause of illness in developed countries and are a major cause of both illness and death in developing countries. In the United States, diarrhea is the second most common infectious illness, accounting for 16% of all infectious diseases. Data compiled by the WHO indicate that diarrheal diseases account for 15 to 34% of all deaths in certain countries. Conservative estimates place the death toll from diarrheal diseases at 4 × 10^7 to 6 × 10^7 deaths per year, with most of these occurring in children of preschool age.

Enterotoxigenic Escherichia coli. A safe and effective vaccine against ETEC would be useful for travelers and young children in areas of the world where ETEC is endemic. Second only to rotavirus as the cause of severe dehydrating diarrhea in young children throughout the world, ETEC is estimated to cause...
more than $4 \times 10^8$ cases of diarrhea and more than $7 \times 10^6$ deaths in children younger than 5 years per year. ETEC is also the major cause of traveler's diarrhea. ETEC possess a number of important antigens which are involved in the pathogenesis of disease, including colonization factor antigens (CFAs), fimbriae, and other adhesive surfaces which mediate attachment of the bacteria to the intestinal epithelial cell lining. Antibodies against CFAs are protective (204), but there are many antigenically different CFAs (335). An efficacious vaccine may have to contain 10 or more different CFAs. ETEC also possess both heat-labile (LT) and heat-stable (ST) enterotoxins which induce a net secretion of electrolytes and water into the gut lumen. ETEC isolates are either LT only, LT-ST, or ST-only producers. To be efficacious, a vaccine will have to elicit antibodies that protect the gut mucosal surface and are targeted towards the ETEC surface antigens and/or its toxins.

Volunteer studies have shown that infection with ETEC generates protective immunity against rechallenge with the same strain (204). On the basis of this observation, several inactivated strains have been developed in an effort to mimic the presentation of important ETEC antigens to the immune system without inducing disease. The vaccine candidate that is furthest in development is composed of a mixture of five formalin-inactivated ETEC strains, which together express the major CFAs important in human disease, combined with a recombinant cholera toxin B subunit, which will elicit antibody reactive with the ETEC LT (346). Data thus far demonstrate that the vaccine is safe and elicits antibody-secreting cell responses to most vaccine antigens in $\approx 70\%$ of vaccinees (218). Two oral doses elicited responses similar to those seen after naturally occurring ETEC diarrhea in Bangladeshi adults (204). In studies conducted in Egypt, this vaccine was found to be safe and immunogenic and to induce both antibody-secreting cell and IgG responses in both adults and children (325, 326). An ongoing study is being conducted with infants 6 to 18 months of age.

Shigella. Shigellosis (bacillary dysentery) is endemic throughout the world. Although there are 30 serotypes of Shigella, usually only 2 or 3 serotypes predominate in a given area. S. sonnei predominates in industrialized countries, whereas S. flexneri is most commonly found in developing countries; both are associated with endemic disease. S. dysenteriae causes epidemic outbreaks of dysentery, as well as significant endemic disease. Thus, a comprehensive vaccine approach to controlling shigellosis must include S. dysenteriae, S. sonnei, and two or more serotypes of S. flexneri.

A large number of candidate vaccines have been developed over the past 50 years, but to date there are no licensed vaccines available. One major reason is the absence of correlates of protection, which makes the assessment of candidate Shigella vaccines difficult. Early attempts to immunize with parenteral vaccines consisting of live or inactivated organisms failed to protect against homologous challenge. Therefore, the focus has shifted to the construction of attenuated vaccines to be given orally (284).

Early studies showed that the O somatic antigens of Shigella are major immunogens and that the most effective attenuated vaccines are those that transport these immunogens to mucosal tissues, where they can generate a local or mucosal immune response. Limited tissue invasion of the vaccine strain would also probably generate better cell-mediated immunity, which is thought to be important for protection against invasive pathogens such as Shigella.

Live attenuated strains of Shigella have been created by deleting known virulence factors. Attenuation of S. flexneri via deletions in the aromatic metabolic pathway creates mutant strains with a severely limited ability to grow intracellularly. Mutant strains illustrated a delicate balance between reactogenicity and immunogenicity when given to volunteers (summarized in reference 284). The inherent virulence of the parent wild-type Shigella strain was shown to dictate the clinical tolerance to vaccine candidate strains with identical attenuated properties. The conclusion was that aromatic auxotrophy alone was probably insufficient for a safe and immunogenic live Shigella vaccine and that additional or alternative mutations or deletions of genes were necessary to increase attenuation with retained immunogenicity.

Recently, two distinct enterotoxins were detected in Shigella. Attenuated strains with deletions of the gene for Shigella enterotoxin have been constructed. Strain CVD1207 is an S. flexneri serotype 2a strain which lacks enterotoxins and has attenuating mutations which interrupt the biosynthesis of guanine nucleotides and reduce intracellular and intercellular spread. This vaccine candidate is in early clinical trials. An S. dysenteriae serotype 1 strain with similar mutations and a deletion in the gene coding for the A subunit of the Shiga toxin has also been developed (284).

Collaboration between the Institut Pasteur and the Walter Reed Army Institute of Research has produced a S. flexneri serotype 2a vaccine candidate strain, SC602, which has mutations which reduce intracellular and intercellular spread and affect the survival of SC602 in the tissues (253). So far, strain SC602 appears to be the most promising live attenuated oral Shigella vaccine candidate. After a single oral dose, this vaccine candidate provided 100% protection against severe shigellosis in North American volunteers when they were challenged with S. flexneri 2a (253). Although SC602 is safe in healthy adults, a key test is to see if it is safe in infants, the primary target population in developing countries where shigellosis is endemic.

Efforts also are under way to develop parenteral vaccines composed of detoxified Shigella lipopolysaccharide (LPS)-protein conjugate. A conjugate vaccine, covalently linking the O-antigen polysaccharide chains of the LPS of S. flexneri serotype 2a and S. sonnei to exoprotein A of P. aeruginosa as a carrier, was given i.m. to Israeli soldiers in a single dose. Four-fold or greater increases of serum IgG and IgA antibody titers against the homologous LPS occurred in 90% of recipients of the S. sonnei conjugate and in 73 to 77% of recipients of the S. flexneri conjugate (133). The S. sonnei conjugate was then assessed in a double-blind trial, which demonstrated an efficacy of 74% in vaccinated Israeli soldiers (134).

Herpesviruses

Herpesviruses present difficult challenges in vaccine development because of their ability to evade immune clearance. Vaccines to prevent illnesses associated with HSV, CMV, and EBV are under development.
Herpes simplex virus. HSV infections are common and produce not only a primary infection but also latent and recurrent infections. Therefore, the goals of an HSV vaccine are different from those of other vaccines and include both prophylaxis and therapy. Six different types of HSV vaccines have been developed. These include attenuated HSV vaccines, replication-limited (or replication-incompetent) HSV vaccines, vaccines consisting of live nonpathogenic replicating vectors engineered to express HSV gene products, inactivated HSV vaccines, HSV component or subunit vaccines, and nucleic acid (plasmid) vaccines (241, 338).

Live attenuated virus vaccines generally induce broader and more durable immune responses than do inactivated virus vaccines. This strategy has been unsuccessful for HSV because genetically stable virus is not produced by the traditional means of attenuation. Development of a live attenuated HSV vaccine also raises safety concerns regarding the ability of a live virus to establish latency, to reactivate, and to recombine with virulent wild-type virus, as well as potential oncogenicity. An alternative strategy is to use molecular genetic methods to engineer stable attenuated viruses (268). A vaccine using this technology is in development (336).

Replication-incompetent or replication-limited mutant HSV vaccines are made by deletion of a gene that is essential for viral replication (178, 274). The defective virus is then cultivated on a genetically engineered cell line that expresses the missing viral gene product. The vaccine virus is capable of infecting normal cells but cannot make the missing gene product required to produce new infectious virions, and, therefore, is limited to a single infectious cycle without spread of infection to other cells. Replication-incompetent mutants do not cause disease in animals but elicit HSV-specific humoral immunity and cell-mediated immune responses that protect the animals from experimental infection (144). One such mutant vaccine is in preclinical trials, while a second vaccine, consisting of an HSV-2 mutant lacking the gene encoding the essential glycoprotein gH, has been immunogenic and well tolerated in phase 1 trials in the United Kingdom and the United States (J. K. Hickling, S. E. Chrisholm, and I. A. Duncan, Abstr. 8th Int. Congr. Infect. Dis., abstr. 22.008, 1998; J. S. C. Roberts, J. A. Uttridge, and J. K. Hickling, Abstr. 8th Int. Congr. Infect. Dis., abstr. 22.009, 1998).

Although vaccines containing genetically attenuated HSV mutants or replication-incompetent mutants probably induce broad and durable immunity, questions about their safety remain. One strategy that retains the advantages of a live virus vaccine while avoiding safety concerns involves the use of replicating vectors. In this approach, an HSV gene encoding an immunogenic protein is inserted into a replication-competent viral or bacterial vector. When immunized with the vector, the host has humoral immunity and cell-mediated immune responses against the proteins encoded by the vector, including the HSV protein. A number of vectors have been proposed, including vaccinia virus, adenovirus, poxvirus, rhinoviruses, canarypox virus, and Salmonella. Studies have shown that live vectors carrying HSV genes can induce HSV-specific immunity and protect animals against disease (338). These vaccines have not yet entered clinical trials.

Killed HSV vaccines have a long and unsuccessful history (338). Since the 1970s, several killed-virus vaccines have been developed for therapeutic and/or prophylactic use (338). While available commercially in some parts of the world, inactivated virion-derived vaccines have not been proved effective.

The development of subunit HSV vaccines has focused largely on two envelope glycoproteins, gB and gD. The recombinant glycoproteins gB and gD are immunogenic and protective in animal challenge studies (338). Four recombinant subunit vaccine preparations have been evaluated in clinical studies. A vaccine that contains recombinant truncated HSV-2 gD (gD2) adsorbed to alum was tested as a therapeutic vaccine for the control of frequent recurrent genital herpes. The vaccine was found to be both immunogenic and modestly effective (341). A second vaccine containing gD2 with a muramyl tripeptide adjuvant was shown to be immunogenic in humans but had an unacceptable reactogenicity profile, especially in HSV-seropositive subjects. This problem led to the development of a third vaccine containing recombinant gD2 and gB2 with MF59, an adjuvant consisting of squalene, polysorbate 80, and sorbitan trioleate. This formulation was immunogenic and only mildly reactogenic in humans (243) but was ineffective in the treatment of recurrent genital herpes (342). The results of two large prophylactic studies showed that this vaccine did not protect recipients from acquiring genital HSV-2 infection (139). The two studies, which included 2,393 volunteers, found a lower acquisition rate during the first 5 months of the trial, but the effect was lost by the end of the 1-year follow-up, with an overall efficacy rate of only 9%. A fourth subunit vaccine containing recombinant truncated gD2 and gum combined with the potent adjuvant 3-de-O-acetylated monophosphoryl lipid A appears to be well tolerated and induces humoral and cellular immune responses superior to those produced by the glycoprotein gD and alum alone (G. Leroux-Roels, E. Moreau, and I. Desombre, Program Abstr. 34th Intersci. Conf. Antimicrob. Agents Chemother., abstr. H57, 1994).

The development of nucleic acid-based vaccines has provided a new strategy for the prevention or treatment of HSV infections. Vaccines consisting of plasmid expression vectors containing the genes encoding HSV-1 glycoprotein gB, gD, or gD2 have been shown to induce humoral immunity and CMI responses and to protect mice and guinea pigs against HSV challenge (46, 338). In the United States, several manufacturers are involved in the preclinical development of DNA-based vaccines for the prevention of HSV infections and one has initiated a phase I trial of its gD2 DNA vaccine.

Cytomegalovirus. CMV is an important cause of congenital infection, a major complication of organ transplantation, and an opportunistic pathogen in HIV-infected patients. The pathogenesis of this virus, like that of the other herpesviruses, is complicated by the ability of the virus to remain latent in the host for many years.

The major goals of a CMV vaccination program would be to protect immunocompromised individuals and to prevent congenital CMV. Development of a vaccine has been difficult since correlates of immunity to CMV are not well understood. Studies with of CMV-immunoglobulin demonstrate that antibody protects against severe infection in immunocompromised patients. CMV gB is the major viral surface antigen and is an important target of neutralizing antibodies and cellular immune responses.

Three major vaccine strategies have been evaluated in hu-
mans, including live attenuated, glycoprotein subunit, and canarypox-vectored vaccines. The first strategy involves the development of live attenuated vaccines. The CMV Towne strain vaccine is a live attenuated vaccine which has been widely studied. This vaccine is safe and immunogenic, stimulating both humoral and cellular immunity, although to a lesser extent than does natural infection. The efficacy of Towne has been evaluated in several clinical studies (301). Vaccination with Towne strain has provided only modest benefit to renal transplant recipients by reducing the severity but not the incidence of CMV infection in several studies (37, 304). In a study of young women, Towne strain vaccine did not reduce the rates of CMV transmission (2).

Protection afforded by Towne strain is less than that afforded by a natural infection, and complete protection has been achieved against only low doses of challenge virus. In an attempt to make Towne more immunogenic, selected parts of its genome were replaced with sequences from nonattenuated strains of CMV. Investigators have constructed hybrid viruses that replace defined portions of the Towne genome with corresponding segments of a nonattenuated strain of CMV as vaccine candidates (270). A phase I clinical trial is planned using one of these chimeric vaccine candidates.

Subunit vaccines induce both humoral and cellular immune responses but have not to date been able to prevent infection or disease. A subunit vaccine consisting of recombinant gB and the adjuvant MF59 has been evaluated in phase I and II trials. The vaccine is well tolerated and highly immunogenic in seronegative adults and toddlers, and it stimulates high levels of neutralizing antibody that cross-neutralize clinical isolates (301). A trial examining the efficacy of this vaccine in the prevention of congenital CMV is under way.

Canarypox-vectored vaccines have been evaluated in humans. Delivery of gB antigen via a canarypox vector induced only weak responses in volunteers after two or three doses (188). However, a booster response to both gB and anti-CMV neutralizing antibody could be elicited by priming with canarypox-gB followed by administration of Towne strain, which produces gB as part of its replication (1). Studies are under way to investigate use of a canarypox-gB vaccine for priming followed by a subunit gB vaccine for boosting.

Epstein-Barr virus. The principal target of EBV neutralizing antibodies is the major virus surface glycoprotein gp220/350. Several vaccine candidates based on this glycoprotein have been developed. A gp220/350 subunit vaccine has elicited a specific antibody response that is at least partially protective in primate studies (179). Human trials of this vaccine are under way. Live recombinant vectors have also been used to express and deliver gp220/350. A recombinant vaccinia vaccine was recently tested in humans in China and shown to induce EBV-specific immune responses (193).

A range of cell-mediated responses to EBV infection have also been described and are likely to be important in controlling persistent infection. Cytotoxic lymphocytes specific for the latent EBV nuclear antigens EBNA-3A, EBNA-3B, and EBNA-3C are predominant in a large portion of seropositive adults and children (350). Clinical trials of a peptide vaccine bearing an EBNA-3A epitope are under way in Australia.

Human Immunodeficiency Virus

There is an urgent need for a prophylactic vaccine to protect individuals from AIDS and to help abate the growing epidemic. Many difficulties have been encountered in the development of effective vaccines against HIV, including the considerable antigenic variability of the virus, its intracellular mode of transmission, its mucosal port of entry, and the persistent nature of the infection.

Progress has been made in the development of vaccines. Approximately 34 candidate vaccines have been tested in phase I clinical trials and 3 have made it to phase II. Another 74 possible vaccines are in basic research or animal testing. Thus far, only one vaccine has reached phase III trials, and only two more vaccines at the most will reach this stage within the next 5 years. Vaccine development has been slowed because of safety concerns and disagreements about criteria for phase III trials (172).

Investigators continue to design and test novel ways to present HIV proteins to the immune system and evaluate new antigen/adjuvant and various vaccine formulations. A brief description of the various types of HIV vaccines being tested and the status of research in each of these areas follows (see references 138, 182, 247, 278, and 280 for more extensive discussions of this topic).

Envelope subunit and peptide approaches were among the earliest attempts to make an HIV vaccine, based on the premise that the envelope protein would be the most important target since it binds to cells and allows viral entry. Phase I trials have been conducted with the full-length env gene product (gp160) or the envelope protein gp120 produced in insect, yeast, or mammalian cells. The highest-titer and most broadly reactive neutralizing antibodies were induced by the mammalian gp120 vaccines. Two gp120 vaccines produced in mammalian cells have been evaluated in phase II trials, and a gp120-based vaccine (AIDSVAX) is the only vaccine in phase III clinical trials in human volunteers.

In addition to subunit proteins, peptide vaccine approaches are under investigation. Peptides can be produced by chemical synthesis. Branched-chain peptides, peptides that include both T-cell and B-cell epitopes, and peptides conjugated to lipids to stimulate cytotoxic lymphocytes are under evaluation.

Historically, live attenuated vaccines have been among the most efficacious viral vaccines. Because of safety considerations, live attenuated HIV vaccines have not been tested in humans. Safety issues include the possibility that such a vaccine could cause AIDS; that attenuated virus in the vaccine could revert to the wild-type, disease-causing virus; or that long-term infection could cause autoimmune or malignant disease. Whole killed HIV vaccines have been developed and tested in animals. These vaccines have not protected immunized chimpanzees against infection with the virus.

Virus-like particle (VLP) or “pseudovirion” AIDS vaccines have been produced by recombinant technology. These vaccines express all or a portion of one or more structural genes of HIV or simian immunodeficiency virus (SIV) and mimic the native expression of the particular viral protein(s). The pseudovirions do not contain the HIV genome, so they cannot produce progeny virus. To date, only one VLP experimental AIDS vaccine has been tested in prophylactic phase I trials. In
an ongoing study, volunteers receive i.m. immunizations followed by boosts of the VLP orally or rectally to determine whether HIV-specific mucosal antibody responses are induced. Other recombinant particle vaccine candidates are in development or in the planning stages.

Recombinant live vector vaccines represent a novel vaccine strategy currently under development for HIV. These vaccines are produced by engineering viral or bacterial genomes to express the desired HIV antigen(s). Viral vectors can be constructed to contain one or more viral genes that cause infected cells to make the coded protein in native form. Recombinant viral vectors enter cells and allow the HIV or SIV proteins to be generated inside the cells; these proteins are then presented to the immune system in the same way that proteins from a virus-infected cell would be. As a result, vector-based vaccines induce both humoral and cellular immune responses. Importantly, immune responses can be generated to the vector as well as to the incorporated antigens. The immune responses to the vector could limit the effectiveness of subsequent immunizations using the same vector. When given in combination with recombinant subunit products, live-vector experimental vaccines have been shown to prime the recipient for augmented immune responses.

Live infectious viral or bacterial vectors, genetically engineered to express genes of HIV or SIV, are being evaluated in nonhuman primates. Vaccines based on vaccinia virus, modified vaccinia ankara, or NYVAC (two attenuated vaccinia virus strains) have protected nonhuman primates from SIV, HIV-2, or HIV-1 infection when they were given alone or followed by immunization with purified envelope protein to boost the antibody response (prime-boost protocol). The data are varied, however; some animals have been protected against infection, some have been protected only against disease, and some have not been protected at all. A phase I clinical trial was conducted to compare recombinant vaccinia virus-HIV gp160 with and without boosting with one of six different candidate recombinant gp120 or recombinant gp160 vaccines. By itself, the vaccinia virus-gp160 vaccine induced little antibody; however, one or two doses of it primed for both gp160-specific cytotoxic T lymphocytes (CTLs) and anti-HIV neutralizing antibodies. The priming effect was strongest in volunteers who had never been vaccinated against smallpox. A phase I trial of a recombinant vaccinia virus-HIV vaccine, incorporating Env, Gag, and Pol antigens and boosted by recombinant gp120 candidate vaccine, is under way.

Vaccines based on the canarypox virus have also protected nonhuman primates from SIV, HIV-2, or HIV-1 infection when given alone or followed by a boost. These vaccines are considered safer than vaccinia virus vaccines since canarypox virus fails to replicate in mammalian cells. Recombinant canarypox virus-HIV vaccines also induce both anti-HIV neutralizing antibodies and CTLs in humans, regardless of prior vaccination with vaccinia virus. Boosting or concomitant administration of recombinant gp120 or gp160 increases the production of HIV neutralizing antibodies and may induce HIV-specific antibodies. Three different types of canarypox virus-HIV gp160 and canarypox virus-HIV gp120 experimental vaccines are undergoing testing in phase I trials in France and the United States. In addition, a phase II trial of recombinant canarypox virus-HIV gp120, alone or in combination with recombinant gp120, is being jointly conducted by AVEG (the NIAID-sponsored AIDS Vaccine Evaluation Group) and the HIVNET (HIV Vaccine Prevention Trials Network) in 420 seronegative volunteers, many of whom were recruited from populations at high risk of HIV infection.

Another live recombinant vector experimental vaccine that has shown protection in nonhuman primates is an adenovirus-HIV envelope vaccine. It generated neutralizing antibodies and anti-HIV CTLs when administered in a prime-boost regimen with HIV envelope protein. A variety of other vector-based approaches are also being developed for HIV vaccines, including recombinant poliovirus, mengovirus, Venezuelan equine encephalitis virus, herpesvirus, Semliki Forest virus, influenza virus, Salmonella, bacille Calmette-Guérin (BCG), Shigella, and Lactococcus. Although initial studies have not shown protection against infection in small numbers of monkeys, further studies are under way.

Additional research is needed in several areas of live recombinant vector AIDS vaccines. Increasing the level of expression of HIV proteins in the recombinant vector needs to be evaluated to determine if it improves immune responses. Vectors containing genes from primary isolates and non-clade B isolates should be evaluated. The optimal route, dose, and schedule of administration and the best way(s) to combine recombinant vector vaccines with subunit, DNA, or other vector experimental vaccines to maximize or optimize the immune response need to be determined.

Several experimental DNA vaccines for HIV and AIDS have been produced and tested in small animals and nonhuman primates. In general, the results of these studies have been promising. DNA vaccines delivered intramuscularly or by gene gun induce both neutralizing antibodies and CTL responses to HIV and SIV antigens. Key issues for DNA vaccine development include optimizing antigen expression by DNA vaccine plasmids and optimizing immune responses to DNA vaccines in nonhuman primates and in human subjects. New expression systems with more potent promoters, immunomodulatory cytokine genes, or costimulatory molecules, as well as formulation of DNA vaccines with adjuvants, cytokines, or novel delivery systems, are also being evaluated as ways to enhance the immunogenicity of DNA vaccines.

Research is also needed to determine the most effective routes of administration and the kinetics of immunization and to evaluate the utility of sequential immunization (prime-boost) strategies using DNA as the primary immunogen followed by secondary immunization with subunit protein or vector-based vaccines. A phase I clinical trial of two DNA candidate vaccines, one containing HIV-1 Env and Rev and the other containing a Gag-Pol construct, is under way.

Respiratory Viruses

Previous vaccines to control respiratory virus infections have been limited to influenza vaccines. Over the last few years, advances in the understanding of immunity to and the importance of respiratory virus infections has led to the development
of both inactivated and live attenuated vaccines against respiratory syncytial virus (RSV) and parainfluenza virus.

**Respiratory syncytial virus.** RSV is the most important cause of viral lower respiratory tract illness (LRI) in infants and children worldwide and causes significant LRI in the elderly and in immunocompromised patients. The goal of RSV vaccination is to prevent serious RSV-associated LRI. Obstacles to the development of successful RSV vaccines include the need to immunize very young infants, who may respond inadequately to vaccination; the existence of two antigenically distinct RSV groups (A and B); and the history of disease enhancement following administration of a formalin-inactivated vaccine. More than one type of vaccine may be needed to prevent RSV LRI in the various populations at risk. Although vector delivery systems, synthetic peptide, and immune-stimulating complex vaccines have been evaluated in animal models, only the purified F protein (PFP) subunit vaccines and live attenuated vaccines have been evaluated in recent clinical trials (162, 225).

A successful RSV vaccine should induce resistance to both subgroup A and B strains. The major difference between RSV subgroups A and B is the G protein, which is responsible for attachment of RSV to a susceptible cell. The F surface protein is highly conserved among the RSV subgroups and functions to promote fusion of the virus and host cell membranes. In animal models of RSV infection, neutralizing antibodies against the G protein confer protection against homologous challenge whereas antibodies against the F protein protect against heterologous challenge.

PFP has been developed as a potential vaccine candidate. PFP-1 was the original vaccine developed. PFP-2 was purified from PFP-1 by ion-exchange chromatography to remove non-F proteins. Both PFP-1 and PFP-2 are safe and immunogenic in studies with 12- to 48-month-old RSV-seropositive children (290). The efficacy of the vaccine could not be determined because of the small numbers of children in these studies. Subunit vaccines may be particularly useful in specific groups of high-risk children and adults. Recent studies of children with cystic fibrosis demonstrated that the PFP-2 vaccine induced a significant antibody response and a significant reduction in the number of lower respiratory tract illnesses and could be given on a yearly basis (299, 300). Two recent studies demonstrated safety and immunogenicity of PFP-2 vaccine in ambulatory and institutionalized adults older than 60 years (175, 176).

Maternal immunization using a PFP vaccine is a strategy being evaluated to protect infants younger than 6 months from RSV disease. The rationale is based on reports of efficient transfer of specific maternal neutralizing antibodies to infants and demonstration of the protection against lower respiratory tract disease and hospitalization in high-risk children by administration of either high-titer anti-RSV polyclonal antiserum or monoclonal antibody directed against the F protein. The advantages of maternal immunization are that infants younger than 6 months are at greatest risk for RSV infection but are least responsive to vaccines, pregnant women respond well immunologically to vaccines, and placental transfer of maternal antibody occurs naturally during the third trimester. Studies with PFP 2 have found the vaccine to be only minimally reactogenic and highly immunogenic in postpartum women and women of childbearing age (168).

Another approach to vaccine development has been to construct live attenuated RSV strains. Early attempts included cold passage, cold adaptation, chemical mutagenesis, temperature-sensitive selection, and combinations of these methods (142, 227). Administration of live attenuated virus preparations has not been associated with enhanced RSV disease on subsequent natural reinfection. Problems that have impeded progress in this area are overattenuation, underattenuation, and concerns about genetic stability. As a result of recently developed technology, it is possible to introduce individual mutations into a cDNA clone of RSV and recover infectious virus, thus providing a mechanism to construct defined attenuated vaccine viruses with improved genetic stability (135).

**Parainfluenza viruses.** Human parainfluenza virus types 1 to 4 (HPIV1 to HPIV4) are important human pathogens that cause upper and lower respiratory tract infections, especially in infants and children. Although HPIV-1 and HPIV-2 generally cause disease in toddlers and preschoolers, HPIV-3 is unique among the parainfluenza viruses in its ability to infect infants younger than 6 months. HPIV-3 infections are second only to RSV infections as a cause of serious respiratory tract disease in infants and children. Several strategies for vaccine development, such as the use of live attenuated, inactivated, recombinant, and subunit vaccines, have been investigated (173). The most promising approach involves the development of live attenuated PIV virus candidates, including a bovine PIV-3 vaccine and cold-passaged HPIV-3 vaccines.

Clinical evaluation of a cold-adapted, temperature-sensitive candidate vaccine (cp-18), derived by cold-passage of the JS strain of HPIV-3, demonstrated that it was not satisfactorily attenuated in children (44). A further attenuated cold-adapted, temperature-sensitive vaccine (cp-45) was then developed. This vaccine was well tolerated when given intranasally to PIV-3-seropositive and seronegative children aged 6 months to 10 years. This study also found that cp-45 vaccine was infectious, immunogenic, and phenotypically stable (229).

A bovine PIV-3 (BPIV-3) vaccine was chosen as a candidate live-virus vaccine because it is antigenically related to HPIV-3. The first phase 1 trial demonstrated that BPIV-3 was safe, infectious, immunogenic, and phenotypically stable when administered to 6- to 36-month-old PIV-3-seronegative infants and children (228). The second study evaluated the BPIV-3 vaccine in two age groups, 2- to 6-month-old infants and 6- to 36-month-old infants and children (226). The vaccine was well tolerated in both age groups and infected 92% of infants younger than 6 months and 89% of infants and children older than 6 months. Serum hemagglutination inhibition antibody responses to HPIV-3 and to BPIV-3 were detected in 42 and 67% of the younger infants, respectively, compared with 70 and 85% of the older infants and children. Additional studies are needed to determine whether two or more doses will enhance the immunogenicity of the BPIV-3 vaccine in young infants.

**VACCINE SAFETY**

Immunizations are among the most cost-effective and widely used public health interventions. Public health recommenda-
tions for vaccine programs and practices represent a dynamic balancing of risks and benefits. Vaccine safety or risk monitoring is necessary to accurately weigh this balance and adjust vaccination policy.

No vaccine is perfectly safe or effective. As the incidence of vaccine-preventable diseases is reduced, public concerns refocus from the risk of getting disease to the health risks associated with vaccines. A higher standard of safety is generally expected of vaccines than of other medical interventions because, in contrast to most pharmaceutical products, which are administered to ill persons for curative purposes, vaccines are generally given to healthy persons to prevent disease. Public tolerance of adverse reactions related to products given to healthy persons, especially healthy infants, is substantially lower than of adverse reactions to products administered to persons who are already sick. This lower risk tolerance for vaccines translates into a greater need to investigate the possible causes of rare adverse events following vaccinations than would be acceptable for other pharmaceutical products. Since vaccination is such a common and memorable event, any health event following immunization may be attributed to the vaccine. Health effects reported as being associated with vaccines may be (i) true adverse reactions or (ii) associated with vaccination only by coincidence. Scientific research that attempts to distinguish true vaccine side effects from unrelated, chance occurrences is crucial. This knowledge is necessary to maintain public confidence in vaccines and immunization programs.

The topic of vaccine safety became prominent during the mid 1970s, with increases in lawsuits filed on behalf of persons presumably injured by the DTP vaccine (181). Legal decisions were made and damages awarded despite the lack of scientific evidence to support vaccine injury claims (181). As a result of the liability, prices soared and several manufacturers halted production. A vaccine shortage resulted, and public health officials became concerned about the return of epidemic disease. To reduce liability and respond to public health concerns, Congress passed the National Childhood Vaccine Injury Act in 1986.

The National Childhood Vaccine Injury Act mandated that all health care providers report certain adverse events that occur following vaccination. As a result, VAERS was established by the FDA and CDC in 1990. VAERS provides a mechanism for the collection and analysis of adverse events associated with vaccines currently licensed in the United States. Adverse events are defined as health effects that occur after immunization and that may or may not be related to the vaccine. VAERS data are continually monitored to detect previously unknown adverse events or increases in known adverse events (119).

The gaps that exist in the scientific knowledge of rare vaccine side effects prompted the CDC to develop the Vaccine Safety Datalink (VSD) project in 1990 (118). This project involved forming partnerships with four large health maintenance organizations to continually monitor vaccine safety. VSD is an example of a large-linked database and includes information on more than $6 \times 10^9$ people. The VSD project allows for planned vaccine safety studies as well as timely investigations of hypotheses.

In the late 1990s, reports in the lay press questioned the safety of routine immunizations, alarming parents with unsupported accounts of the dangers of vaccines. One major national television network broadcast a feature piece which linked diabetes to childhood immunizations. In the United Kingdom, reports linked receipt of measles vaccine to the development of autism, and in France hepatitis vaccine was reported to cause multiple sclerosis.

### Hib Vaccine and Diabetes

Classen and Classen have suggested that certain vaccines, if given at birth, may decrease the occurrence of type 1 diabetes whereas if initial vaccination is performed after 2 months of age the occurrence of diabetes increases (124). Other researchers have not found an increased risk of diabetes associated with vaccination (217). The Classen theory is based on results from experiments in laboratory animals, as well as comparisons of the rates of diabetes between countries with different immunization schedules (124). Applying findings from laboratory animals to humans is fraught with uncertainties. Comparison of diabetes rates between countries with different vaccination policies also provides weak evidence because many factors, including vaccination schedules, may differ by country. In addition, other factors, including genetic predisposition and a number of possible environmental exposures unrelated to vaccines, may influence the development of diabetes.

The most rigorous epidemiologic study of infant vaccinations and type 1 diabetes to date found that measles vaccine was associated with a decreased risk and that there was no association with BCG, smallpox, tetanus, pertussis, rubella, or mumps vaccine (51). In a large clinical trial of Hib vaccine conducted in Finland, no statistically significant association was found between the receipt of Hib vaccine and the development of type 1 diabetes over 10 years of follow-up (230). Current evidence does not support a causal association between any vaccine and type 1 diabetes in humans (208).

### Measles Vaccine and Autism

The causes of autism are unknown. Most experts agree, however, that autism is a condition that begins before birth (316). Genetics seems to play a major role in the development of autism. It is usually diagnosed in children when they are 18 to 30 months old, shortly after children have received many of the recommended vaccinations. Because of this coincidence in timing, some parents of children with autism believe that an immunization may have caused their child’s condition.

A 1998 published report in The Lancet of 12 patients who had inflammatory bowel disease and autism raised the hypothesis that there might be a link between the MMR vaccine and autism (364). The authors speculated that MMR vaccine was the possible cause of bowel problems, with the resultant malabsorption of essential vitamins and nutrients leading to autism.

Epidemiologic studies in both the United States and Great Britain do not support a causal association between MMR and inflammatory bowel disease (149, 273). Nor do epidemiologic studies support a causal association between MMR (or other measles virus-containing vaccines) and autism (31, 54, 155, 156, 187, 352; H. Peltola, A. Patja, P. Leinikki, M. Valle, I. Davidkin, and M. Paunio, Letter, Lancet 351:1327–1328, 1998). A
large retrospective study of California children born from 1980 to 1994 was conducted to further examine any possible association between autism and receipt of the MMR vaccine. No correlation was observed between MMR immunization coverage and the number of children with autism (148). Expert panels convened by both IOM and AAP have examined the available data on autism and MMR vaccine. Both panels concluded the available evidence does not support the hypothesis that MMR vaccine causes autism or associated disorders or inflammatory bowel disease (198, 211).

**Hepatitis B Vaccine and Multiple Sclerosis**

Reports of multiple sclerosis developing after hepatitis B vaccination have led to the concern that HBV immunization may precipitate the onset of multiple sclerosis or lead to relapses. Since licensure, the safety of the HBV vaccine has continued to be monitored. Several reviews have been performed and have not shown a scientific association between hepatitis B vaccination and severe neurological adverse events such as optic neuritis and Guillain-Barré syndrome. Two recently published large epidemiologic studies examined the risk of an association between vaccines and multiple sclerosis. The first, a case-control study with a large cohort of nurses, has shown no significant association between hepatitis B vaccination and development of multiple sclerosis (36). A French study of patients with multiple sclerosis found that vaccination did not appear to increase the short-term risk of relapse (138).

**CONCLUSION**

English physician Edward Jenner’s observation that milkmaids stricken with a disease called cowpox were rarely victims of smallpox prompted him to devise the first vaccine 200 years ago. In one of the world’s great medical successes, a modern-day version of this vaccine led to the total eradication of smallpox by 1980. Since Jenner’s time, advances in virology, bacteriology, and immunology have led to an enhanced understanding of how the human body defends itself against invading microorganisms.

The development of vaccines against more than 20 infectious diseases has revolutionized our approach to public health. Since 1990, at least 10 new or improved vaccines have become available. Today, tremendous advances in molecular biology enable scientists to devise new approaches to developing vaccines against diseases that continue to plague the world’s population. The challenge will be for society to ensure that these vaccines are made available to all who need them in both the developed and developing world.

**REFERENCES**


135. Choo, S., L. Seymour, R. Morris, S. Quataert, S. Lockhart, K. Cartwright,


Downloaded from http://cmr.asm.org/ on 22nd February 2023 by guest


