

Supplementary statement on newly licensed Haemophilus influenzae type B (Hib) conjugate vaccines in combination with other vaccines recommended for infants

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Currently, there are three Hib conjugate vaccines licensed in Canada for use in infants 2 months of age and older. The Bureau of Biologics recently approved two new vaccine products that allow single-needle administration of (a) polyribose ribitol phosphate-tetanus toxoid (PRP-T) with diphtheria toxoid-pertussis vaccine-tetanus toxoid-inactivated poliovirus vaccine (DPT-IPV), and (b) oligosaccharide conjugate Hib (HbOC) with DPT. Information about each product is briefly summarized below along with recommendations for use and an indication of areas where knowledge is still limited.

PRP-T Hib conjugate vaccine reconstituted with DPT-IPV (PENTA)

PRP-T (Act-HIB, Pasteur Mérieux, distributed in Canada by Connaught Laboratories Limited, Willowdale, Ont.) is supplied as a lyophilized powder that can be reconstituted either with the supplied diluent or the DPT Adsorbed vaccine manufactured and distributed by Connaught. In January 1994 the Bureau of Biologics gave approval for PRP-T to be reconstituted with Connaught's DPT-Polio Adsorbed vaccine. Thus, for provinces using inactivated polio vaccine, it is now possible to use a single injection per visit to immunize infants against diphtheria, pertussis, tetanus, poliomyelitis and Hib.

Both preparations used in the combination product, PRP-T and DPT-IPV, are available separately and are fully described in the *Canadian Immunization Guide*.^[1] Like the previously approved combination of PRP-T/DPT (Act-HIB reconstituted with Connaught's DPT Adsorbed), PRP-T/DPT-IPV (Act-HIB reconstituted with Connaught's DPT-Polio Adsorbed) is supplied in a carton containing five single doses of each product.

A comparison of the immunogenicity and reactogenicity of combined PRP-T/DPT-IPV versus separate-site injections of PRP-T and DPT-IPV for the 2, 4 and 6-month primary immunization series was conducted in 439 Canadian infants.^[2] After two doses of vaccine, infants receiving the combined vaccine had a lower anti-PRP response than those receiving separate-site injections of PRP-T and DPT-IPV, as evaluated by geometric mean titre (GMT) (0.24 v. 0.42 µg/mL; $p < 0.05$) and the proportion of infants with any measurable anti-PRP antibody (66.8% v. 79.1%; $p < 0.005$). However, after the third dose 98% of recipients had protective levels of anti-PRP antibody, and

there was no significant difference in GMT between the two groups.

The antibody responses to the other four vaccine components, as measured one month after the third vaccine dose, were comparable between the two groups of infants, with two exceptions. First, a smaller proportion of infants receiving the combination vaccine achieved pertussis agglutinin titres of 1:256 or greater than did those receiving separate injections (39.8% v. 50.2%; $p < 0.005$). However, there were no significant differences between the groups in either the GMT or the percentage with measurable agglutinin titres. Second, fewer infants given the combination vaccine achieved tetanus antibody responses of 2.0 IU/mL or greater than did infants receiving separate injections (3.3% v. 12.3%; $p < 0.001$). Although the GMT was significantly lower in the combination vaccine group (0.50 v. 0.76 IU/mL), protective levels of 0.01 IU/mL or greater were achieved by all vaccinees except one in the combined vaccine group.

With respect to local and systemic adverse reactions, there were no noteworthy differences observed between the two groups throughout the primary series.

Recommended usage

In areas where inactivated polio vaccine is used, PRP-T reconstituted with DPT-IPV can be used for the primary series according to currently recommended schedules. It can also be used for the 18-month booster dose.

HbOC Hib conjugate vaccine combined with Tri-Immunol DPT (TETRAMUNE)

Until recently, HbOC (HibTITER, Lederle Laboratories Division of Cyanamid Canada, Markham, Ont.) had to be given as a single injection in a separate limb from DPT. In April 1994 a new product (TETRAMUNE, Lederle) that combines in a premixed liquid formulation HbOC with the previously approved Tri-Immunol diphtheria and tetanus toxoids and whole-cell pertussis vaccine adsorbed was licensed. Both preparations, HbOC and DPT, used in the combined vaccine are also licensed separately and are fully described in the *Canadian Immunization Guide*.^[1]

The combination has a similar safety profile to that of the DTP vaccine given alone.^[3] Antibody responses to the Hib component are enhanced by the combination, perhaps as a result of an adjuvant effect of the whole-cell pertussis component.^[4] Antibody responses to other constituents are also significantly higher with the combination vaccine than with the separately administered products.

Recommended usage

Combined HbOC-DTP can be used for the primary series according to currently recommended schedules. It can also be used for the 18-month booster dose.

Limitations of knowledge

PRP-T Hib conjugate vaccine reconstituted with DPT-IPV (PENTA)

The protective efficacy of PRP-T vaccine has not been directly measured but is assumed adequate

on the basis of immune responses to vaccination and clinical experience to date.

Regarding the DPT-IPV/PRP-T combination, it is not known whether the lower anti-PRP responses observed after two doses, or the attenuated pertussis agglutinin or tetanus antitoxin responses seen after three doses, have any significant implications for protection from these diseases. It is also uncertain whether 18 months of age is the optimal time to administer booster doses, because this practice is based upon currently recommended immunization schedules rather than on studies of anti-PRP decay. Finally, there is insufficient information regarding the lot-to-lot variability in immunogenicity or reactogenicity of PRP-T when given in combination with either DPT or DPT-IPV.

HbOC Hib conjugate vaccine combined with Tri-Immunol DPT (TETRAMUNE)

The efficacy, safety and immunogenicity of this Hib conjugate vaccine have been extensively documented in US populations. TETRAMUNE has been widely used in the United States since its licensure in 1993. Systematic studies on Tri-Immunol, HibTITER and TETRAMUNE use in Canadian children have been limited.

Interchangeability of Hib conjugate combination products

It is not yet known whether combination products containing PRP-T or HbOC are interchangeable with each other in infants who have already begun but not completed the primary immunization series. Preliminary data suggest that PRP-T, HbOC and PRP-outer-membrane protein complex (PRP-OMP), administered as separate injections, can be interchanged with each other for the 2, 4 and 6-month injections with no significant difference in antibody responses after completion of the primary immunization series. These studies involved limited numbers of infants and examined only a few of the possible schedule combinations. Thus, until more supporting data are available completion of the primary series with a single product is preferable. Nevertheless, it seems reasonable to use when necessary one of the licensed combination products containing either PRP-T or HbOC to complete the primary series in infants who have already received one or two doses of a different Hib conjugate vaccine. Any of the licensed Hib conjugate vaccines can be used for the booster dose given at 15 to 18 months of age irrespective of which Hib conjugate was used in the primary series.

Postmarketing surveillance of Hib conjugate vaccines

Since long-term protection remains to be demonstrated for all Hib vaccines in current use, postmarketing surveillance is considered to be essential for all products used to immunize infants against Hib infection. Continuing surveillance for any vaccination failures will remain a high priority for several more years.

References



1. National Advisory Committee on Immunization: *Canadian Immunization Guide*, 4th ed (cat no H49-8/1993E), Health Canada in collaboration with the Canadian Medical Association, Ottawa, 1993: 41-44, 96-99, 151-152
2. Gold R, Scheifele D, Barreto L et al: Safety and immunogenicity of *Haemophilus influenzae* vaccine (tetanus toxoid conjugate) administered concurrently or combined with diphtheria and tetanus toxoids, pertussis vaccine and inactivated poliomyelitis vaccine to healthy infants at two, four and six months of age. *Pediatr Infect Dis J* 1994; 13: 348-355

3. Black SB, Shinefield HR, Ray P et al: Safety of combined oligosaccharide conjugate *Haemophilus influenzae* type b (HbOC) and whole-cell diphtheria-tetanus toxoids-pertussis vaccine in infancy. *Pediatr Infect Dis J* 1993; 12: 981-985
4. Paradiso PR, Hagerman DA, Madore DA et al: Safety and immunogenicity of combined diphtheria, tetanus, pertussis and *Haemophilus influenzae* type b vaccine in young infants. *Pediatrics* 1993; 92: 827-832

Source: National Advisory Committee on Immunization. **Members:** Dr. D. Scheifele (chairman), Dr. J. Spika (executive secretary), N. Armstrong (advisory committee secretariat officer), Drs. W.L. Albritton, F. Aoki, P. Déry, P. DeWals, R. Gold, S. Halperin, B. Law, M. Naus, L. Palkonyay, Y. Robert. **Liaison members:** Dr. J. Waters (Alberta Health), Dr. A. Carter (CMA), Dr. S. Hadler (US Centers for Disease Control and Prevention), Dr. J.H.V. Marchessault (Canadian Pediatric Society), Major R. Nowak (National Defence), Dr. H. Robinson (Medical Services Branch).

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