Evaluation of *Haemophilus influenzae* type b conjugate vaccine (meningococcal protein conjugate) in Canadian infants

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OBJECTIVE: To assess adverse effects and immune responses with a three-dose series of *Haemophilus influenzae* type b meningococcal protein conjugate (PedvaxHIB or Hib.OMP) vaccine, including any immunological response alterations from concurrent administration with routine vaccines for infants.
DESIGN: Randomized, controlled trial with treatment group crossover for dose 3.
SETTING: Two public health units near Vancouver.
PARTICIPANTS: One hundred and ten healthy infants eight to 14 weeks old were enrolled; 105 completed the study (95%).
INTERVENTIONS: All participants received two doses of diphtheria-pertussis-tetanus (DPT) vaccine (at two and four months of age) and one dose of measles-mumps-rubella (MMR) vaccine at 12 months. In each instance, Hib.OMP was given either concurrently in another limb or after a delay of two weeks (after DPT) or four weeks (after MMR).
MAIN OUTCOME MEASURES: Adverse effects, particularly fever and local erythema, were monitored by parents for 72 h after each dose of Hib.OMP vaccine. Five blood samples were taken at prescribed intervals to assess responses to each dose of Hib.OMP and to selected other vaccine antigens.
MAIN RESULTS: Follow-up was obtained after all 322 doses of Hib.OMP. Local adverse effects were infrequent and mild: 13% had redness, 17% tenderness. Systemic effects in those given Hib.OMP alone included fever in 8%, irritability in 29%. Anti-polyribose-ribitol phosphate (PRP) responses to Hib.OMP were not impaired by coadministration with DPT or MMR vaccines, nor were tetanus or diphtheria antitoxin levels or rubella or measles response rates affected. After two doses of Hib.OMP, 92% were seropositive and 64% had greater than 1.0 µg/mL of anti-PRP. After three doses, 100% were seropositive and 82% exceeded 1.0 µg/mL.
CONCLUSION: Hib.OMP vaccine was well tolerated, immunogenic and compatible with vaccines routinely given to infants in Canada.

Key Words: Haemophilus influenzae *type b, Meningococcal protein conjugate vaccine, Prevention, Vaccine*

Évaluation du vaccin conjugué contre *Haemophilus influenzae* de type b (protéine méningococcique conjuguée) chez des nourrissons canadiens

OBJECTIF : Évaluer les effets secondaires et les réponses immunitaires suite à une série de trois doses de vaccin conjugué contre *Haemophilus influenzae* de type b, complexe de protéine méningococcique, (PedvaxHIB ou Hib.OMP), y compris les modifications de la réponse immunitaire découlant de l'administration concomitante d'autres vaccins d'usage courant chez le nourrisson.

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MODÈLE : Essai randomisé contrôlé, avec croisement des groupes thérapeutiques pour la dose 3.
CONTEXTE : Deux établissements de santé publique de la région de Vancouver.
PARTICIPANTS : Cent-dix nourrissons en santé, âgés de huit à 14 semaines ont été inscrits; 105 ont terminé l'étude (95 %).
INTERVENTIONS : Tous les participants ont reçu deux doses de vaccin DCT (diphthérie, coqueluche, tétanos) (à deux et quatre mois de vie) et une dose de vaccin contre la rougeole, les oreillons et la rubéole (ROR) à 12 mois. Dans chaque cas, Hib.OMP a été administré soit concomitamment dans un autre membre ou après un délai de deux semaines (après le DCT) ou quatre semaines (après le ROR).
PRINCIPAUX PARAMÈTRES MESURÉS : Les effets indésirables, particulièrement la fièvre et l'érythème localisé, ont été surveillés par les parents durant une période de 72 h après chaque dose de vaccin Hib.OMP. Cinq échantillons de sang ont été prélevés à des intervalles prescrits afin d'évaluer les réactions à chaque dose de Hib.OMP et aux autres antigènes vaccinaux.
PRINCIPAUX RÉSULTATS : Un suivi a été obtenu après que les 322 doses de Hib.OMP aient été administrées. Les effets indésirables locaux ont été rares et légers : 13 % ont présenté une rougeur, 17 % une sensibilité. Les effets systémiques chez les nourrissons qui ont reçu Hib.OMP seul ont été, entre autres, la fièvre chez 8 % des patients et l'irritabilité chez 29 %. La réponse anti-polyribose-ribitol phosphate (PRP) au Hib.OMP n'a pas été altérée par une administration concomitante de DCT ou de ROR et les taux d'antitoxines anti-tétaniques ou antidiphtériques ou les taux de réponse à la rubéole ou à la rougeole n'ont pas été affectés. Après deux doses de Hib.OMP, 92 % se sont révélés séropositifs et 64 % présentaient un taux supérieur à 1,0 µg/mL d'anti-PRP. Après trois doses, 100 % étaient séropositifs et 82 % excédaient 1,0 µg/mL.
CONCLUSION : Le vaccin Hib.OMP a été bien toléré et s'est révélé immunogène et compatible avec les vaccins administrés d'office aux nourrissons au Canada.

INVASIVE INFECTIONS RESULTING FROM *HAEMOPHILUS INFLUENZAE* type b (Hib) have been a serious threat to children younger than five years of age. Before the introduction of vaccination programs, over 2000 cases were estimated to occur annually in Canada, 1000 of which included purulent meningitis (1). An important virulence factor of Hib is its polysaccharide capsule, composed of repeating units of ribose, ribitol and phosphate (PRP). Serum antibody to PRP activates complement-mediated bactericidal and opsonic activity in vitro and correlates with protection against invasive Hib disease in experimental animals (2) and humans (3,4). A vaccine composed of purified PRP had an estimated protective efficacy of over 90% in Finnish children 17 months of age and older (5). Based on these and other data, Hib vaccine was licensed in Canada in 1986 for immunization of children 24 to 60 months of age (6).

Subsequently a second generation of vaccines was introduced with the ability to stimulate anti-PRP responses from the first months of life, protecting infants before the period of peak risk at six to 18 months of age (1,7). These vaccines contain PRP that has been conjugated to selected carrier proteins, eliciting T cell help for antibody responses to PRP (8). With most such vaccines, anti-PRP responses can be elicited from two months of age, stimulated to high levels with a series of doses and later strongly reinforced with a booster dose (9), resulting in high rates of protection (10,12).

A unique Hib conjugate vaccine consists of PRP covalently conjugated to an outer membrane protein complex from serogroup B *Neisseria meningitidis* (13). Conjugate molecules have a molecular weight greater than 1000 kDa and are visible as particles under the electron microscope. This product (PedvaxHIB, referred to as Hib.OMP) proved to be highly immunogenic in young infants (14,15). In studies of infants aged two to six months (15), 99% (236 of 239) responded to the first dose with levels of anti-PRP of 0.15 µg/mL or greater, while 78% had levels of 1.0 µg/mL or greater. After a second dose two months later, 88% had anti-PRP levels of 1.0 µg/mL or greater (geometric mean titre 4.63 µg/mL). Antibody responses were principally within the immunoglobulin (Ig) G_1 subclass and were associated with demonstrable bactericidal activity in most subjects (16). Anti-PRP levels decline over subsequent months (15,16) but are effectively boosted by a reinforcing dose given at 12 months of age.

Compatibility of Hib.OMP with measles-mumps-rubella (MMR) vaccine at about 15 months of age or with diphtheria-pertussis-tetanus (DPT) vaccine and oral poliovirus vaccine (OPV) at about 18 months of age was examined in American infants receiving a single dose of Hib vaccine (17). Neither type of concurrent use affected responses to any of the administered antigens or increased systemic adverse effects.

The study reported here was undertaken to evaluate Hib.OMP in Canadian infants, in support of its subsequent licensure (as PedvaxHIB, Merck Frosst Canada Inc). The specific objectives were, first, to measure the safety and immunogenicity of two doses of Hib.OMP vaccine given to infants at two and four months of age, with and without coadministration of DPT and OPV vaccines and, second, to assess in similar terms a booster dose at 12 months of age, with and without coadministration of MMR vaccine. We considered such data to be an important supplement to experience in the United States where PedvaxHIB had recently been licensed. In particular, Canadian infants would receive a DPT vaccine that is substantially different from the ones assessed as compatible with Hib.OMP in the United

States, and they would routinely receive the 12-month Hib.OMP booster with MMR vaccine because of the different timing of MMR vaccination in the Canadian schedule.

PATIENTS AND METHODS

Children were eligible for the study if they were eight to 14 weeks old, healthy and suitable recipients of DPT vaccine. Exclusion criteria included immunological impairment, any neurological condition, prior Hib disease or receipt of another Hib vaccine, and planned relocation during the study. Vaccination was delayed in the event of acute febrile illness. Children were recruited from the clientele of two public health units in suburban Vancouver, responsible for delivering 40 to 50% of childhood vaccines within their jurisdictions. Written informed consent was obtained from a parent or guardian of each child enrolled in the study. The project was approved by the ethics committee of the University of British Columbia. It was carried out between January 1991 and May 1992.

Participants were randomly assigned to treatment group A or B. Assignments were linked to serially dispensed study participant numbers and disclosed by opening sealed, numbered envelopes. The randomization sequence was developed from a list of randomly generated numbers, in balanced blocks of 10. Assignments stipulated treatments at each of two, four and 12 months of age, as outlined in Table 1. As a purpose of the study was to compare responses to vaccines given concurrently or separated by an interval, masking of treatments was not feasible. When routine and Hib.OMP vaccines were to be given at separate visits, routine vaccines (DPT or MMR) were given first. Hib.OMP vaccine was given two weeks following DPT doses (to conform with the practice of many vaccinators who prefer to avoid two injections per visit) and four weeks after MMR (to allow recovery of immune responsiveness following live virus vaccination).

One lot of Hib.OMP vaccine (PedvaxHIB, lot 1726S) was used for both primary doses while another (1240C) was used for booster doses. Both were supplied by Merck Frosst Canada Inc. Each 0.5 mL dose of lyophilized vaccine contained 15 µg Hib polysaccharide, approximately 250 µg group B meningococcal outer membrane protein complex and 2 mg lactose. The supplied diluent contained approximately 225 µg aluminum as aluminum hydroxide and 25 µg of thimerosal.

DPT vaccine, adsorbed (Connaught Laboratories Ltd) was obtained as one lot (3884) from supplies of the British Columbia Ministry of Health. This product contained 25 Lf diphtheria toxoid, 5 Lf tetanus toxoid, four to 12 protective units of pertussis vaccine, 1.5 mg of aluminum phosphate and thimerosal (0.01%) per 0.5 mL dose. M-M-RII vaccine was supplied from one lot (PO369) by Merck Frosst Canada Inc. Oral poliovirus vaccine, trivalent (Connaught Laboratories Ltd) was provided by the British Columbia Ministry of Health; lot number was not controlled. Vaccines were stored at recommended temperatures before use.

TABLE 1
Scheduled immunizations in the two treatment groups

Age (months)	Group A	Group B
2	Hib.OMP, DPT and OPV at one visit	DPT and OPV at initial visit; Hib.OMP two weeks later
4	Hib.OMP, DPT and OPV at one visit	DPT and OPV at initial visit; Hib.OMP two weeks later
6	DPT only	DPT only
12	MMR at first visit; Hib.OMP four weeks later	MMR and Hib.OMP at one visit

DPT Diphtheria-pertussis-tetanus; MMR Measles-mumps-rubella; OPV Oral polio vaccine

The schedule of immunizations is summarized in Table 1. All DPT and Hib.OMP immunizations were given intramuscularly in the anterolateral thigh using 25 gauge, $\frac{7}{8}$ inch needles. MMR vaccinations were given subcutaneously in the upper arm using 25 gauge, $\frac{5}{8}$ inch needles. Acetaminophen prophylaxis (15 mg/kg at 0, 4 and 8 h following immunization) was recommended after DPT but not other vaccinations, in accord with British Columbia Ministry of Health health unit policy. When children were given bilateral thigh injections, parents were not told which vaccine was which. Participants received dose 3 of DPT vaccine at six months of age from their routine providers.

For 72 h after each dose of Hib.OMP vaccine parents were asked to observe and record in a diary supplied by the investigators changes in their child's health and to report immediately any events of concern. Parents were also given a clear celluloid template with linear and circular scales to aid measurement of redness or swelling at injection sites and a digital thermometer to encourage measurement of rectal temperature at least daily. Acetaminophen samples were supplied to all parents to aid compliance with fever prophylaxis after DPT injections. Parents' observations were reviewed systematically during a telephone interview with study staff 72 h following immunization. This interview had a structured format and used open-ended questions. Parents' responses were recorded by interviewers on a report form. Active surveillance of adverse effects was not performed when DPT or MMR vaccines were given alone because their safety profiles are well known. Parents were questioned about any severe adverse effects from the vaccines at subsequent visits for Hib.OMP administration.

Blood was obtained from subjects via fingerprick before each dose of Hib.OMP and one month after the second and third doses, to assess antibody responses. Timing of blood samples was constant between groups

TABLE 2
Subject demographics for the two treatment groups

Parameter	Group A (%)	Group B (%)
Males:Females	26:28	23:31
Mean birthweight (g)	3454.5	3362.7
Mean gestation (weeks)	39.5	39.1
Mean age at dose I Hib.OMP (weeks)	8.6	10.7
range	8-11	9-13
Acetaminophen prophylaxis used with Hib.OMP (±DPT):		
dose 1	54 (100)	17 (31.5)
dose 2	51 (94.4)	12 (25.9)
Intercurrent illness within 72 h of Hib.OMP:		
dose 1	10 (18.5)	5 (9.3)
dose 2	8 (14.8)	6 (11.1)
dose 3	6 (11.8)	8 (14.5)

DPT Diphtheria-pertussis-tetanus

TABLE 3
Adverse effects following each dose of Hib.OMP vaccine

Adverse effect within 72 h	Dose 1 (2 months) (%)	Dose 2 (4 months) (%)	Dose 3 (12 months) (%)
Fever 38.0°C or greater*	5 of 54 (9.3)	2 of 54 (3.7)	5 of 37 (13.5)
Redness at injection site, any	20 of 108 (18.5)	18 of 108 (16.7)	5 of 106 (4.7)
10 mm or greater	13 (12)	17 (15.7)	4 (3.8)
Swelling at injection site	5 of 108 (4.6)	4 of 108 (3.7)	3 of 106 (2.8)
Tenderness at injection site	19 of 108 (17.6)	19 of 108 (17.6)	17 of 106 (16.0)
Irritability within 24 h*	17 of 54 (31.5)	15 of 54 (27.8)	16 of 55 (29.1)
Increased drowsiness*	14 of 54 (25.9)	8 of 54 (14.8)	9 of 55 (16.4)
Decreased food intake*	5 of 54 (9.3)	8 of 54 (14.8)	9 of 55 (16.4)
Parents rating of reactions in toto*			
none	33 of 54 (61.1)	38 of 54 (70.4)	34 of 55 (61.8)
mild	19 (35.2)	14 (25.9)	17 (30.9)
moderate	2 (3.7)	2 (3.7)	4 (7.3)
severe	0	0	0

**Recipients of Hib.OMP given alone*

relative to Hib.OMP doses but was necessarily asynchronous relative to DPT and MMR doses. Sera were stored at –20°C and shipped frozen. They were submitted for testing bearing coded labels. All sera were tested for total binding anti-PRP antibody by radioimmunoassay at Merck Research Laboratories, Pennsylvania. The lower limit of detection of this assay was 125 ng/mL. When sufficient serum was available, samples were also tested by the authors for Hib-specific IgG antibodies using a capture-type enzyme-linked immunoadsorbent assay (ELISA) (18). Samples obtained following dose 2 were tested by the authors for diphtheria and tetanus antitoxins using standardized enzyme immunoassays. Samples obtained after dose 3 were tested for measles antibodies at Merck Research Laboratories and for rubella antibodies by the authors, using enzyme immunoassays in each instance.

Data were assembled and analyzed at the Vaccine Evaluation Center. Principal safety outcome measures defined before the study were fever and injection site erythema, as these were the most objective of the observations requested from parents. Incidence rates of these and other adverse events were compared using two-tailed Fisher exact tests. Antibody responses were contrasted as threshold ratios using Fisher's exact test. Serological responses were also analyzed in terms of geometric mean titres, calculated from log-transformed data. Normally distributed titre data were compared using Student's *t* test; otherwise the Kruskal-Wallis test was used. The outcome measure for rubella and measles responses was limited to seroconversion rates because of asynchronous sampling times between groups. P values less than 0.05 were considered significant.

RESULTS

One hundred and ten infants were enrolled: 108 are included in this analysis. Omitted were one child whose initial dose of Hib.OMP was delayed excessively by intercurrent illness and another who received DT instead of DPT for dose 2 at the parent's request. Participants were similar between the two groups (Table 2). Females accounted for 54.6% of subjects, predominating slightly in each group. One subject was born before 35 weeks gestation and weighed less than 2000 g at birth. The intended schedule of immunizations was met for most subjects. The first dose of Hib.OMP was given between eight and 11 weeks of age in 99 instances (91.7%). The separation between DPT and Hib.OMP doses in group B members averaged 14.9 days for dose 1 and 15.4 for dose 2, the aim having been 14 days in each instance. Of children receiving MMR and Hib.OMP concurrently, 48 of 51 (94.1%) were 52 to 56 weeks old (mean 53.7 weeks). All children in group B completed the protocol; three from group A were lost to follow-up between doses 2 and 3 of Hib.OMP (overall completion rate 97.2 %).

Compliance with acetaminophen prophylaxis when DPT and Hib.OMP were given together was excellent, exceeding 94% of subjects (Table 2). There was an unintended carryover of use in those receiving Hib.OMP alone, averaging 27% of subjects receiving dose 1 and 2. About 13% of subjects reportedly developed signs of intercurrent illness within three days after each dose of Hib.OMP (Table 2). Almost all illnesses consisted of cold and/or cough symptoms. These occurrences could falsely increase adverse effects attributed to vaccination but have been retained in the analysis.

TABLE 4
Anti-PRP responses measured by RIA to successive doses of Hib.OMP vaccine by treatment group

Anti-PRP (μg/mL)	Pre-immunization		After dose 1		After dose 2		Before dose 3		After dose 3	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
<0.125	41 (75.9)[1]	38 (70.4)	6 (11.1)	11 (20.4)	2 (3.8)	8 (15.4)	18 (34.6)	20 (38.5)	0	0
0.125-0.49	8 (14.8)	10 (18.5)	6 (11.1)	11 (20.4)	5 (9.4)	9 (17.3)	21 (40.4)	18 (34.6)	6 (11.8)	7 (13.2)
0.50-0.99	2 (3.7)	5 (9.3)	6 (11.1)	6 (11.1)	6 (11.3)	8 (15.4)	7 (13.5)	8 (15.4)	1 (2.0)	5 (9.4)
>1.0	3 (5.6)	1 (1.9)	36 (66.7)	24 (48.1)	40** (75.5)	27** (51.9)	6 (11.5)	6 (11.5)	44 (86.3)	41 (77.4)
Geometric mean	0.101	0.105	1.232*	0.783*	2.147*	1.090*	0.269	0.218	4.251*	2.857*
95% confidence interval	0.078-0.129	0.083-0.134	0.827-1.835	0.489-1.254	1.489-3.094	0.685-1.734	0.183-0.398	0.155-0.307	2.751-6.567	1.919-4.253
Comparisons betweem groups	No significant differences		*P=0.014 (Kruskal-Wallis test)		**P=0.015 (Fisher's exact test) *P=0.039 (Kruskal-Wallis test)		No significant differences		*P=0.18 (Student's *t* test)	

PRP Ribose, ribitol, phosphate polysaccharide capsule; RIA Radioimmunoassay; [1]Number of subjects with antibody level indicated (%); Group A Concurrent vaccination; Group B Sequential vaccination

Follow-up data are available for all 322 Hib.OMP vaccinations and for all 163 visits in which Hib.OMP was given alone. Adverse effects are tabulated for each dose in Table 3. At least 96% of parents made temperature measurements during the first 24 h after doses 1 and 2 of Hib.OMP, but compliance decreased to 73% after dose 3. Fever was detected after 8.3% of doses but no instance exceeded 39.0°C. Given alone Hib.OMP was followed by irritability, increased drowsiness or decreased appetite in about one-third of recipients. Considering all subjects, redness was noted at 43 of 322 Hib.OMP injection sites (13.4%), the largest diameter being 15 mm. Most (60.5%) instances cleared within 48 h. Tenderness was noted with similar frequency (17.1% of doses), but only one instance was rated as severe by the parents. Local swelling after Hib.OMP was infrequent (3.7%); all reactions were less than 15 mm in diameter. Asked to rate adverse reactions to Hib.OMP (alone) in summary after 72 h, no parents rated them as severe. No seizures, hypotonic-hyporesponsive episodes or physician visits were reported during observation periods. Morbidity after DPT vaccine (given with Hib.OMP) is not detailed here since comparison cannot be made with children receiving DPT vaccine alone as detailed follow-up was not obtained after such visits.

Regarding serological tests, anti-PRP assays were completed by radioimmunoassay (RIA) in 421 of 426 intended instances (98.8%). Pre-immunization levels of anti-PRP were comparable in groups A and B (Table 4). Eight weeks following dose 1 of Hib.OMP nearly 85% were seropositive (greater than 0.125 μg/mL) and 57.4% had greater than 1.0 μg/mL of anti-PRP. Four weeks after dose 2, 90.5% were seropositive. Levels greater than 1.0 μg/mL of anti-PRP were seen more often in concurrently than in sequentially vaccinated children (75.5% versus 51.9%, P=0.015, Fisher's exact test). Levels were lower at 12 months when only 63.5% were seropositive, and 11.5% exceeded 1.0 μg/mL of anti-PRP. Strong responses followed most booster doses. Concurrent administration of Hib.OMP with MMR did not impair anti- PRP responses.

Sera obtained at baseline and after two doses of Hib.OMP were also tested for anti-PRP by IgG capture ELISA in every subject. Baseline data resembled the results obtained by RIA (eg, 82.7% in each of groups A and B had 0.15 μg/mL or less). After two doses of Hib.OMP, no significant difference existed between groups in seropositivity rates (88% in group A, 77% in group B) or rates of responses 1.0 μg/mL or greater (40.7% in group A, 42.6% in group B).

Antitoxins for tetanus and diphtheria were assayed in all children following the second dose of DPT vaccine. Tetanus antitoxins were detected in all subjects with no significant differences between groups in threshold response rates or geometric mean titres. Diphtheria antitoxin responses were strong and detectable in all subjects. The geometric mean diphtheria antitoxin level was greater after concurrent vaccinations (6.83 versus 4.17 AU/mL, P=0.045, Student's *t* test) probably as a result of asynchronous timing of samples between groups.

Measles antibody levels were assayed in 104 subjects (96%). The seroconversion rates were 98% after concurrent vaccinations (Hib.OMP and MMR) and 89% after sequential vaccinations (P not significant), averaging 94%. Rubella antibody levels were assayed in 64 subjects (59.3%). The seroconversion rates were 100% after concurrent vaccinations and 94.1% after sequential vaccinations (P not significant). Comparison of antibody levels was not meaningful because of asynchronous timing of samples between groups.

DISCUSSION

This study confirmed the safety of Hib.OMP vaccine and the feasibility of giving it concurrently with routine childhood vaccines. After Hib.OMP alone, fever was

infrequently detected and uniformly mild (39.0°C or less). Local changes were also infrequent, mild and of short duration. General symptoms of irritability, increased drowsiness or decreased appetite, seen in about one-third of subjects, are difficult to attribute to vaccination without reference to a control group because of the likelihood of observer bias. The accuracy of our assessment of safety was possibly influenced by the unintended prophylactic use of acetaminophen after 27% of primary doses and by the development of intercurrent respiratory infections after 13% of doses. Nevertheless the observed incidence rates of adverse effects correspond closely with other reports (15).

Serological responses to Hib.OMP were somewhat lower in this study than in previous reports (15,16). The manufacturer has since determined that the Hib.OMP vaccine lots we used were less immunogenic than usual, although they met all the potency requirements in effect at the time (19). Altered immunogenicity resulted from a higher ratio of PRP to carrier molecules than was present in preproduction vaccine lots. Subsequently, all production lots have been kept within both a minimum and a maximum PRP to carrier molecule ratio, as defined by a particular conjugation reaction byproduct (13). The 13 children whose anti-PRP levels were less than 0.5 μg/mL after the booster dose were given an additional dose of vaccine from current stocks. We might have been overly cautious in doing so because the ability to respond to PRP may be more important to long term protection against Hib than any specific level of antibody soon after vaccination with conjugate products (20). All of our subjects were seropositive after the booster (third) dose of Hib.OMP.

Our assessment of the compatibility of Hib.OMP with concurrently injected DPT or MMR vaccines should be valid despite the possibly reduced potency of the Hib.OMP vaccine we used. Groups were closely matched in terms of pre-immunization anti-PRP levels and age at immunization. After one dose, anti-PRP levels did not differ significantly between those given concurrent or sequential vaccinations (Table 4). After two doses, anti-PRP levels were significantly lower in those sequentially vaccinated in terms of total antibody (measured by RIA, P=0.039) but not IgG antibody (measured by ELISA, P>0.05). Because vaccination with Hib.OMP elicits anti-PRP antibodies with relatively low avidity (21) and the measurement of such antibodies by RIA is influenced by avidity variations, the observed difference in RIA-based measurements between groups may not be meaningful. Hetherington et al (22) demonstrated that anti-PRP antibodies in Hib.OMP vaccines differ in affinities in a normally distributed fashion. Thus, it is possible that the RIA-based measurements differed in our study because of sampling error, given the limited size of the treatment groups. We interpret our aggregate serological data to mean that no definite influence on anti-PRP responses resulted from sequential vaccinations. To date there have been no reports concerning influences of DPT immunization on responses to other antigens presented somewhat later. No difference in anti-PRP levels was evident between groups at 12 months of age, before dose 3. Responses to dose 3 were comparable whether Hib.OMP was given concurrently with MMR or later, both in terms of the incidence rates of high-level responses and group geometric mean titres (P=0.18).

Concurrent use of Hib.OMP and DPT vaccines did not affect response rates to tetanus or diphtheria toxoids, compared with sequential administration. Our observations apply to the first two doses of toxoids, responses to which are normally modest in magnitude and presumably, therefore, are sensitive indicators of any interference. Responses to pertussis vaccine were not measured, as a simple serological correlate of immunity to this disease is not available. Concurrent use of Hib.OMP and MMR vaccines did not significantly alter response rates to rubella or measles viruses. Seroconversion rates of 100% and 98%, respectively, were observed.

CONCLUSIONS

Hib.OMP vaccine appears to be compatible with both Canadian-type DPT and MMR vaccines. Physicians may chose to give Hib.OMP concurrently with DPT or MMR or to wait for an interval and give it separately. The former seems preferable for its greater convenience and cost-effectiveness.

Hib.OMP vaccine was licensed in Canada in September 1991. It has been favoured by the Territorial and Northern Health Services because the strong response to the first dose is an advantage where Hib infections tend to occur at an early age, as in some aboriginal populations (11,23). However, its use in the provinces has been limited. Nevertheless, Hib.OMP vaccine is noteworthy for its novel construction and unique ability to elicit responses very rapidly in young infants.

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