Haemophilus b Conjugate Vaccines for Prevention of Haemophilus influenzae Type b Disease Among Infants and Children Two Months of Age and Older Recommendations of the ACIP

Recommendations and Reports

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These recommendations include information on use of two vaccines recently licensed for use with infants: Haemophilus b Conjugate Vaccine (Diphtheria CRM 197 Protein Conjugate) (HbOC), manufactured by Praxis Biologics, Inc., and Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate) (PRP-OMP), manufactured by Merck Sharp and Dohme, newly licensed for use with infants. This statement also updates recommendations for use of these and other Haemophilus b conjugate vaccines with older children and adults.

INTRODUCTION

Haemophilus influenzae type b (Hib) is the leading cause of invasive bacterial disease among children in the United States. Before effective vaccines were introduced, one in 200 children developed invasive Hib disease by the age of 5 years. Sixty percent of these children had meningitis; 3%-6% died. Permanent sequelae, ranging from mild hearing loss to mental retardation, affect 20%-30% of all survivors of meningitis. Ninety-five percent of the cases of invasive H. influenzae disease among children less than 5 years of age are caused by organisms with the type b polysaccharide capsule. Approximately two-thirds of all cases of Hib disease affect infants and children less than 15 months of age, a group for which a vaccine has not previously been available (1).

Three Haemophilus b conjugate vaccines are currently licensed for administration to children greater than or equal to 15 months of age in the United States. Recently, the Food and Drug Administration approved the use of HbOC (October 4, 1990) and PRP-OMP (December 13, 1990) for routine administration to infants beginning at 2 months of age. This statement a) summarizes available information about Haemophilus b conjugate vaccines, b) offers guidelines for use of HbOC and PRP-OMP for infants for prevention of Hib disease, and c) advises how to use conjugate vaccines for older children. It should be noted that HbOC and PRP-OMP have different schedules for administration, which are discussed below.

Immunology of Hib

The polyribosylribitol phosphate (PRP) capsule of Hib is a major virulence factor for the organism. Antibody to PRP is the primary contributor to serum bactericidal activity, and increasing levels of antibody are associated with decreasing risk of invasive Hib disease. The human immune response to PRP resembles the murine response to T-cell independent antigens: B cells provide the primary response without a contribution from T-helper cells. In contrast to T-cell dependent antigens, T-cell independent antigens are characterized by a) induction of a poor antibody response in less than 18-month-old infants and children, b) a variable and quantitatively smaller antibody response than that seen with T-cell dependent antigens, c) production of a higher proportion of immunoglobulin M (IgM), and d) inability to induce a booster response.

POLYSACCHARIDE VACCINES

Vaccines derived from PRP alone (polysaccharide vaccines) were developed in the 1970s. After demonstration of safety, immunogenicity, and induction of serum bactericidal activity, an efficacy of 90% (95% confidence interval (CI) = 50%-95%) was shown for one dose of vaccine given to children 18-71 months old in a large trial in Finland. However, the vaccine was ineffective for infants 3-17 months of age (2). Beginning in 1985, several PRP vaccines were licensed for use in the United States for children greater than or equal to 18 months of age, and a series of post-licensure case-control studies demonstrated variable efficacy. Four of five studies showed efficacy in the range of 41%-88%, and one study showed no efficacy (3).

CONJUGATE VACCINES

Covalent linkage (conjugation) of PRP with T-cell dependent protein antigens was evaluated in an attempt to overcome the T-cell independent characteristics of PRP. At present three different Haemophilus b conjugate vaccines are licensed for use with older children -- HbOC, PRP-OMP, and Haemophilus b conjugate vaccine (Diphtheria Toxoid Conjugate, Connaught Laboratories, Inc.) (PRP-D). As noted above, two of these vaccines, HbOC and PRP-OMP, have recently been licensed for use with 2-month-olds. The conjugate vaccines differ by protein carrier, polysaccharide size, and method of chemical conjugation, including use of a spacer (a linking moiety) between the PRP and protein carrier (4) (Table_1).

Immunogenicity

Immunogenicity studies of each of the three conjugate vaccines have been performed among 2- to 6-month-old children. Comparisons of these individual evaluations are difficult, however, because assays for antibody to PRP are not standardized and study designs differ. Recent studies among Alaskan Native infants and infants in California, however, suggest that the three conjugate vaccines induce

markedly different immunologic responses (5,6) (Table_2). The immunogenicity of HbOC among non-Alaskan Natives was not evaluated in these studies. A separate study in which HbOC was administered to infants and children in New York State and Pennsylvania showed higher immunogenicity than that reported for Alaskan natives; however, the assays were performed in different laboratories. Studies comparing administration of the three vaccines to 2- to 6-month-old infants in Nashville also demonstrated substantial differences in immunologic responses (7). The precise level of antibody required for protection, particularly in the presence of immunologic memory stimulated by conjugate vaccines, is not known; however, geometric mean titers of 1 ug/mL are considered to be indicative of long-term protection (8).

Similar comparative data for the different conjugate vaccines among 7- to 14-month-old children are not available. However, among 432 children who received two doses of HbOC, with the initial dose given at 7-14 months of age, more than 99% achieved serum antibody levels greater than 1 ug/mL (Praxis Biologics, Inc., unpublished data). In a separate study among 94 children who received two doses of PRP-OMP, with the initial dose given at 7-11 months of age, 94% achieved serum antibody levels greater than 1 ug/mL (9).

Efficacy

Results of efficacy trials among infants are available for the three conjugate vaccines. The first efficacy trial of an Hib conjugate vaccine among infants was completed in Finland using the PRP-D vaccine. In a systematic, unblinded trial involving 60,000 infants (30,000 of whom received the vaccine at 3, 4, and 6 months of age), the point estimate of efficacy was 87% (95% CI = 50%-96%) (10). In a randomized, double-blind, placebo-controlled study of 2,102 Alaskan Natives, however, the point estimate of efficacy was 35% (95% CI = (-57%)-73%) (11). Immunogenicity of the vaccine was limited in both trials. In the Finnish trial, less than 40% of infants had attained an antibody level of greater than 1 ug/mL 1 month after receiving the third of three doses (geometric mean titer (GMT) = 0.42 ug/mL). In Alaska, infants with a similar vaccination schedule had lower mean titers (GMT = 0.2 ug/mL) 3 months after receiving the third dose. A subsequent immunogenicity study documented antibody responses that were similar to those in the Alaskan and Finnish efficacy trials (Table_2).

The reason for the observed differences in efficacy estimates between Alaskan Native and Finnish infants is unclear. These populations have been observed to have differences in age distribution of Hib disease as well as differences in other risk factors. For example, in Finland 28% of the reported cases of Hib disease among less than 5-year-old children occur before the children are 1 year of age; this percentage is 64% for Alaskan Natives (12) and 54% for the United States population.

A recent study of HbOC vaccine was conducted among 60,000 infants who were enrolled in the Northern California Kaiser Permanente Health Plan and who were vaccinated at 2, 4, and 6 months of age. Approximately one-half of these infants received HbOC vaccine. Twelve of the unvaccinated children and none of the children who had received a full series of vaccine (i.e., three doses) subsequently had Hib disease, an efficacy of 100% (lower 95% CI = 68%). Three children who had received one dose of the vaccine and none of the children who had received two doses had Hib disease (13). Although children were not randomly assigned to vaccine and comparison groups, analysis of the results suggests that the observed efficacy was not due to lack of comparability between the two groups.

A randomized, placebo-controlled, double-blind trial of PRP-OMP vaccine was performed among Navajo infants vaccinated at 2 and 4 months of age. Vaccine efficacy was evaluated for 3,486 infants who completed the primary two-dose regimen. Fourteen cases of invasive Hib disease occurred in the placebo group compared with one case in the vaccine group, an efficacy of 93% (95% CI = 45%-99%) (M. Santosham, personal communication). Among infants who received only one dose of vaccine or placebo, eight cases of Hib disease occurred in the placebo group, compared with none in the vaccine group (p=0.008).

RECOMMENDATIONS FOR VACCINE USE

1. On the basis of the above considerations, the ACIP recommends that

all children receive one of the conjugate vaccines licensed for infant use (HbOC or PRP-OMP), beginning routinely at 2 months of age (Table_3). Administration of the vaccine series may be initiated as early as age 6 weeks.

2. If HbOC is to be used, previously unvaccinated infants 2-6 months of age should receive three doses given at least 2 months apart. Unvaccinated infants 7-11 months of age should receive two doses of HbOC, given at least 2 months apart, before they are 15 months old (Table_4). Unvaccinated children 12-14 months of age should receive a single dose of vaccine before they are 15 months of age. An additional dose of HbOC should be given to all children at 15 months of age, or as soon as possible thereafter, at an interval not less than 2 months after the previous dose. The other two conjugate vaccines licensed for use at 15 months of age may be used for this dose, but there are no data demonstrating that a booster response will occur. An interval as short as 1 month between doses is acceptable but not optimal.

3. If PRP-OMP is to be used, previously unvaccinated infants 2-6 months of age should receive two doses 2 months apart and a booster dose at 12 months of age. Children 7-11 months of age not previously vaccinated should receive two doses 2 months apart and a booster dose at 15 months of age (or as soon as possible thereafter), not less than 2 months after the previous dose. Children 12-14 months of age not previously vaccinated should receive a single dose and a booster dose at 15 months of age (or as soon as possible thereafter), not less than 2 months after the previous dose. The other two conjugate vaccines licensed for use at 15 months of age may be used for this dose, but there are no data demonstrating that a booster response will occur. An interval as short as 1 month between doses is acceptable but not optimal.

4. Unvaccinated children 15-59 months of age may be given any one of the three conjugate vaccines licensed for this age group.

5. Ideally, the same conjugate vaccine should be used throughout the entire vaccination series (according to the schedule outlined in Table_4). No data exist regarding the interchangeability of different conjugate vaccines with respect to safety, immunogenicity, or efficacy. However, situations will arise in which the vaccine provider does not know which type of Hib conjugate vaccine the child to be vaccinated had previously received. Under these circumstances, it is prudent for vaccine providers to ensure that at a minimum an infant 2-6 months of age receives a primary series of three doses of conjugate vaccine. These recommendations may change as data become available regarding the response to different conjugate vaccines in a primary series.

6. Children less than 24 months of age who have had invasive Hib disease should still receive vaccine, since many children of that age fail to develop adequate immunity following natural disease. The vaccine series can be initiated (or continued) at the time of hospital discharge.

7. Chemoprophylaxis of household or day-care classroom contacts of children with Hib disease should be directed at both vaccinated and unvaccinated contacts because immune individuals may asymptomatically carry and transmit the organism. Because of the time required to generate an immunologic response, vaccination following exposure should not be used to prevent secondary cases. However, the ACIP strongly supports extensive use of the Hib vaccine for infants attending day-care facilities; that action should substantially decrease the occurrence of primary cases of Hib disease in day-care facilities. If every child in a household or day-care classroom has been fully

vaccinated, chemoprophylaxis is unnecessary.

8. Conjugate vaccine may be given simultaneously with diphtheria and tetanus toxoids and pertussis vaccine adsorbed (DTP); combined measles, mumps, rubella vaccine (MMR); oral poliovirus vaccine (OPV); or inactivated poliovirus vaccine (IPV). Any of the vaccines may be injected in the thigh, and two injections may be given in the same deltoid. All licensed conjugate vaccines should be administered by the intramuscular route. There are no known contraindications to simultaneous administration of any Hib conjugate vaccine with either pneumococcal or meningococcal vaccine.

9. No efficacy data are available on which to base a recommendation concerning use of the vaccine for older children and adults with the chronic conditions associated with an increased risk of Hib disease. Studies suggest, however, good immunogenicity in patients with sickle cell disease (15), leukemia (16), patients who have had splenectomies (17) or who have HIV infection (18,19), and administering vaccine to these patients is not contraindicated.

Side Effects and Adverse Reactions

Reported reactions to the three conjugate vaccines have been mild among both infants and children. In one study, approximately 300 1- to 6-month-old infants who received HbOC vaccine (without simultaneous administration of DTP) were evaluated; within 24 hours of injection, no serious side effects were noted. Following the third dose, 2.2% were noted to have a temperature greater than 38.3 C, 2.2% had localized redness, 1.1% had swelling, and less than 1% had warmth (14). Adverse events following the first and second doses were less frequent.

Serious adverse reactions to PRP-OMP also have been rare. Among 4,459 healthy Navajo infants 6-12 weeks of age, no differences were reported in the type and frequency of serious adverse events among those who received PRP-OMP and those who received placebo. Of the infants in the group who were 2-14 months of age, 3%-4.3% had a temperature greater than 38.3 C within 48 hours of receiving a second dose of vaccine, 0.7%-1.2% had erythema of greater than 2.5 cm in diameter, and 0.9%-3.7% had swelling and induration of greater than 2.5 cm in diameter. Adverse events following the first dose were less frequent.

Precautions and Contraindications

Conjugate vaccines that contain either diphtheria toxoid or protein should not be considered as an immunizing agent against diphtheria; no changes in the schedule for administering DTP are recommended. A conjugate vaccine that contains meningococcal protein should not be considered as an immunizing agent against meningococcal disease.

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Pending formal approval.

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. Characteristics of Haemophilus b conjugate vaccines (4)

Vaccine (producer)	Polysaccharide	Protein carrier	Linkage
HbOC, HibTITER (TM) (Lederle-Praxis)	small	CRM subscript 197 mutant Corynebacterium diphtheriae protein	no spacer
PRP-OMP, PedvaxHIB (TM) (Merck Sharp and Dohme)	medium	Neisseria meningitidis outer membrane protein complex	spacer
PRP-D, ProHIBIT (TM) (Connaught Laboratories)	medium	diphtheria toxoid	spacer

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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 b conjugate vaccines in infants (5-7)

Age (months)/ vaccine dose *	PRP-D		PRP-OMP		HbOC	
	Alaska	California	Alaska	California	Alaska	New York +
2/Pre	0.06 (4%) & (12%)	0.04 (3%)	0.16 (14%)	0.09 (6%)	0.15 (6%)	0.20
4/Post1	0.04 (2%) (15%)	0.03 (0%)	1.37 (57%)	2.15 (73%)	0.07 (0%)	0.30
6/Post2	0.06 (11%) (84%)	0.14 (25%)	2.71 (79%)	3.76 (92%)	0.59 (43%)	5.11
7/Post3	0.55 (43%) (98%)	0.46 (37%)	--	--	13.72 (94%)	16.84
9-12 Post-2 or -3	0.20 (20%) (94%)	0.13 (22%)	0.53 (29%)	0.98 (52%)	3.70 (81%)	7.41
15-18/ Post-2 or -3	0.04 (0%)	--	0.21 (16%)	--	1.94 (71%)	

* PRP-D, HbOC given as three doses at 2, 4, and 6 months; PRP-OMP given at 2 and 4 months. Pre = blood drawn before any vaccine is administered; Post 1 = blood drawn after one dose of vaccine; Post 2 = blood drawn after two doses of vaccine; Post 3 = blood drawn after three doses of vaccine.

\+ Assays for this study were performed in different laboratories from others in this table. Due to interlaboratory variability, definitive comparisons between this group of vaccines and others in this table cannot be made based on these data.

& Anti-PRP antibody geometric mean titer expressed in migrograms per microliter (%>1 ug/mL).

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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. ACIP-recommended Haemophilus influenzae type b (Hib) routine vaccination schedule

Vaccine	2 months	4 months	6 months	12 months	15 months
HbOC	dose 1	dose 2	dose 3		booster
PRP-OMP	dose 1	dose 2		booster	

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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. Detailed vaccination schedule for Haemophilus b conjugate vaccines

Vaccine	Age at 1st dose (months)	Primary series	Booster
HbOC (Lederle-Praxis)	2-6	3 doses, 2 mo. apart	15 mo. *
	7-11	2 doses, 2 mo. apart	15 mo. *
	12-14	1 dose	15 mo. *
	15-59	1 dose	--
PRP-OMP (Merck Sharp and Dohme)	2-6	2 doses, 2 mo. apart	12 mo. *
	7-11	2 doses, 2 mo. apart	15 mo. *
	12-14	1 dose	15 mo. *
	15-59	1 dose	--
PRP-D (Connaught)	15-59	1 dose	--

* At least 2 months after previous dose.