Recommendations for Use of Haemophilus b Conjugate Vaccines and a Combined Diphtheria, Tetanus, Pertussis, and Haemophilus b Vaccine Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Recommendations and Reports

September 17, 1993 / 42(RR-13)

Summary

These recommendations include information on two vaccines recently licensed for use among infants: Haemophilus b Conjugate Vaccine (PRP-T {ActHIBTM, OmniHIBTM}), manufactured by Pasteur Merieux Vaccins, and TETRAMUNETM, manufactured by Lederle Laboratories/Praxis Biologics. This statement also updates recommendations for use of other available Haemophilus b vaccines (PRP-D {ProHIBiT(registered)}; HbOC {HibTITER(registered)}; and PRP-OMP {PedvaxHIB(registered)}) for infants and children. INTRODUCTION

The incidence of Haemophilus influenzae type b (Hib) disease in the United States has declined since the mid-1980s (1). Before the introduction of effective vaccines, Hib was the leading cause of bacterial meningitis and other invasive bacterial disease among children less than 5 years of age; approximately one in 200 children developed invasive Hib disease before the age of 5 years. Nearly all infections occurred among children less than 5 years of age, and approximately two thirds of all cases occurred among children less than 18 months of age. Meningitis occurred in approximately two thirds of children with invasive Hib disease, resulting in hearing impairment or neurologic sequelae in 15%-30%. The case-fatality rate was 2%-5% (2).

In 1985, the first Hib vaccines were licensed for use in the United States. These vaccines contained purified polyribosylribitol phosphate (PRP) capsular material from type b strains. Antibody against PRP was shown to be the primary component of serum bactericidal activity against the organism. Although the vaccine was highly effective in trials in Finland among children greater than or equal to 18 months of age (3), postmarketing efficacy studies in the United States demonstrated variable efficacy (4,5). PRP vaccines were ineffective in children less than 18 months of age because of the T-cell-independent nature of the immune response to PRP polysaccharide (3).

Conjugation of the PRP polysaccharide with protein carriers confers T-cell- dependent characteristics to the vaccine and substantially enhances the immunologic response to the PRP antigen. By 1989, Hib conjugate vaccines (PRP-D {ProHIBiT(registered)}; HbOC {HibTITER(registered)}; and PRP-OMP {PedvaxHIB(registered)}) were licensed for use among children greater than or equal to 15 months of age. In late 1990, following two prospective studies, PRP-OMP (6) and HbOC (7) were licensed for use among infants. On the basis of findings establishing comparable immunogenicity, a third conjugate vaccine, PRP-T (ActHIBTM, OmniHIBTM) has now been licensed for use among infants. Specific characteristics of the four conjugate vaccines available for infants and children vary (e.g., the type of protein carrier, the size of the polysaccharide, and the chemical linkage between the polysaccharide and carrier) (Table_1).

Current recommendations for universal vaccination of infants require parenteral administration of three different vaccines (diphtheria-

tetanus-pertussis {DTP}, Hib conjugate, and hepatitis B) during two or three different visits to a health-care provider. Combination vaccines were developed to reduce the number of injections at each visit. TETRAMUNETM is the first licensed combination vaccine that provides protection against diphtheria, tetanus, pertussis, and Hib disease.

This statement a) summarizes current immunogenicity and efficacy data regarding Hib conjugate vaccines, including PRP-T; b) summarizes available information regarding the safety and immunogenicity of TETRAMUNETM; and c) provides updated recommendations from the Advisory Committee on Immunization Practices (ACIP) for use of conjugate Hib vaccines and TETRAMUNETM for infants and children. HIB CONJUGATE VACCINES Immunogenicity

Studies have been performed with all four Hib conjugate vaccines to determine immunogenicity in infants 2-6 months of age. Direct comparison of studies is complicated by differing vaccination and blood collection regimens and interlaboratory variation in assays for measurement of PRP antibody. Also, the precise level of antibody required for protection against invasive disease is not clearly established. However, a geometric mean titer (GMT) of 1 ug/mL 3 weeks postvaccination correlated with protection in studies following vaccination with unconjugated PRP vaccine and suggests long-term protection from invasive disease (8).

After three vaccinations at ages 2, 4, and 6 months, each of three Hib conjugate vaccines -- HbOC, PRP-OMP, and PRP-T -- produced protective levels of anticapsular antibody (9-13). One study reported comparative immunogenicity with PRP-OMP, HbOC, and PRP-T

protective levels of antiCapsular antibody (< 1). One study reported comparative immunogenicity with PRP-OMP, HbOC, and PRP-T (12), and two other studies compared immunogenicity with all four conjugate vaccines (11,13) (Table_2). In this age group, only PRP-OMP vaccine produced a substantial increase in antibody after one dose (12,13). Antibody response among infants following a series of three infant vaccinations with PRP-D is limited (only 15%-45% of infants develop a GMT greater than or equal to 1 ug/mL after 3 doses) (11,13,14) and is lower than with HbOC, PRP-OMP, or PRP-T.

With each conjugate vaccine, antibody levels decline after administration of the primary series. Regardless of the conjugate vaccine used in the primary series for infants, booster vaccination of children greater than or equal to 12 months of age with any of the licensed conjugate vaccines will likely elicit an adequate response, as studies indicate that a) unconjugated PRP (administered at 12-14 months of age) elicits a good booster response in infants who are administered PRP-OMP (15), HbOC (15,16), or PRP-T (15,16,) during infancy; b) PRP-D administered as a booster at age 15 months induces adequate immunologic response regardless of the Hib conjugate administered in the initial series (17); and c) each conjugate vaccine demonstrates adequate immunogenicity when administered as a single vaccination to children greater than or equal to 15 months of age (18,19).

Limited information is available regarding the interchangeability of different Hib vaccines for the primary series at 2, 4, and 6 months of age (Table_3). Preliminary findings from two studies suggest that the vaccination series consisting of PRP-OMP at 2 months, followed by either PRP-T (20,21) or HbOC (20,22) at 4 months and 6 months, induces adequate anti-PRP antibody response. The sequence HbOC, PRP-T, PRP-T was also immunogenic (20) after the complete primary series was administered. This information suggests that any combination of three doses of Hib conjugate vaccines licensed for use among infants will provide adequate protection.

The carrier proteins used in PRP-T, PRP-D, and HbOC (but not PRP-OMP) are derived from the toxoids used in DTP vaccine (Table_1). Limited data have indicated that prior or concurrent administration of DTP vaccine may enhance anti-PRP antibody response following vaccination with these Hib vaccines (23-26). It has been suggested that priming T-cells to the carrier proteins may be important for optimal antibody response to the conjugated vaccine. For infants, the immunogenicity of PRP-OMP (which has a carrier derived from the meningococcal outer membrane protein) appears to be unaffected by the absence of prior or concurrent DTP vaccination (24). Efficacy

Efficacy studies of PRP-D, PRP-OMP, HbOC, and PRP-T vaccines administered to infants 2-6 months of age are summarized in this report (Table_4). Two randomized, double-blind trials evaluating PRP-T vaccine efficacy were discontinued in the United States in October 1990 after licensure was granted to HbOC and PRP-OMP vaccines. A third efficacy trial of PRP-T in England has recently been completed.

Efficacy of the PRP-D conjugate has varied with the age of the population studied. Postlicensure studies performed in the United States among children aged 15-60 months demonstrated point estimates of efficacy ranging from 74%-96%. Two studies have prospectively evaluated efficacy of PRP-D administered to children less than 12 months of age. In a trial in Finland involving 114,000 infants vaccinated at 3, 4, and 6 months of age, the point estimate of efficacy was 89% (95% confidence interval {CI} = 70-96) (27). In comparison, among Alaskan Natives vaccinated at ages 2, 4, and 6 months, the point estimate of efficacy was 35% (95% CI = -57-73) and not significantly different from zero (28).

PRP-OMP was shown to be 93%-100% efficacious in Navajo infants (a population at particularly high risk of disease) vaccinated at 2 and 4 months of age (6). Two studies have indicated a point estimate of efficacy of greater than or equal to 97% following the administration of two doses of HbOC (in Finland) (29) or three doses of vaccine (in the United States) (7) to infants.

Although the trials evaluating PRP-T vaccine efficacy among infants in the United States were terminated early, no cases of invasive Hib disease were reported among more than 6,200 vaccinees at the time of termination (30, J.C. Parke, Carolinas Medical Center, unpublished data). In a trial in Great Britain, PRP-T was protective in infants vaccinated at ages 2, 3, and 4 months (31). Efficacy of PRP-T was also suggested in a nationwide immunization program that was implemented in Finland in January 1990. There were no reported cases of invasive Hib disease among more than 97,000 infants who received greater than or equal to 2 doses of PRP-T. Two children developed disease after one dose of vaccine (32).

In the United States, 30-50 cases of invasive Hib disease have been reported among children who had received appropriate vaccination with the Hib conjugate vaccine and therefore were expected to have had adequate levels of protective antibody (33- 35). These cases may represent vaccine failure. Results of immunologic evaluation of children who had vaccine failure vary with the age of the child. In a study of children vaccinated with Hib conjugate vaccine at age greater than or equal to 15 months, subnormal immunoglobulin concentrations were present in approximately 40% of those who developed invasive Hib disease (33). However, in a separate study that evaluated fully vaccinated children less than 12 months of age who developed invasive Hib disease, only 9% had evidence of low immunoglobulin levels (34). COMBINATION VACCINES TETRAMUNETM

On March 30, 1993, the Food and Drug Administration licensed TETRAMUNETM, a vaccine manufactured by Lederle Laboratories/Praxis Biologics by combining a licensed DTP vaccine (TRI-IMMUNOL(registered)) and HbOC (HibTITER(registered)). TETRAMUNETM contains 12.5 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, an estimated 4 protective units of pertussis vaccine, 10 ug of purified Hib polysaccharide, and approximately 25 ug of CRM197 protein. The single-dose volume is 0.5 mL to be administered intramuscularly. Safety and Immunogenicity

The safety of TETRAMUNETM vaccine was evaluated in a study of 6,497 infants in California who received doses at ages 2, 4, and 6 months, compared with 3,935 infants who received DTP (TRI-IMMUNOL(registered)) and HbOC vaccines as separate concurrent injections (36, Lederle Laboratories/Praxis Biologics, unpublished data). Based on follow-up of a randomized subset of 1,411 infants (for whom 1,347 parents were interviewed), the risk for local and systemic reactions was similar for infants who received the combination product when compared with those who received two separate injections of DTP and HbOC. The infants who received the combination vaccine, however, experienced a higher likelihood of restless sleep following the second dose and greater than or equal to 1 inch of swelling at the injection site after administration of the first dose of the combination vaccine (Table_5).

Immunogenicity studies among infants who received TETRAMUNETM at ages 2, 4, and 6 months (37, Lederle Laboratories/Praxis Biologics, unpublished data) indicated that antibody responses to Hib PRP, diphtheria, and tetanus toxins were comparable to or higher than those in persons who received separate, but concurrent administration of DTP and HbOC vaccines. Similarly, antibody responses to pertussis toxin, filamentous hemagglutinin, 69-kd outer-membrane protein (pertactin), and pertussis agglutinins were comparable to or higher than those following separate concurrent administration of DTP and HbOC vaccines (Table_6). Comparable immunogenicity results also were reported for children aged 15-18 months (who had received prior doses of DTP, but not Hib vaccine) following a dose of TETRAMUNETM when compared with separate but concurrent administration of DTP and HbOC vaccines.
Efficacy

No efficacy information is available for TETRAMUNETM, but the immunogenicity information suggests TETRAMUNETM will provide similar protection against Hib disease and diphtheria, tetanus, and pertussis as will the separate administration of HbOC or DTP vaccines. Other combination vaccines

vaccines. Other combination vaccines

Published studies have evaluated the safety and immunogenicity of other vaccines that combine DTP (or DTaP {acellular pertussis component}) and Hib in the same formulation or the same syringe. However, none of these formulations (PRP-D-DTaP {38 }, HbOC-DTaP {39,40}, or PRP-T-DTP {41}) have been licensed for use. Two studies have shown a slight reduction in the immune response to pertussis when certain Hib vaccines were combined with DTP (42,43), but the magnitude of the effect is unlikely to be clinically relevant. Simultaneous vaccination

Large prelicensure and postlicensure studies have demonstrated the safety, immunogenicity, and efficacy of each of the licensed Hib conjugate vaccines administered to infants concurrently with DTP vaccine and oral polio vaccine (OPV) (6,7,9,32) as well as the safety and immunogenicity of TETRAMUNETM when administered concurrently with OPV in recommended schedules (36,37). More limited data also support the safety and immunogenicity of Hib conjugate vaccines when administered simultaneously with hepatitis B vaccine to infants, and with DTP, OPV, measles, mumps, and rubella (MMR) and/or hepatitis B vaccine when administered at ages 12-18 months. Recommendations for Hib Vaccination General

All infants should receive a conjugate Hib vaccine (separate or in combination with DTP {TETRAMUNETM}), beginning at age 2 months (but not earlier than 6 weeks). If the first vaccination is delayed beyond age 6 months, the schedule of vaccination for previously unimmunized children should be followed (Table_7). When possible, the Hib conjugate vaccine used at the first vaccination should be used for all subsequent vaccinations in the primary series. When either Hib vaccines or TETRAMUNETM is used, the vaccine should be administered intramuscularly using a separate syringe and administered at a separate site from any other concurrent vaccinations. HbOC or PRP-T

Previously unvaccinated infants aged 2-6 months should receive three doses of vaccine administered 2 months apart, followed by a booster dose at age 12-15 months, at least 2 months after the last vaccination. Unvaccinated children ages 7-11 months should receive two doses of vaccine, 2 months apart, followed by a booster dose at age 12-18 months, at least 2 months after the last vaccination. Unvaccinated children ages 12-14 months should receive two doses of vaccine, at least 2 months apart. Any previously unvaccinated child aged 15-59 months should receive a single dose of vaccine. PRP-OMP

Previously unvaccinated infants ages 2-6 months should receive two doses of vaccine administered at least 2 months apart. Although PRP-OMP induces a substantial antibody response after one dose, all children should receive all recommended doses of PRP-OMP. Because of the substantial antibody response after one dose, it may be advantageous to use PRP-OMP vaccine in populations that are known to be at increased risk for disease during early infancy (e.g., Alaskan Natives). A booster dose should be administered to all children at 12-15 months of age at least 2 months after the last vaccination. Unvaccinated children ages 7-11 months should receive two doses of vaccine, 2 months apart, followed by a booster dose at 12-18 months of age, at least 2 months after the last dose. Unvaccinated children ages 12-14 months should receive two doses of vaccine, 2 months apart. Any previously unvaccinated child 15-59 months of age should receive a single dose of vaccine. PRP-D

One dose of PRP-D may be administered to unvaccinated children aged 15-59 months. This vaccine may be used as a booster dose at 12-18 months of age following a two- or three-dose primary series, regardless of the vaccine used in the primary series. This vaccine is not licensed for use among infants because of its limited immunogenicity and variable protective efficacy in this age group. TETRAMUNETM

The combination vaccine TETRAMUNETM may be used for routine vaccination of infants, beginning at age 2 months, to prevent diphtheria, tetanus, pertussis, and invasive Hib disease. Previously unvaccinated infants aged 2-6 months should receive three doses administered at least 2 months apart. An additional dose should be administered at 12-15 months of age, after at least a 6-month interval following the third dose. Alternatively, acellular DTP and Hib vaccine can be administered as separate injections at 12-15 months of age. Acellular DTP is preferred for doses four and five of the five-dose DTP series. For infants who begin both Hib and DTP vaccinations late (after 2 months of age), TETRAMUNETM may be used for the first and second doses of the vaccine series. However, because delay in initiation of the DTP series does not reduce the number of required doses of DTP, additional doses of DTP without Hib are necessary to ensure that all four doses are administered. Infants ages 7-11 months who have not previously been vaccinated with DTP or Hib vaccines should receive two doses of TETRAMUNETM, administered at least 2 months apart, followed by a dose of DTP vaccine 4-8 weeks after the second dose of TETRAMUNETM. An additional dose of DTP and Hib vaccines should then be administered: DTP vaccine at least 6 months after the third immunizing dose against diphtheria, tetanus, and pertussis; and Hib vaccine at 12-18 months of age, at least 2 months after the last Hib dose.

TETRAMUNETM may be used to complete an infant immunization series started with any Hib vaccine (licensed for use in this age group) and with any DTP vaccine if both vaccines are to be administered simultaneously. Completion of the primary series using the same Hib vaccine, however, is preferable. Conversely, any DTP vaccine may be used to complete a series initiated with TETRAMUNETM (see the general ACIP statement on Diphtheria, Tetanus and Pertussis: Recommendations for Vaccine Use and Other Preventive Measures {44} for further information). Other considerations for Hib vaccination

Other considerations for Hib vaccination are discussed in the following section:

1. Although an interval of 2 months between doses of Hib vaccine in the primary series is recommended, an interval of 1 month is acceptable, if necessary.

2. Unvaccinated children aged 15-59 months may be administered a single dose of any one of the four Hib conjugate vaccines or TETRAMUNETM (if both Hib and DTP vaccines are indicated).

3. After the primary infant vaccination series is completed, any of the four licensed Hib conjugate vaccines (or TETRAMUNETM if both Hib vaccine and DTP vaccine are indicated) may be used as a booster dose at age 12-15 months.

4. The primary vaccine series should preferably be completed with the same Hib conjugate vaccine. If, however, different vaccines are administered, a total of three doses of Hib conjugate vaccine is adequate. Any combination of Hib conjugate vaccines that is licensed for use among infants may be used to complete the primary series.

5. Infants born prematurely should be vaccinated according to the schedule recommended for other infants, beginning at age 2 months.

6. Hib conjugate vaccines may be administered simultaneously with DTP (or DTaP) vaccine, OPV, IPV, MMR, influenza, and hepatitis B vaccines. TETRAMUNETM may be administered simultaneously with OPV, IPV, MMR, influenza, and hepatitis B vaccines.

7. Because natural infection does not always result in the development of protective anti-PRP antibody levels (45), children less than 24 months of age who develop invasive Hib disease should receive Hib vaccine as recommended in the schedule. These children should be considered unimmunized, and vaccination should start as soon as possible during the convalescent phase of the illness.

8. Hib vaccine is immunogenic in patients with increased risk for invasive disease, such as those with sickle-cell disease (46), leukemia (47), human immunodeficiency virus (HIV) infection (48,49), and in those who have had splenectomies (50). However, in persons with HIV infection, immunogenicity varies with stage of infection and degree of immunocompromise. Efficacy studies have not been performed in populations with increased risk of invasive disease (see the general ACIP statement on Use of Vaccines and Immune Globulins in Persons with Altered Immunocompetence {51}).

9. Children who attend day care are at increased risk for Hib disease. Therefore, efforts should be made to ensure that all day care attendees less than 5 years of age are fully vaccinated.

10. Rifampin chemoprophylaxis for household contacts of a person with invasive Hib disease is no longer indicated if all contacts ages less than 4 years are fully vaccinated against Hib disease. A child is considered fully immunized against Hib disease following

    a. at least one dose of conjugate vaccine at greater than or equal to 15 months of age, b) two doses of conjugate vaccine at 12-14 months of age, or c) two or more doses of conjugate vaccine at less than 12 months of age, followed by a booster dose at greater than or equal to 12 months of age. In households with one or more infants less than 12 months of age (regardless of vaccination status) or with a child aged 1-3 years who is inadequately vaccinated, all household contacts should receive rifampin prophylaxis following a case of invasive Hib disease that occurs in any family member. The recommended dose is 20 mg/kg as a single daily dose (maximal daily dose 600 mg) for 4 days. Neonates (less than 1 month of age) should receive 10 mg/kg once daily for 4 days. Adverse reactions

Adverse reactions to each of the four Hib conjugate vaccines are generally uncommon. Swelling, redness, and/or pain have been reported in 5%-30% of recipients and usually resolve within 12-24 hours. Systemic reactions such as fever and irritability are infrequent. Available information on side effects and adverse reactions suggests that the risks for local and systemic events following TETRAMUNETM administration are similar to those following concurrent administration of its individual component vaccines (i.e., DTP and Hib vaccines), and may be due largely to the pertussis component of the DTP vaccine (52).

Surveillance regarding the safety of TETRAMUNETM, PRP-T, and other Hib vaccines in large-scale use aids in the assessment of vaccine safety by identifying potential events that may warrant further study. The Vaccine Adverse Event Reporting System (VAERS) of the U.S. Department of Health and Human Services encourages reports of all serious adverse events that occur after receipt of any vaccine.* Invasive Hib disease is a reportable condition in 43 states. All health-care workers should report any case of invasive Hib disease to local and state health departments. Contraindications and Precautions

Vaccination with a specific Hib conjugate vaccine is contraindicated in persons known to have experienced anaphylaxis following a prior dose of that vaccine. Vaccination should be delayed in children with moderate or severe illnesses. Minor illnesses (e.g., mild upper-respiratory infection) are not contraindications to vaccination.

Contraindications and precautions of the use of TETRAMUNETM are the same as those for its individual component vaccines (i.e., DTP or Hib) (see the general ACIP statement on Diphtheria, Tetanus, and Pertussis: Recommendations for Vaccine Use and Other Preventive Measures {44} for more details on the use of vaccines containing DTP).

References

1. Adams WG, Deaver KA, Cochi SL, et al. Decline of childhood Haemophilus influenzae type b (Hib) disease in the Hib vaccine era. JAMA 1993;269:221-6.

2. Broome CV. Epidemiology of Haemophilus influenzae type b infections in the United States. Pediatr Infect Dis J 1987;6:779-

3. Peltola H, Kayhty H, Sivonen A, et al. Haemophilus influenzae type b capsular polysaccharide vaccine in children: a double-blind field study of 100,000 vaccinees 3 months to 5 years of age in Finland. Pediatrics 1977;60:730-7.

4. Ward JI, Broome CV, Harrison LH, Shinefield HR, Black SB. Haemophilus influenzae type b vaccines: lessons for the future. Pediatrics 1988;81:886-93.

5. Harrison LH, Broome CV, Hightower AW, et al. A day care-based study of the efficacy of Haemophilus b polysaccharide vaccine. JAMA 1988;260:1413-8.

6. Santosham M, Wolff M, Reid R, et al. The efficacy in Navajo infants of a conjugate vaccine consisting of Haemophilus influenzae type b polysaccharide and Neisseria meningitidis outer-membrane protein complex. N Engl J Med 1991;324:1767-72.

7. Black SB, Shinefield HR, Fireman B, et al. Efficacy in infancy of oligosaccharide conjugate Haemophilus influenzae type b (HbOC) vaccine in a United States population of 61,080 children. Pediatr Infect Dis J 1991;10:97-104.

8. Kayhty H, Peltola H, Karanko V, Makela PH. The protective level of serum antibodies to the capsular polysaccharide of Haemophilus influenzae type b. J Infect Dis 1983;147:1100.

9. Black SB, Shinefield HR, Lampert D, et al. Safety and immunogenicity of oligosaccharide conjugate Haemophilus influenzae type b (HbOC) vaccine in infancy. Pediatr Infect Dis J 1991;10:92-

10. Parke JC, Schneerson R, Reimer C, et al. Clinical and immunologic responses to Haemophilus influenzae type b-tetanus toxoid conjugate vaccine in infants injected at 3,5,7, and 18 months of age. J Pediatr 1991;118:184-90.

11. Decker MD, Edwards KM, Bradley R, Palmer P. Comparative trial in infants of four conjugate Haemophilus influenzae type b vaccines. J Pediatr 1992;120:184-9.

12. Granoff DM, Anderson EL, Osterholm MT, et al. Differences in the immunogenicity of three Haemophilus influenzae type b conjugate vaccines in infants. J Pediatr 1992;121:187-94.

13. Bulkow LR, Wainwright RB, Letson GW, Chang SJ, Ward JI. Comparative immunogenicity of four Haemophilus influenzae type b conjugate vaccines in Alaska Native infants. Pediatr Infect Dis J 1993;12:484-92.

14. Ward JI, Brenneman G, Lepow M, Lum M, Burkhart K, Chiu CY. Haemophilus influenzae type b anticapsular antibody responses to PRP-Pertussis and PRP-D vaccines in Alaska native infants. J Infect Dis 1988;158:719-23.

15. Granoff DM, Holmes SJ, Osterholm MT, et al. Induction of immunologic memory in infants primed with Haemophilus influenzae type b conjugate vaccines. J Infect Dis 1993;168:663-71.

16. Kayhty H, Eskola J, Peltola H, Saarinen L, Makela PH. High antibody response to booster doses of either Haemophilus influenzae capsular polysaccharide or conjugate vaccine after primary immunization with conjugate vaccines. J Infect Dis 1992;165(suppl 1):S165-6.

17. Decker MD, Edwards KM, Bradley R, Palmer P. Responses of children to booster immunization with their primary conjugate Haemophilus influenzae type b vaccine or with polyribosylribitol phosphate conjugated with diphtheria toxoid. J Pediatr 1993;122:410-3.

18. Turner RB, Cimino CO, Sullivan BJ. Prospective comparison of response of infants to three Haemophilus influenzae type b vaccines. Pediatr Infect Dis J 1991;10:108-12.

19. Holmes SJ, Murphy TV, Anderson RS, et al. Immunogenicity of four Haemophilus influenzae type b vaccines in 17- to 19-month-old children. J Pediatr 1991;118:364-71.

20. Greenberg DP, Lieberman JM, Marcy SM, et al. Safety and immunogenicity of mixed sequences of Haemophilus influenzae type B (HIB) conjugate vaccines in infants {Abstract #997}. Pediatr Res 1993;33:169A.

21. Daum RS, Milewski WM, Ballanco GA. Interchangeability of H. influenzae type B vaccines for the primary series ("mix and match") -- a preliminary analysis {Abstract #976}. Pediatr Res 1993;33:166A.

22. Anderson EL, Decker MD, Edwards KM, Englund JA, Belshe RB. Interchangeability of conjugated Haemophilus influenzae type B (HIB) vaccines in infants {Abstract #493}. Pediatr Res 1993;33:85A.

23. Schneerson R, Robbins JB, Chu C, et al. Serum antibody responses of juvenile and infant rhesus monkeys injected with Haemophilus influenzae type b and pneumococcus type 6A capsular polysaccharide-protein conjugates. Infect Immun 1984;45:582-91.

24. Vella PA, Ellis RW. Immunogenicity of Haemophilus influenzae type b conjugate vaccines in infant rhesus monkeys. Pediatr Res 1991;29:10-3.

25. Granoff DM, Holmes SJ, Belshe RB, Anderson EL. The effect of carrier priming on the anticapsular (PRP) antibody responses to Haemophilus influenzae type b (Hib) conjugate vaccines {Abstract # 994}. Pediatr Res 1993;33:169A.

26. Lieberman JM, Greenberg DP, Wong VK, et al. Does newborn immunization with diphtheria-tetanus toxoid (DT) prime for enhanced antibody responses to H. influenzae type B (HIB) conjugate vaccines? {Abstract #1028}. Pediatr Res 1993;33:174A.

27. Eskola J, Peltola H, Takala AK, et al. Efficacy of Haemophilus influenzae type b polysaccharide-diphtheria toxoid conjugate vaccine in infancy. N Engl J Med 1987;317:717-22.

28. Ward J, Brenneman G, Letson GW, Heyward WL. Alaska H. influenzae Vaccine Study Group. Limited efficacy of a H. influenzae type b conjugate vaccine in Alaska Native infants. N Engl J Med 1990;323:1381-7.

29. Eskola J, Peltola H, Takala A, Palmgren J, Makela PH. Protective efficacy of the Haemophilus influenzae type b conjugate vaccine HbOC in Finnish infants. {Abstract #60}. Thirtieth Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlanta, Georgia, October 1990.

30. Vadheim CM, Greenberg DP, Partridge S, Jing J, Ward JI. Effectiveness and safety of an Haemophilus influenzae type b conjugate vaccine (PRP-T) in young infants. Pediatrics 1993;92:272-

31. Booy R, Moxon ER, Macfarlane JA, Mayon-White RT, Slack MPE. Efficacy of Haemophilus influenzae type b conjugate vaccine in Oxford region. Lancet 1992;340:847.

32. Fritzell B, Plotkin S. Efficacy and safety of a Haemophilus influenzae type b capsular polysaccharide-tetanus protein conjugate vaccine. J Pediatr 1992;121:355-62.

33. Holmes SJ, Lucas AH, Osterholm MT, Froeschle JE, Granoff DM and the Collaborative Study Group. Immunoglobulin deficiency and idiotype expression in children developing Haemophilus influenzae type b disease after vaccination with conjugate vaccine. JAMA 1991;266:1960-5.

34. Holmes SJ, Osterholm MT, Zangwill KM, Wenger JD, Granoff DM, Vaccine Failure Group. Haemophilus influenzae type b disease in infants vaccinated with Hib conjugate vaccine at less than 12 months {Abstract #976}. Thirty-second Interscience Conference on Antimicrobial Agents and Chemotherapy, Anaheim, California, October 1992.

35. Frasch CE, Hiner EE, Gross TP. Haemophilus b disease after vaccination with Haemophilus b polysaccharide or conjugate vaccine. Am J Dis Child 1991;145:1379-82.

36. Black S, Shinefield H, Hiatt R, Fireman B, Ray P, Lewis N. Safety of HDTP -- a combined oligosaccharide conjugate (HbOC) Haemophilus influenzae type b (Hib) vaccine and DTP vaccine -- in infancy. Pediatr Res {Abstract #932} 1992;31:158A.

37. Paradiso P, Hogerman D, Madore D, et al. Safety and immunogenicity in infants of a tetravalent vaccine composed of HbOC (HibTITER) and DTP (TRI-IMMUNOL). Pediatr Res {Abstract #1028} 1992;31:174A.

38. Kovel A, Wald ER, Guerra N, Serdy C, Meschievitz CK. Safety and immunogenicity of acellular diphtheria-tetanus-pertussis and Haemophilus conjugate vaccines given in combination or at separate injection sites. J Pediatr 1992;120:84-7.

39. Shinefield H, Black S, Adelman T, Ensor K. Safety and immunogenicity of DTaP-HbOC -- a combined oligosaccharide conjugate (HbOC, HibTITER) Haemophilus influenzae type b and acellular DTP vaccine (CTaP) in toddlers. {Abstract #306}. Thirty-second Interscience Conference on Antimicrobial Agents and Chemotherapy, Anaheim, California, October 1992.

40. Paradiso P, Madore D, Hogerman D, Black S, Shinefield H. Immunogenicity of DTaP-HbOC in toddlers primed by DTP and HbOC as separate injections or DTP-HbOC combination vaccine {Abstract #307}. Interscience Conference on Antimicrobial Agents and Chemotherapy, Anaheim, California, October 1992.

41. Ferreccio C, Clemens J, Avendano A, et al. The clinical and immunologic response of Chilean infants to Haemophilus influenzae type b polysaccharide-tetanus protein conjugate vaccine coadministered in the same syringe with diphtheria-tetanus toxoids-pertussis vaccine at two, four, and six months of age. Pediatr Infect Dis J 1991;10:764-71.

42. Clemens JD, Ferreccio C, Levine MM, et al. Impact of Haemophilus influenzae type b polysaccharide-tetanus protein conjugate vaccine on responses to concurrently administered diphtheria-tetanus-pertussis vaccine. JAMA 1992;267:673-8.

43. Rothstein E, Bernstein M, Schiller K, et al. Safety and immunogenicity of PRP-D and DTP administered as a single injection {Abstract #1078}. Pediatr Res 1991;29:182A.

44. CDC. Diphtheria, tetanus, and pertussis: recommendations for vaccine use and other preventive measures. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1991;40(No. RR-10):1-28.

45. Edmonson MB, Granoff DM, Barenkamp SJ, Chesney PJ. Outer membrane protein subtypes and investigation of recurrent Haemophilus influenzae type b disease. J Pediatr 1982;100: 202-8.

46. Frank AL, Labotka RJ, Rao S, et al. Haemophilus influenzae type b immunization of children with sickle cell diseases. Pediatrics 1988;82:571-5.

47. Feldman S, Gigliotti F, Shenep JL, Roberson PK, Lott L. Risk of Haemophilus influenzae type b disease in children with cancer and response of immunocompromised leukemic children to a conjugate vaccine. J Infect Dis 1990;161:926-31.

48. Steinhoff MC, Auerbach BS, Nelson K, et al. Antibody responses to Haemophilus influenzae type b vaccines in men with human immunodeficiency virus infection. N Engl J Med 1991;325:1837-42.

49. Janoff EN, Worel S, Douglas JM, et al. Natural immunity and response to conjugate vaccine for Haemophilus influenzae type b in men with HIV {Abstract #609}. Thirtieth Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlanta, Georgia, October 1990.

50. Jakacki R, Luery N, McVerry P, Lange B. Haemophilus influenzae diphtheria protein conjugate immunization after therapy in splenectomized patients with Hodgkin Disease. Ann Intern Med 1990;112:143-4.

51. CDC. Recommendations of the Advisory Committee on Immunization Practices (ACIP): use of vaccines and immune globulins in persons with altered immunocompetence. MMWR 1993;42(No. RR-4):1-18.

52. Madore DV, Johnson CL, Phipps DC, et al. Safety and immunologic response to Haemophilus influenzae type b oligosaccharide CRM197 conjugate vaccine in 1- to 6-month-old infants. Pediatrics 1990;85:331-7.

* Questions about reporting requirements, completion of report forms, or requests for reporting forms should be directed to VAERS at 1-800-822-7967.

Table_1

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 1. Haemophilus influenzae type b conjugate vaccines licensed for use among children

Vaccine	Trade name (manufacturer)	Polysaccharide	Linkage	Protein carrier
PRP-D	ProHIBiT(R) (Connaught)	Medium	6-carbon	Diphtheria toxoid
HbOC*	HibTITER(R) (Lederle-Praxis)	Small	None	CRM197 mutant Corynebacterium diphtheriae toxin protein
PRP-OMP	PedvaxHIB(R) (Merck Sharp and Dohme)	Medium	Thioether	Neisseria meningitidis outer membrane protein complex
PRP-T	ActHIB(TM) OmniHIB(TM) (Pasteur Merieux Vaccins)	Large	6-carbon	Tetanus toxoid

* TETRAMUNE(TM) consists of HbOC and DTP vaccine (TRI-IMMUNOL(R)), manufactured by Lederle Laboratories/Praxis Biologics.

Return to top.

Table_2

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 2. Immunogenicity of three Haemophilus influenzae type b vaccines among infants

Vaccine +	Study site	Geometric mean titer, ug/mL (% >1 ug/mL) * Before vaccination	After dose 1 &	After dose 2	After dose 3
Study 1	Tennessee (11)				
PRP-D		0.07	--	0.08	0.28 (29)
PRP-OMP @		0.11	0.83	0.84 (50)	1.14 (55)
HbOC		0.07	0.09	0.13	3.08 (75)
PRP-T		0.10	0.05	0.30	3.64 (83)
Study 2	Alaska (13)				
PRP-D		0.06 (4)	0.04 (2)	0.06 (11)	0.55 (45)
PRP-OMP @		0.16 (14)	1.37 (57)	2.71 (79)	--
HbOC		0.15 (5)	0.07 (0)	0.59 (43)	13.70 (94)
PRP-T		0.18 (13)	0.06 (0)	0.32 (20)	2.46 (78)
Study 3	Minnesota/Missouri/				
PRP-OMP @	Texas (12)	0.18	2.69 (80)	4.00 (85)	5.21 (88)
HbOC		0.17	0.11	0.45 (23)	6.31 (90)
PRP-T		0.25	0.19	1.25 (56)	6.37 (97)

* Measured by radioimmunoassay.
+ In all studies, vaccine was administered at 2, 4, and 6 months of age.
& Antibody level after one dose includes data from only one of four data collection sites in Tennessee.
@ Current recommendations require only two doses of PRP-OMP in the primary series. For studies 1 and 3, three doses were administered.
-- Data not available.

Return to top.

Table_3

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 3. Summary of preliminary immunogenicity data using different Hib conjugate vaccine sequences among infants

Vaccine +	Study site	Sample size	Geometric mean titer, ug/mL * Before vaccination	After dose 1	After dose 2	After dose 3
Study 1	Tennessee (22)					
O-H-H &@		55	0.113	--	0.90	5.63
H-O-O @		57	0.082	--	0.56	0.67
Study 2	Chicago (21)					
O-T-T		27	0.14	--	--	6.98
Study 3	California (20)					
O-H-H		10	0.10	3.68	5.84	16.4
O-H-H @		23	0.09	0.48	2.72	12.7
H-T-T		24	0.16	0.11	3.13	11.1
O-T-T		28	0.06	2.42	6.10	12.3

* Measured by radioimmunoassay.
+ In all studies, vaccine was administered at 2, 4, and 6 months of age.
& O=PRP-OMP, H=HbOC, T=PRP-T.
@ The manufacturer reported that immunogenicity conferred by PRP-OMP lots in these sequences was less than expected.
-- Data not available.

Return to top.

Table_4

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 4. Efficacy of Hib conjugate vaccines among infants

Vaccine	Population	Design	Age at vaccination (mos)	% efficacy (95% CI *)
PRP-D	Finland (27)	Open, randomized	3, 4, 6	89 (70- 96)
	Alaskan Natives (28)	Placebo-controlled, randomized	2, 4, 6	35 (-57- 73)
PRP-OMP	Navajo (6)	Placebo-controlled, randomized	2, 4	93 (53- 98) * 100 (67-100) &
HbOC	California (7)	Open, partially randomized	2, 4, 6	100 (67-100)
	Finland (29)	Open	4, 6	97 @
PRP-T	California (30)	Controlled, randomized	2, 4, 6	**
	North Carolina (see text)	Placebo-controlled	2, 4, 6	**
	United Kingdom (31)	Open, controlled	2, 3, 4	++
	Finland (32)	Historical controls	4, 6	++

* Confidence interval.
+ Includes cases that occurred before 18 months of age.
& Includes cases that occurred before 15 months of age.
@ Confidence intervals not reported.
** Studies evaluating efficacy of PRP-T vaccine in the United States were terminated before completion.
++ Point estimate and confidence intervals not reported.

Return to top.

Table_5

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 5. Reactions following administration of TETRAMUNE(TM) compared with concurrent separate administration of DTP and HbOC vaccine among infants *+

	After dose 1		After dose 2		After dose 3	
Reaction	Combined (n=585)	Separate & (n=550)	Combined (n=540)	Separate (n=430)	Combined (n=470)	Separate (n=380)
Local						
Redness	15.7	16.1	20.7	19.1	19.5	17.8
Redness >=1 inch	4.9	3.0	1.8	1.6	1.5	0.8
Swelling	22.4	19.8	14.0	18.6	15.3	16.2
Swelling >=1 inch	8.0 @	4.3	3.0	3.5	2.5	3.4
Tenderness	31.6	29.8	22.8	22.1	24.3	21.6
Tenderness >=1 inch	9.6	6.6	6.0	5.2	5.4	3.8
Systemic	(n=585)	(n=570)	(n=550)	(n=450)	(n=485)	(n=395)
Perceived fever	38.0	35.6	39.7	38.4	40.0	38.3
Irritability	53.8	56.5	51.9	50.8	56.0	52.7

Irritability	35.8	36.5	31.9	30.8	30.6	32.7
Restless sleep	19.9	24.1	32.0 @	26.1	31.1	32.0
Vomiting	1.7	2.6	1.8	2.2	2.1	2.0
Diarrhea	1.4	1.2	1.1	0.7	0.8	2.3
Loss of appetite	3.9	3.5	3.3	2.2	3.7	4.8
Other **	7.3	9.2	7.8	8.3	6.6	9.4

* Percentage of infants experiencing event within 24 hours of vaccination.
+ From reference 36 and unpublished data from manufacturer.
& For the separate group, no attempt was made to sum reactions that occurred at both injection sites; reactions only to DTP site were counted.
@ p<0.05, combined vs. separate vaccination groups.
** Rash, lethargy, congestion, runny nose/eyes, changes in bowel movement other than diarrhea, increased appetite/thirst, bruising/bleeding/hot at injection site.

Return to top.

Table_6

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 6. Immunogenicity of TETRAMUNE(TM) versus separate injections of DTP and HbOC in infants *

	Geometric mean titer +		
Component	Combined (n=189)	Separate (n=189)	P-value &
HbOC (ug/mL)			
Pre	0.09	0.09	0.762
Post 1	0.12	0.10	0.002
Post 2	0.66	0.34	<0.001
Post 3	6.67	4.42	0.034
Diphtheria (IU/mL)			
Pre	0.04	0.05	0.624
Post 3	0.71	0.40	0.009
Tetanus (U/mL)			
Pre	0.45	0.50	0.404
Post 3	8.20	4.51	<0.001
Pertussis agglutinins (reciprocal dilution)			
Pre	6.53	4.69	0.121
Post 3	51.93	23.34	0.008
Pertussis toxin +@			
Pre	1.09	1.80	
Post 3	85.92	17.60	0.001 **
Pertactin (69K) +@			
Pre	6.13	5.98	
Post3	66.43	41.55	0.11 **
FHA +@			
Pre	3.97	4.73	
Post 3	2.32	0.79	0.0001 **

* From reference 37 and unpublished data from manufacturer. Combined (DTP/HbOC) or separate (DTP and HbOC) vaccine administered at 2, 4, and 6 months of age.
+ Antibody titers are measured in enzyme-linked immunosorbent assay units per mL unless otherwise indicated.
& Based on model controlling for treatment, study site, vaccine lot, age of infant, and baseline antibody level.
@ Subset of n=52 for combined group; n=34 for separate group.
** Calculated using a Wilcoxon 2-sample test.

Return to top.

Table_7

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 7. Schedule for Hib conjugate vaccine administration among previously vaccinated children

Vaccine	Age at first vaccination (mos)	Primary series	Booster
HbOC/PRP-T*	2- 6	3 doses, 2 mos apart	12-15 mos
	7-11	2 doses, 2 mos apart	12-18 mos
	12-14	1 dose	2 mos later
	15-59	1 dose	--
PRP-OMP	2- 6	2 doses, 2 mos apart	12-15 mos
	7-11	2 doses, 2 mos apart	12-18 mos
	12-14	1 dose	2 mos later
	15-59	1 dose	--
PRP-D	15-59	1 dose	--

* TETRAMUNE(TM) may be administered by the same schedule for primary immunization as HbOC/PRP-T (when the series begins at 2-6 months of age). A booster dose of DTP or DTaP should be administered at 4-6 years of age, before kindergarten or elementary school. This booster is not necessary if the fourth vaccinating dose was administered after the fourth birthday. See ACIP statement for information on use of DTP and contraindications for use of pertussis vaccine (44).

-- Not applicable.

Return to top.

Page converted: 09/19/98