Haemophilus influenzae Type b Conjugate Vaccines: Recommendations for Immunization With Recently and Previously Licensed Vaccines

Committee on Infectious Diseases

This updated statement on Haemophilus influenzae type b conjugate vaccines includes recommendations for use of a newly licensed Haemophilus conjugate vaccine, and a newly licensed combination vaccine that combines one of the Haemophilus conjugate vaccines and diphtheria, tetanus toxoids, and pertussis (DTP). The statement also includes revised guidelines for the use of all conjugate vaccines. The changes concern use of different vaccine products in children younger than 15 months of age; timing for booster doses for completion of the immunization schedule in children 12 months of age and older; schedules for children in whom vaccination has been delayed in initiation, or has lapsed; choice of vaccine in children in whom vaccination against DTP or diphtheria and tetanus toxoids (DT) is deferred; number of doses for children with immunologic impairment associated with increased risk of H influenzae type b disease; and indications for rifampin prophylaxis in households where contacts have been vaccinated. Related information on the basis for these new recommendations also is given.

As of 1993, four H influenzae type b conjugate vaccines, and a combination vaccine that combines one of these vaccines with DTP, are licensed in the United States. The newly licensed conjugate vaccine consists of polyribosylribitol phosphate (PRP) conjugated to tetanus toxoid (PRP-T; ActHIB/OmniHib, prepared by Institut Merieux and distributed in the United States by Connaught Laboratories and SmithKline Beecham). The combination vaccine consists of a licensed conjugate of PRP oligomers covalently linked to diphtheria-CRM197 protein (HbOC; HIBTITER) with DTP (TRI-IMMUNOL), and is referred to as HbOC-DTP (TETRAMUNE; manufactured by Lederle-Praxis). Both new vaccines are approved for use beginning at 2 months of age.

The four licensed vaccines are summarized in Table 1. Their composition differs in several important respects, including the carrier protein used, the polysaccharide molecular size, and the method of conjugating the saccharide to the protein. These chemical differences result in different immunologic properties. The evaluation of H influenzae type b conjugate vaccines has included studies of immunogenicity (the ability to elicit antibody responses), efficacy (the ability of vaccination to decrease the incidence of disease), and safety.

IMMUNOGENICITY

Healthy Infants

The relationship between protection and the magnitude of the antibody response following vaccination is complex. Some infants with low antibody responses may be protected against disease when exposed to H influenzae type b because conjugate vaccination primes infants1 and provides them with an ability to mount a serum antibody response rapidly upon encountering the organism. Qualitative differences in the avidity (a measure of the functional affinity of serum antibody to bind to antigen) of antibody elicited by different conjugate vaccines also suggest that the concentration of anti-PRP antibody is not the only determinant of protection.2 Postvaccination sera with high antibody avidity require much lower antibody concentrations for in vitro bacterial killing than sera with low antibody avidity in which higher antibody concentrations are required.2 The clinical importance of these differences in antibody avidity has yet to be determined.

The four licensed H influenzae type b conjugate vaccines elicit different patterns of serum antibody response in infants vaccinated at 2, 4, and 6 months of age (Figure).3,4 The PRP-OMP (PedvaxHIB) elicits significant increases in antibody concentration after a single injection at 2 months of age, whereas the other three conjugates do not. After a second injection of PRP-OMP at 4 months of age, modest increases in antibody concentration occur. Because of the low responses to the first injection of PRP-T or HbOC at 2 months of age, the fold increases in antibody concentration to the second injection of these vaccines are higher than those with PRP-OMP.4 However, after two injections, the geometric mean antibody concentration is highest in PRP-OMP recipients, followed by that in recipients of PRP-T, HbOC, and PRP-D (see Figure).3,4

For infants vaccinated at 2 and 4 months of age, a third injection of conjugate vaccine is recommended at 6 months of age for infants receiving HbOC or PRP-T. A third dose at this age is not recommended.
for PRP-OMP because the antibody concentrations are high after two doses of this vaccine and there is only a minimal increase after a third dose given at 6 months of age (Figure). The anti-PRP antibody responses of infants vaccinated at 2, 4, and 6 months of age with HbOC-DTP are similar to those observed in infants given HbOC and DTP as separate injections (see “Combination Vaccines”). For infants scheduled to receive separate injections of HbOC and DTP, HbOC-DTP can be substituted. The Academy considers that this combination vaccine and all three of the individual conjugate vaccines are likely to be equivalent in the protection achieved against *H. influenzae* type b disease after completing the recommended primary series of two or three doses (depending on the product).

Until recently, immunogenicity studies conducted in infants younger than 12 months of age used the same conjugate vaccine product for all doses. Because conjugate vaccines differ chemically and immunologically, how infants given sequential doses of different vaccines would respond is not known. Several ongoing studies are addressing this question. Until additional data from these studies are available, the Academy recommends that when feasible the same conjugate vaccine should be used for subsequent doses for infants younger than 12 months of age as was used for the initial dose. However, for infants given doses of different conjugate vaccines, it is not necessary to give more than three doses of any vaccine to complete the primary series.

After administration of the recommended initial two doses of PRP-OMP at 2 and 4 months of age, or the initial three doses of HbOC or PRP-T at 2, 4, and 6 months of age, serum antibody concentrations decline rapidly. At 12 months of age, the antibody concentrations have decreased approximately three- to six-fold compared with the respective peak concentrations. Therefore, a booster dose of conjugate vaccine is recommended at 12 to 15 months of age. For this dose, any conjugate vaccine (PRP-D, HbOC, PRP-OMP, or PRP-T) is acceptable, regardless of which vaccine was used for the primary series. The reasons are several: (1) Unconjugated PRP (no longer commercially available in the United States) when given at 12 months of age elicits a memory antibody response in infants previously given PRP-OMP, HbOC, or PRP-T. (2) PRP-D given as a booster dose at 15 months of age is as or more immunogenic than a booster dose of the conjugate vaccine used for the initial series. (3) In previously unvaccinated 15-month-olds, a single dose of any of the licensed conjugate vaccines confers protection. Similar protection can be expected in previously vaccinated children receiving a booster or reinforcing dose at 12 to 15 months of age.
At 15 months of age, HbOC-DTP may be used in children scheduled to receive DTP and a booster injection of conjugate vaccine. However, at this age, DTaP vaccines, containing acellular pertussis, are approved for use, and are associated with fewer local, febrile, and minor systemic reactions than DTP vaccine containing whole-cell pertussis. Currently, a licensed combination conjugate vaccine containing DTaP is not available. Therefore, in children 15 months of age or older, separate injections of any HbOC-type b conjugate vaccine and DTaP, DTP, or a dose of HbOC-DTP, are acceptable.

For children whose initial vaccination is given at 12 to 14 months of age, the Academy considers that any conjugate vaccine (PRP-D, HbOC, PRP-OMP, or PRP-T) also is acceptable. Currently, the Food and Drug Administration (FDA) has approved labeling for PRP-D for use beginning at 15 months of age. The rationale for the Academy recommending use of PRP-D beginning at 12 months of age is as follows: (1) At 12 to 14 months of age, two doses of conjugate vaccine are recommended, separated by 2 months. (2) At this age, two doses of PRP-D elicited higher serum antibody concentrations, and higher bactericidal titers, than one dose given at 18 months. Therefore, similar protection can be expected in children receiving two doses at 12 to 15 months of age compared with those receiving the recommended one dose at 15 to 18 months.

Children in Whom DTP or DT Vaccination Is Deferred

The carrier proteins used in PRP-T, PRP-D, and HbOC (but not PRP-OMP) are chemically and immunologically related to toxoids contained in DTP (Table 1). In most published immunogenicity studies, H influenzae type b conjugate vaccines were administered to infants who received DTP before or simultaneously with the conjugate vaccination. Data from experiments in infant animals and humans indicate that, in the absence of previous or simultaneous vaccination with DTP, vaccination with conjugate vaccines is insufficient to elicit consistent antibody responses to the carrier protein. Previous or simultaneous vaccination with DTP also may be required to elicit maximal anti-PRP antibody responses to PRP-T, PRP-D, or HbOC but not to PRP-OMP. Thus, in infants vaccinated with a Haemophilus conjugate vaccine in whom DTP or DT vaccination is deferred, PRP-OMP may be advantageous.

Children With Immunologic Impairment

Children with chronic illnesses associated with increased risk of H influenzae type b disease may have impaired antibody responses to conjugate vaccination. Examples include children with human immunodeficiency virus (HIV) infection, immunoglobulin deficiency, bone marrow transplants, anatomic or functional asplenia, and recipients of chemotherapy for malignancy. Although most infants with sickle cell disease who are vaccinated with Haemophilus conjugate vaccine in the first year of life appear to respond with protective antibody, some children in whom vaccination is initiated in the second or third year of life after development of functional hyposplenia show subnormal antibody responses. However, these children usually will respond if given an additional dose. Infants with selective IgG2 subclass immunoglobulin deficiency also frequently have impaired antibody responses to conjugate vaccination, but many will respond to additional doses as they get older. Thus, some children with immunologic impairment may benefit from additional doses of conjugate vaccine beyond those normally indicated.

CONJUGATE VACCINE EFFICACY

Summary of Clinical Trials

Results of the prelicensure conjugate vaccine efficacy studies are summarized in Table 2. PRP-D protected Finnish infants vaccinated at 3, 4, and 6 months of age, but this vaccine did not provide significant protection to native Alaskan infants vaccinated at 2, 4, and 6 months. In contrast, in Navajo infants, another population with an increased risk of H influenzae type b disease, vaccination with PRP-OMP was highly efficacious when administered at 2 and 4 months of age (Table 2). Short-term protection also was observed after a single dose of PRP-OMP given at 2 months of age, a finding that correlates with the ability of this vaccine at that age to elicit serum antibody responses after one injection (Figure).

The efficacy of HbOC was evaluated in a trial performed in Northern California. After a three-dose schedule vaccine efficacy was high (Table 2). The vaccine also may be protective after two doses, but the small number of patient-months of follow-up between the second and third doses and the corresponding small number of cases observed in the unvaccinated controls in this period limited the analysis. No significant protection was observed in this trial after one dose of HbOC.

Two randomized, controlled trials to evaluate the efficacy of PRP-T vaccine given at 2, 4, and 6 months of age were terminated before completion because FDA approval (October 1990) of Haemophilus conjugate vaccines was not anticipated.

<table>
<thead>
<tr>
<th>Location of Population</th>
<th>Vaccine</th>
<th>Design</th>
<th>Age, mo</th>
<th>% Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland19</td>
<td>PRP-D</td>
<td>Open randomized</td>
<td>3,4,6</td>
<td>89 (70 to 96)</td>
</tr>
<tr>
<td>Alaskan nates20</td>
<td>PRP-D</td>
<td>Placebo-controlled randomized</td>
<td>2,4,6</td>
<td>35 (-57-73)</td>
</tr>
<tr>
<td>Northern California22</td>
<td>HbOC</td>
<td>Open quasarandomized</td>
<td>2,4,6</td>
<td>100 (68-100)</td>
</tr>
<tr>
<td>Navajo24</td>
<td>PRP-OMP</td>
<td>Placebo-controlled randomized</td>
<td>2,4</td>
<td>93 (53-98)</td>
</tr>
</tbody>
</table>

* PRP-T was evaluated in two US efficacy studies that could not be completed (see text). PRP-T was found to be efficacious in an open trial in the United Kingdom, where infants were vaccinated at 2, 3, and 4 months of age. CI = confidence interval.

**TABLE 2. Summary of Prelicensure Conjugate Vaccine Efficacy Studies**
haemophilus with conjugate vaccine at 15 months of age or older.

Type b disease can still occur if the conjugate vaccine is administered more than 2 weeks after vaccination. In some children, onset of disease occurred within a week of conjugate vaccination but, because it takes 1 to 2 weeks for vaccination to elicit serum antibody responses, infants are not expected to be protected during this immediate postvaccination period. There is no evidence, to date, of any increased risk of disease during the 1 to 2 weeks after conjugate vaccination.

Cases of Haemophilus disease also have occurred more than 2 weeks after vaccination. In one study, more than one third of children vaccinated with conjugate vaccine at 15 months of age or older who subsequently developed Haemophilus disease had subnormal serum immunoglobulin concentrations, particularly IgG2. In contrast, immunoglobulin deficiency may be less common in infants failing vaccination at younger than 12 months of age. However, longer follow-up is needed in this age group, because it is possible that vaccination failure may be a marker for an evolving immunodeficiency that is not yet reflected in abnormal serum immunoglobulin concentrations. Children who develop disease despite vaccination at 15 months of age or older may benefit from immunologic evaluation. Consideration also should be given for evaluation of infants failing vaccination at a younger age if there are other factors present suggesting increased susceptibility to infection.

Rifampin Prophylaxis. Despite the occurrence of disease in a few vaccinated children, available data indicate that conjugate vaccination is highly effective in preventing disease, particularly in fully vaccinated children (defined as at least one dose of conjugate vaccine given at 15 months of age or older, or two doses at 12 to 14 months, or two or more doses when younger than 12 months of age with a booster or reinforcing dose at 12 months of age or older (see Tables 3, 4, and 5). Previously, the Academy suggested: "Rifampin prophylaxis is recommended for all household contacts, irrespective of age, in households with at least one contact younger than 48 months, regardless of the immunization status of the contacts." (See recommendations in the 1991 Report of the Committee on Infectious Diseases.31) Households without such a member were excluded from that recommendation. The Academy now considers that an otherwise healthy child who is fully immunized is at minimal risk of acquiring disease, even if exposed to a child with Haemophilus type b disease. Therefore, rifampin prophylaxis is no longer indicated for management of households where all contacts younger than 48 months are fully immunized according to the above definitions.

COMBINATION VACCINES

The FDA recently licensed HbOC-DTP (TETRAMUNE) for use in infants as young as 2 months of age. The vaccine is administered intramuscularly in a dose of 0.5 mL, which contains the same quantities of

**TABLE 3. Recommendations for Haemophilus Conjugate Vaccination in Children Immunized Beginning at 2 to 6 Months of Age**

<table>
<thead>
<tr>
<th>Vaccine Product at Initiation</th>
<th>Total No. of Doses to Be Administered</th>
<th>Currently Recommended Vaccine Regimens*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbOC or PRP-T</td>
<td>4</td>
<td>Three doses at 2-mo intervals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>When feasible same vaccine for doses 1-3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fourth dose at 12-15 mo of age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any conjugate vaccine for dose 4†</td>
</tr>
<tr>
<td>PRP-OMP</td>
<td>3</td>
<td>Two doses at 2-mo intervals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>When feasible same vaccine for doses 1-2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Third dose at 12-15 mo of age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any conjugate vaccine for dose 3†</td>
</tr>
</tbody>
</table>

* See text. The HbOC, PRP-T, or PRP-OMP should be given in a separate syringe and at a separate site from other immunizations. HbOC is also available as a combination vaccine with DTP (HbOC-DTP). This combination can be used in infants scheduled to receive separate injections of DTP and HbOC.
† The safety and efficacy of PRP-OMP, PRP-D, PRP-T, and HbOC are likely to be equivalent in children 12 months of age and older.
diphtheria toxoid, tetanus toxoid, whole cell pertussis vaccine, and diphtheria-CRM$_{197}$ protein conjugated to PRP oligosaccharide, as DTP and HbOC vaccines.

The anti-PRP antibody responses of infants vaccinated at 2, 4, and 6 months of age with HbOC-DTP were similar to those observed in infants given HbOC and DTP as separate injections. Similarly, the antibody responses to diphtheria and tetanus toxoids, and to the components of whole-cell pertussis vaccine, were similar to or enhanced in the group given the combination vaccine compared with those given separate injections of HbOC and DTP. For these reasons, although efficacy data are not available, HbOC-DTP is expected to provide equivalent protection against $H$ influenzae type b disease, and against diphtheria, tetanus, and pertussis, as when the vaccines are administered as separate injections. Therefore, in infants scheduled to receive separate injections of DTP and HbOC, HbOC-DTP can be substituted.

Physicians should not mix $H$ influenzae type b conjugate vaccines in the same syringe with other vaccines unless specific combinations are approved by the FDA. Studies are underway to evaluate both additional fixed combination vaccines and some specific combinations that may be mixed together just before vaccination.

**SAFETY**

Adverse reactions to the four licensed $H$ influenzae type b conjugate vaccines are few. Pain, redness, and/or swelling at the injection site occur in about 25% of recipients, but these symptoms typically are mild and last less than 24 hours.3 Systemic reactions such as fever and irritability are infrequent. When conjugate vaccines are administered during the same visit as when DTP vaccine is given, the rates of systemic reactions do not differ from those observed when only DTP vaccine is administered. Similarly, when the combination DTP-HbOC vaccine is administered, no clinically important differences in the respective rates of systemic or local reactions have been observed in comparison with those of infants given HbOC and DTP as separate injections.

**RECOMMENDATIONS**

1. All children should be immunized with an $H$ influenzae type b conjugate vaccine beginning at approximately 2 months of age or as soon as possible thereafter (Table 3). Only HbOC, PRP-OMP, or PRP-T should be given to children younger than 12 months of age.
   a. The $H$ influenzae type b conjugate immunization can be initiated as early as 6 weeks of age.
   b. When DT or DTP vaccination is deferred, use of PRP-OMP may be advantageous (see Recommendation 4c).
   c. $H$ influenzae type b conjugate vaccination can be given during visits when vaccines for DTP, DTaP, polio, hepatitis B, or measles, mumps, rubella (MMR) are given.
   d. HbOC, PRP-T, or PRP-OMP should be given in a separate syringe and at a separate site from...
TABLE 5. Recommendations for Haemophilus Conjugate Vaccination in Children With a Lapse in Vaccination

<table>
<thead>
<tr>
<th>Age at Presentation, mo</th>
<th>Previous Vaccination History</th>
<th>Recommended Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>7–11</td>
<td>1 dose*</td>
<td>One dose of conjugate at 7–11 mo, with a booster dose given at least 2 mo later, at 12–15 mo† Same as above</td>
</tr>
<tr>
<td>12–14</td>
<td>2 doses of HbOC or PRP-T</td>
<td>A single dose of any licensed conjugate‡</td>
</tr>
<tr>
<td>12–14</td>
<td>2 doses before 12 mo*</td>
<td>Two additional doses of any licensed conjugate, separated by 2 mo‡</td>
</tr>
<tr>
<td>15–59</td>
<td>Any incomplete schedule</td>
<td>A single dose of any licensed conjugate‡</td>
</tr>
</tbody>
</table>

* PRP-OMP, PRP-T, or HbOC. HbOC is also available as a combination vaccine with DTP (HbOC-DTP). This combination can be used in infants scheduled to receive separate injections of DTP and HbOC. In children 15 months of age or older eligible to receive DTaP (containing acellular pertussis), HbOC-DTP or separate injections of conjugate vaccine and DTaP can be given, because of the lower rate of febrile and minor local and systemic reactions associated with DTaP.
† For the dose given at 7 to 11 months, when feasible, the same vaccine should be given as was used for the dose given at 2 to 6 months. For the dose given at 12 to 15 months, any licensed conjugate can be used (see below).
‡ The Academy considers that safety and efficacy of PRP-OMP, PRP-D, PRP-T, or HbOC are likely to be equivalent when used in children ≥ 12 months of age.

2. For routine immunization of children younger than 7 months of age.
   a. Primary series. Either a three-dose series of HbOC, or PRP-T, or a two-dose series of PRP-OMP, should be administered (Table 3). Doses are given at approximately 2-month intervals. When feasible, the conjugate vaccine product used for the first dose should be used for subsequent doses in children younger than 12 months of age. When sequential doses of different vaccine products are given, it is not considered necessary to administer more than a total of three doses of any conjugate vaccine to complete the primary series. In infants scheduled to receive separate injections of DTP and HbOC, the combination HbOC-DTP vaccine can be used in infants previously given any DTP vaccine. The safety and efficacy of the different vaccines given in their recommended schedules appear to be equivalent.
   b. Reinforcing/booster vaccination at 12 to 15 months of age. For children who have completed a primary series, an additional dose of conjugate vaccine is recommended at 12 to 15 months of age, or as soon as possible thereafter. Any conjugate vaccine (PRP-D, HbOC, PRP-OMP, or PRP-T) is acceptable for this dose regardless of the vaccine used previously. For infants scheduled to receive both HbOC and DTP, a single injection of the combination vaccine, HbOC-DTP, can be substituted. However, for this dose in children 15 months of age or older, separate injections of Haemophilus b conjugate and DTaP vaccines are acceptable, because of the lower frequency of local and minor systemic reactions associated with use of acellular pertussis vaccine.

   The MMR vaccination can be given at the same time as Haemophilus type b conjugate vaccine, but it should be given at a separate site and in a separate syringe. Some physicians may choose to give these injections in more than one visit. In this circumstance, for patients who have not been immunized previously against measles, priority should be given to administration of the MMR vaccination when the age of the patient is appropriate.

3. Children younger than 5 years of age who did not receive Haemophilus conjugate vaccine in the first 6 months of life should be immunized according to the following recommended schedules (Table 4):
   a. For children in whom immunization is initiated at 7 to 11 months of age, the recommended schedules for HbOC, PRP-OMP, and PRP-T are identical and require three doses. The first two doses are given at 2-month intervals using the same vaccine product, when feasible, for both doses. The third (booster) dose should be given at 12 to 18 months of age, preferably 2 months after the second dose. For the third dose, any licensed conjugate vaccine is acceptable.
   b. For children in whom immunization is initiated at 12 to 14 months of age, the recommended regimens for PRP-D, HbOC, PRP-OMP, or PRP-T are identical and require two doses given at a 2-month interval.
   c. For children in whom immunization is initiated at 15 months of age or older, and who have not yet reached their fifth birthday (ie, 59 months of age or younger), the recommended regimen is a single dose of any licensed conjugate vaccine.
   d. Circumstances may suggest a need for more rapid “catch-up” immunization in which case a 1-month interval between doses is the minimum.
e. For infants in whom immunization with both DTP and conjugate vaccination is initiated late, the HbOC-DTP combination can be substituted for separate injections of the two vaccines. However, additional doses of DTP alone may be necessary to complete the primary DTP immunization because, in contrast to Haemophilus type b vaccination, delay in DTP vaccination does not decrease the total number of required injections.

4. Special Circumstances

a. **Lapsed immunizations.** Recommendations for vaccination of children who have had a lapse in the schedule of immunizations are based on limited data. The interim recommendations are summarized in Table 5.

b. **Premature infants.** For infants born prematurely, immunization should be based on chronologic age and initiated at 2 months of age according to recommendations in Table 3. Data are needed on responses of these infants to Haemophilus conjugate vaccines. However, experiences with other antigens that are T-cell dependent such as diphtheria and tetanus toxoids justify this interim recommendation.

c. **Deferring DTP or DT vaccination.** Infants with certain neurologic disorders occasionally have DTP and DT vaccination deferred until the first birthday. (See current Report of the Committee on Infectious Diseases.31 pp367–369) Use of PRP-OMP may be advantageous in this circumstance because PRP-OMP conjugate vaccine is immunogenic in the absence of vaccination with diphtheria or tetanus toxoids.9,10 Simultaneous or previous vaccination with diphtheria or tetanus toxoids may be required for an optimal anticapsular antibody response to PRP-T or HbOC.8,9,10 In infants in whom a decision has been made to use DT vaccine instead of DTP, these considerations do not apply and any *H influenzae* type b conjugate vaccine may be used.

d. **In infants in whom pertussis vaccination is contraindicated, HbOC-DTP should not be used.** These contraindications include a history of an immediate anaphylactic reaction after administration of DTP, or development of encephalopathy within 7 days after DTP, defined as a severe acute central nervous system disorder that may manifest by major alterations of consciousness or generalized focal seizures that persist more than a few hours without recovery within 24 hours. Similarly, all the “precautions” that apply to pertussis vaccination also apply to the use of HbOC-DTP (see 1991 Report of the Committee on Infectious Diseases.31 pp367–369).

e. **Immunologic impairment associated with increased risk of invasive *H influenzae* type b disease (eg, patients with HIV infection, IgG2 subclass deficiency, bone marrow transplants, sickle cell disease, splenectomy, and those receiving chemotherapy for malignancies).** When children with splenectomy or sickle cell disease have completed a primary series of immunizations and have received a booster dose at 12 months of age or older, additional doses are not needed. For children with malignancies, some experts recommend an additional dose of conjugate vaccine be given before undergoing chemotherapy and/or splenectomy. The currently available data on the antibody responses of children with HIV infection or IgG2 deficiency are limited. Whether children with these conditions will benefit from additional doses if they have completed a primary series of immunizations and have received a booster dose at 12 months of age or older is not known.

For those children 12 to 59 months of age with one of these underlying conditions predisposing to *H influenzae* type b disease who are unvaccinated, or who received only one dose of conjugate vaccine before 12 months of age, two doses of any conjugate vaccine, separated by 2 months, are recommended. For those in this age group who received two doses before 12 months of age, one additional dose of conjugate vaccine is recommended.

Unvaccinated children with underlying diseases predisposing to *H influenzae* type b disease who are older than 59 months of age should be vaccinated with any licensed conjugate vaccine. One dose appears sufficient in this age group for children with sickle cell disease or asplenia.13,17 Two doses separated by 1 to 2 months are suggested, based on limited data, for children with HIV infection, IgG2 deficiency, bone marrow transplants, or malignancies.11–14 Because DTP vaccination is not recommended routinely for persons 7 years of age or older, HbOC-DTP also is not recommended for use at this age.

No known contraindications exist to simultaneous administration of *Haemophilus* conjugate vaccine with pneumococcal vaccine or meningococcal vaccine when given in separate syringes at different sites.

f. **Prior *H influenzae* type b disease.** Children who had invasive *H influenzae* type b disease when younger than 24 months of age frequently have low anticapsular antibody concentrations in convalescent sera and may remain at risk of developing a second episode of disease.35 Any conjugate vaccination given before developing disease should be ignored, and conjugate vaccination in these patients should be readministered during convalescence according to the age-appropriate schedule for unvaccinated children (Tables 3 through 5). Revaccination should be initiated 1 month after onset of disease, or as soon as possible thereafter.

Children whose disease occurred at age 24 months or older do not need immunization, irrespective of previous vaccination status, because the disease most likely induced a protective immune response and second episodes of disease at this age are rare.

Immunized children who experience inva-
5. Rifampin chemoprophylaxis of contacts of patients with *H influenzae* type b disease. Based on the high efficacy of conjugate vaccination, household members do not require rifampin prophylaxis when all the contacts younger than 48 months are fully immunized: defined as at least one dose of conjugate vaccine at 15 months of age or older, or two doses at 12 to 14 months, or two or more doses when younger than 12 months of age with a booster dose at 12 months of age or older (see Tables 3, 4, and 5). All members of a household with a child younger than 12 months of age (eg, children who have not yet received the booster/reinforcing dose) should receive rifampin prophylaxis, irrespective of the vaccination status of the child, although the risk of secondary disease is very low in a child of this age who has completed the primary two- or three-dose series. Members of households with a fully vaccinated immunocompromised child should receive rifampin because of concern that the vaccination may have been ineffective.

6. Reporting of *H influenzae* type b disease and adverse reactions after immunization. All important adverse reactions occurring at any time after immunization, including cases of disease occurring in fully or partially immunized children, should be reported promptly to the Vaccine Adverse Event Reporting System (VAERS) of the Department of Health and Human Services. (For reporting form, call 1–800–822–7967.) In addition, all cases of invasive *H influenzae* type b disease, including those in fully or partially vaccinated children, should be reported to the Centers for Disease Control (CDC) through the state and local health department. The time after immunization when protection can be anticipated is not known with precision and probably differs depending on the number of previous doses. Providers should be aware of this uncertainty and not expect protection simultaneously with vaccine administration.

**FUTURE DEVELOPMENTS**

Studies are in progress to assess the safety and immunogenicity of *H influenzae* type b conjugate vaccines when combined with DTP, hepatitis B, enhanced potency inactivated poliovirus vaccine, or MMR in the same syringe, and to evaluate the safety and immunogenicity of regimens employing several conjugate vaccines.

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Pediatrics 1993;92;480

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