



AMERICAN ACADEMY OF PEDIATRICS

Committee on Infectious Diseases

***Haemophilus influenzae* Type b Conjugate Vaccines: Recommendations for Immunization of Infants and Children 2 Months of Age and Older: Update**

This statement is provided in response to the December 1990 US Food and Drug Administration (FDA) approval of labeling for a second *Haemophilus influenzae* type b conjugate vaccine, PRP-OMP (Table 1), for administration to infants as young as 2 months of age. The following recommendations supercede previous American Academy of Pediatrics (AAP) guidelines for the use of *H influenzae* type b conjugate vaccines.

In October 1990, the FDA approved labeling for one *H influenzae* type b conjugate vaccine, HbOC (Table 1), stating that it was safe and effective for administration to infants beginning at 2 months of age. The Academy recommended that all infants be immunized at 2 months of age or as soon as possible thereafter. This and related recommendations were communicated to AAP members in a PedComm in October and published in *AAP News* (Vol 6, November 1990).

Prior to October 1990, the Academy had recommended that all children receive a dose of an *H influenzae* type b conjugate vaccine at 15 months of age (*AAP News*, Vol 6, July 1990). The Academy continues to believe that the safety and efficacy of all three licensed conjugate vaccines—PRP-D, HbOC, and PRP-OMP (Table 1)—are likely to be equivalent when administered to children 15 months of age or older.

The FDA's approval of the new labeling for both HbOC and PRP-OMP for use in infants was based

in part on a review of two recent trials performed in infants in the United States that demonstrated the efficacy of these vaccines. The results of these trials will be published in the near future.

Because of differences in the immunogenicity of HbOC and PRP-OMP and in the regimens used in these trials, the recommendations for the use of these two vaccines differ.

RECOMMENDATIONS

See Table 2 for summary.

1. All infants should be immunized with an *H influenzae* type b conjugate vaccine at about 2 months of age or as soon as possible thereafter. Currently, the FDA has only approved HbOC and PRP-OMP for administration to children younger than 15 months of age. *H influenzae* type b immunization can be given during visits currently scheduled for other routine immunizations, such as diphtheria-tetanus-pertussis, oral poliovirus, and measles-mumps-rubella (MMR), and can be initiated as early as 6 weeks of age. HbOC or PRP-OMP vaccine should be given intramuscularly at a separate site from other immunizations and utilizing a separate syringe.

2. For routine immunization of infants younger than 7 months of age, **either** a three-dose series of HbOC **or** a two-dose series of PRP-OMP should be administered with the doses given at 2-month intervals (Table 2). The Academy considers the safety and efficacy of regimens using either HbOC or PRP-OMP are likely to be equivalent. No data are available at present regarding the interchangeability of *H influenzae* type b conjugate vaccines. Therefore, the Academy recommends that for doses given to children younger than 15 months of age,

The recommendations in this publication do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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TABLE 1. *Haemophilus influenzae* Type b Conjugate Vaccines

Manufacturer	Abbreviation	Trade Name	Carrier Protein	Licensed by the FDA (as of April 91)
Connaught Laboratories	PRP-D	ProHIBit	Diphtheria toxoid	For children \geq 15 months of age
Praxis Biologics, Inc. (distributed by Lederle Laboratories)	HbOC	HibTITER	CRM197 (a non-toxic mutant diphtheria toxin)	For infants & children \geq 2 months of age
Merck Sharp & Dohme	PRP-OMP	PedvaxHIB	OMP (an outer membrane protein complex of <i>Neisseria meningitidis</i>)	For infants & children \geq 2 months of age
Pasteur Merieux	PRP-T		Tetanus toxoid	Not licensed

the vaccine product used for the first dose should also be used for subsequent doses.

- a. For regimens initiated with HbOC, a fourth dose of an *H influenzae* type b conjugate vaccine is recommended at **15 months of age** or as soon as possible thereafter. For this dose, the Academy considers any licensed conjugate vaccine—PRP-D, HbOC, or PRP-OMP—to be acceptable. Because several injections are required to complete the routine childhood immunizations recommended at this age, some may choose to give these injections in more than one visit. In this circumstance, for children who have not been immunized previously against measles, priority should be given to administering the MMR vaccine.
 - b. For regimens initiated with PRP-OMP, a third dose of PRP-OMP is recommended for administration at **12 months of age** or as soon as possible thereafter. If this dose inadvertently is delayed until the recipient is 15 months of age or older, the Academy considers any licensed conjugate vaccine—PRP-OMP, PRP-D, or HbOC—to be acceptable.
 - c. For regimens initiated in infants younger than 7 months of age with an unknown conjugate vaccine, completion of a four-dose regimen should provide immunity. However, data to support this recommendation explicitly are currently unavailable.
 - d. *H influenzae* type b conjugate vaccine and MMR vaccine can be administered simultaneously. However, they should be administered at separate sites and in separate syringes.
3. The efficacy of HbOC and PRP-OMP has not been evaluated when immunization is initiated in infants beyond the first few months of life. However, the Academy believes that efficacy can be

predicted from the available efficacy and immunogenicity data and recommends that immunization be performed as follows (Table 2):

- a. When immunization is initiated in infants 7 to 11 months of age, the recommended regimens for **both HbOC and PRP-OMP** are identical and require three doses. The first two doses are given at 2-month intervals. The third dose may be given at 15 to 18 months of age. For this dose, the Academy believes that any licensed conjugate vaccine—PRP-D, HbOC, or PRP-OMP—is acceptable.
- b. When immunization is initiated in children 12 to 14 months of age, the recommended regimens for **both HbOC and PRP-OMP** are identical and require two doses given at a 2- to 3-month interval. The Academy recommends that if both doses are given before the child is 15 months of age, the same vaccine product should be used for both doses. The Academy believes that in children who receive the second dose at 15 months of age or older, any licensed conjugate vaccine—PRP-D, HbOC, or PRP-OMP—is acceptable. However, in this instance, some experts believe that a two-dose regimen of the homologous conjugate vaccine might enhance immunogenicity.
- c. When immunization is initiated in children 15 months of age or older who have not yet reached their fifth birthday (up to 60 months of age), the recommended regimen is a single dose of any licensed conjugate vaccine—PRP-D, HbOC, or PRP-OMP.
4. For infants born prematurely, immunization should be initiated at the chronologic age of 2 months, as recommended for other infants (see recommendation 2).

TABLE 2. Summary of Recommended Regimens For Use of *Haemophilus influenzae* Type b Vaccines

Age Immunization Initiated, mo	Vaccine Product Used at Initiation	Total Number of Doses to be Administered	Currently Recommended Vaccine Regimens (see text)
2-6	HbOC	4	a. Initial 3 doses at 2-month intervals b. Fourth dose at 15 months of age† c. HbOC for doses 1-3 d. HbOC, PRP-OMP, or PRP-D for dose 4†
	PRP-OMP	3	a. Initial 2 doses at 2-month intervals b. Third dose at 12 months of age c. PRP-OMP for all 3 doses‡
7-11	HbOC	3	a. Initial 2 doses at 2-month intervals b. Third dose at 15-18 months of age† c. HbOC, for doses 1-2 d. HbOC, PRP-OMP, or PRP-D for dose 3†
	PRP-OMP	3	a. Initial 2 doses at 2-month intervals b. Third dose at 15-18 months of age† c. PRP-OMP for doses 1-2 d. PRP-OMP, PRP-D, or HbOC for dose 3†
12-14	HbOC	2	a. 2-3-month interval between doses b. If the second dose is given at or after 15 months, HbOC, PRP-OMP, or PRP-D may be given†
	PRP-OMP	2	a. 2-3-month interval between doses b. If the second dose is given at or after 15 months, PRP-OMP, PRP-D, or HbOC may be given†
15-59	HbOC, PRP-OMP, PRP-D	1	HbOC, PRP-OMP, or PRP-D†
60 and older§	HbOC, PRP-OMP, PRP-D	1	HbOC, PRP-OMP, or PRP-D†

† The Academy considers that safety and efficacy are likely to be equivalent for PRP-OMP, PRP-D, and HbOC for use in children 15 months of age and older.

‡ If the third dose is delayed inadvertently until the child is 15 months of age or older, the Academy considers that the safety and efficacy are likely to be equivalent for PRP-OMP, PRP-D, and HbOC for this third dose.

§ Only for children with chronic illness known to be associated with an increased risk for *H. influenzae* type b disease (see text).

5. Special circumstances may suggest a need for more rapid "catch-up" immunization and administration of HbOC or PRP-OMP at intervals more frequent than 2 months. In such circumstances, the Academy believes that a 1-month interval between doses is the minimum. However, few data exist that have examined the immune response when vaccines are given at intervals of less than 2 months.

6. Completion of a recommended regimen is important to assure immunity to *H influenzae* type b disease. In the efficacy trial performed with HbOC in the United States, cases of invasive *H influenzae* type b disease were observed after a single dose in infants in whom immunization was initiated before 7 months of age. In the efficacy trial performed with PRP-OMP in the United States, no cases of

invasive *H influenzae* type b disease occurred after the administration of the first dose, but one case did occur in a 16-month-old child who did not receive the third dose of vaccine. This case underscores the importance of this third dose to assure continuing immunity.

7. Unimmunized children 5 years of age or older with a chronic illness known to be associated with increased risk of *H influenzae* type b disease should be given a single dose of any licensed conjugate vaccine. Examples are children with sickle cell anemia and those with anatomic or functional asplenia (including those who have undergone splenectomy). Until further data are available, patients with Hodgkin disease should be immunized 10 to 14 days (approximately 2 weeks) or more prior to the initiation of chemotherapy, or if that is not possible, 3 months or more after the cessation of chemotherapy. No known contraindications exist to simultaneous administration of PRP-OMP, PRP-D, or HbOC with pneumococcal vaccine and/or meningococcal vaccine when they are given in separate syringes at different sites.

8. Unimmunized children who experience invasive *H influenzae* type b disease when younger than 24 months of age should be immunized according to the age-appropriate schedule in Table 2 upon convalescence. Children whose disease occurs at 24 months of age or later do not need immunization because the disease most likely induced an immune response.

9. For the present, the Academy continues to recommend rifampin prophylaxis for all appropriate contacts exposed to an individual with invasive *H influenzae* type b disease. (See recommendations in the current *Report of the Committee on Infectious Diseases* [Red Book]).

10. To date, no increased incidence of disease has been demonstrated during the first 2 weeks after immunization with HbOC or PRP-OMP. However, all cases of invasive *H influenzae* type b disease occurring at any time after immunization should be reported promptly to the manufacturer, the FDA, or the Centers for Disease Control.

FUTURE DEVELOPMENTS

PRP-T (Table 1), and perhaps other conjugate vaccines, may have labeling approved for use in children younger than 15 months of age in the future. Moreover, studies are currently in progress

to assess the safety and immunogenicity of *H influenzae* type b conjugate vaccines when combined with diphtheria-tetanus-pertussis or MMR vaccines in the same syringe.

The Academy plans to issue a more complete statement regarding these trials and other issues related to the use of *H influenzae* type b conjugate vaccines in the future.

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