Effectiveness of *Haemophilus influenzae* type b vaccines

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Purpose: To determine the clinical effectiveness of *Haemophilus influenzae* type b (Hib) vaccines.

Study identification and selection: Computerized searches of MEDLINE, EMBASE and SCISEARCH databases were performed, and the reference list of each retrieved article was reviewed. Two prospective clinical trials of Hib polyribosyl ribitol phosphate conjugated with diphtheria toxoid (PRP-D) were identified. In addition, one cohort study of the PRP-D vaccine, two trials of the PRP vaccine, five case-control studies of the PRP vaccine and 10 randomized controlled trials of the immunogenicity of the PRP-D vaccine were identified.

Data extraction: Study quality was assessed and descriptive information concerning the study populations, the interventions and the outcome measurements was extracted.

Results: The difference in the effectiveness of the PRP-D vaccine between the prospective trials, in which a three-dose schedule had been used beginning at 2 to 3 months of age, was clinically important (37% v. 83%) but not statistically significant. The PRP vaccine, which induces lower antibody responses than the PRP-D vaccine does, was clinically effective only in a subgroup of one prospective trial; 90% effectiveness was reported among children 18 to 60 months of age.

Conclusions: Hib vaccine appears to be less effective in high-risk populations. None the less, because of the large variation in baseline risk, the number of children who would have to be vaccinated to prevent one case of invasive Hib disease is substantially less for high-risk than for low-risk populations. The vaccination of children at high risk, such as native children, with the PRP-D vaccine using a four-dose schedule (at 2, 4, 6 and 14 months of age) seems warranted. The currently available evidence does not strongly support a policy of universal vaccination with either a one-dose or a four-dose schedule.

But: Connaître l'efficacité clinique des vaccins contre l'*Haemophilus influenzae* du type b (Hib).

Repérage et choix des travaux: On fait appel aux banques de données MEDLINE, EMBASE et SCISEARCH. On passe en revue la bibliographie de chaque article repéré. On trouve deux essais cliniques prospectifs et cinq essais comparatifs sujets-témoins du vaccin de polyribosyl-phosphate de ribitol (PRP), deux essais prospectifs et une étude par cohortes du même vaccin conjugué à l'anatoxine diphtérique (PRP-D). On trouve aussi 10 études comparatives de l'immunogénicité du vaccin PRP-D.

Extraction des données: On juge de la qualité des travaux et procède à l'extraction de l'information sur les populations à l'étude, les interventions et la mesure des résultats.

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Résultats: L'efficacité du vaccin PRP-D diffère dans les deux essais prospectifs d'un régime de trois doses à partir de l'âge de 2 ou 3 mois: 37% contre 83%; cette différence, importante du point de vue clinique, n'atteint pas la signification statistique. Quant au vaccin PRP, qui produit moins d'anticorps que le PRP-D, il n'est efficace que dans un sous-groupe de l'un des essais prospectifs (soit à 90% chez les enfants âgés de 18 à 60 mois).

Conclusions: Le vaccin Hib semble être d'autant moins efficace que le risque de contracter la maladie dans la population est plus grand. Comme ce risque varie beaucoup, le nombre de vaccinations qu'il faut faire afin de prévenir un cas d'infection envahissante à Hib est moindre lorsqu'il est élevé que lorsqu'il est bas. Il semble indiqué de vacciner les enfants à risque élevé, comme les aborigènes, par quatre doses de PRP-D, à 2, 4, 6 et 14 mois. Les connaissances actuelles ne militent pas fortement pour la vaccination de tous les enfants, ni en une dose ni en quatre.

The pathogen *Haemophilus influenzae* type b (Hib) is a major cause of serious invasive infections in infants and young children. The most frequent manifestation is meningitis; others include epiglottitis, arthritis, cellulitis and pneumonia.[1-8] About 50% to 70% of patients with Hib meningitis are under 18 months of age, and 90% are 5 years old or less.[1,2,5,8] Whereas the prevalence of Hib infection may vary among children 5 years old or less, most children more than 5 years of age and most adults have naturally acquired immunity.

Although the incidence is generally relatively low, invasive Hib infection is still the most common cause of bacterial meningitis in children under 5 years and is associated with considerable mortality and morbidity rates.[7-10] The case-fatality rate for Hib meningitis is from 2% to 8%,[1,2,5,6,8] and serious complications such as blindness, deafness, seizures, mental retardation and hydrocephalus occur in 20% to 45% of survivors.[2,6,8] Moreover, the incidence may vary in different populations (Table 1) and from year to year in the same population.[11] Children who attend day-care centres may be among those with an increased risk of Hib disease, although reliable estimates of the magnitude of the risk are lacking because of limitations of the available data, which are derived from case-control and cross-sectional studies.[12-15]

In 1986 the first Hib vaccine was licensed in Canada and recommended for routine use in children at 24 months of age.[16] US recommendations differed in suggesting that children at high risk, such as immunocompromised children and day-care attendees, should be vaccinated at 18 to 24 months.[17] The vaccine, which was prepared from the polyribosyl ribitol phosphate (PRP) capsular Hib polysaccharide,[18] had limited immunogenicity in children under 2 years of age.[19,20]

Attempts to improve the immunogenicity of PRP through the application of the carrier-hapten immunologic principle resulted in several products,[21-27] of which PRP-D (PRP conjugated with diphtheria toxoid) is the most widely studied and the only licensed conjugate vaccine in Canada. Unlike the PRP vaccine, this vaccine induces high antibody responses, particularly in younger children, and elicits booster responses on revaccination[1,21,28] (Dr. Juhani Eskola: personal communication, 1988). PRP-D vaccine was licensed in 1988 in Canada for use in children 18 months of age or older;[1,29] however, considerable uncertainty still exists regarding the effectiveness of Hib vaccines, who should be vaccinated and at what age.

Variable results have been reported from both clinical trials and immunogenicity studies of Hib vaccines. Previously published reviews of the effectiveness of such vaccines have not usually been comprehensive, the quality of the available research

Table 1: Annual incidence of invasive *Haemophilus influenzae* type b (Hib) infections per 100 000

	Canada*		United States†[3]		Northwest Territories†[4]		Alaska†[5]	
Age, mo	Meningitis[2]	All Hib infection[1]	Meningitis	All Hib infection	Meningitis	All Hib infection	Meningitis	All Hib infection
0–5	51	52	112	153	2333	–	871	1702
6–11			192	298				
12–17	13	17	113	162	275	–	396	1100
18–23			59	122			264	528
24–35			33	56	265	–	93	186
36–47			17	47	–	–	0	72
48–59	–	–	8	24	–	–	0	0

*Physician-reported data.
†Data from active surveillance.

has not been systematically assessed, wide-ranging estimates of vaccine effectiveness have been cited (from −86% [harmful] to +90% [highly effective]), and conclusions have been reached without a systematic analysis and synthesis of the findings.[1,6,8-10,29-44] Available "reviews" consist primarily of commentaries,[34-38] policy statements[1,29-32,39] and sections of textbooks.[6,9,10] For the most part the reviews highlight rather than reduce or clarify the uncertainty that exists about the effectiveness and appropriate use of Hib vaccines.

To facilitate informed decision-making by clinicians and other health care professionals and policymakers about the appropriate use of Hib vaccines we systematically consolidated the currently available evidence on the clinical effectiveness of Hib vaccines. We also reviewed studies of the immunogenicity of the PRP-D vaccine and the risk of adverse reactions. Finally, we calculated the expected number of children who would have to be vaccinated to prevent one case of invasive Hib disease, given the various estimates of the baseline risk of infection and of the effectiveness of the vaccine.

Methods

Study identification and selection

We searched the MEDLINE database for review articles published from January 1986 to November 1988 using the MeSH headings "*Haemophilus influenzae*", "vaccines" and "review". In addition, we reviewed current textbooks and obtained the most recent policy statements made by various advisory groups, including in Canada the National Advisory Committee on Immunization[1] and the Task Force on the Periodic Health Examination (Dr. Ronald Gold: personal communication, 1988) and in the United States the Immunization Practices Advisory Committee,[30] the Preventive Services Task Force (Dr. Marc La Force: personal communication, 1988) and the American Academy of Pediatrics.[32] We identified 21 articles;[1,6,8-10,29-44] all of the reviews, policy statements, textbook sections and commentaries that reached a conclusion regarding the clinical effectiveness of Hib vaccine were critically appraised with the use of previously published guidelines[45] before we reviewed the primary research.

We then searched MEDLINE for articles on primary research published from January 1966 to October 1989 using the MeSH terms "*Haemophilus influenzae*", "vaccine" and "clinical trials"; the Excerpta Medica database (EMBASE) was searched for articles published from January 1972 to November 1989 with the use of the same terms. We also searched MEDLINE for studies published from January 1983 to November 1988 on the immunogenicity of the PRP-D vaccine using the MeSH terms "vaccine" or "bacterial vaccine" and the text word "conjugate". We searched the Science Citation database (SCISEARCH) using two major papers, generating a list of citations in which either of the two key papers was included as a reference.[19,28] To ensure that all of the relevant literature was obtained we also asked the first-named authors of the prospective studies if they were aware of any other published or unpublished data.

The following criteria were used to select studies of the clinical effectiveness of Hib vaccines: target population, children 2 months to 6 years of age; intervention, Hib PRP or PRP-D vaccine; outcomes, invasive Hib infection (including meningitis, epiglottitis, arthritis, osteomyelitis, cellulitis and pneumonia); study design, concurrent control group or case-control study.

One of us (D.M.S.) reviewed the computer searches and the reference lists of all the retrieved articles for studies of the clinical effectiveness of Hib vaccines. When the relevance of a citation was uncertain the complete text was reviewed. Ten primary studies of clinical effectiveness were identified from 11 papers.[19,20,28,46-53]

The immunogenicity studies and the relevant reference lists were reviewed by another author (H.H.F.), who used the following inclusion criteria: subjects, children up to 2 years of age; intervention, Hib PRP-D vaccine; outcomes, geometric mean titre of anti-PRP antibody or proportion of subjects with antibody titres of 0.15 μg/ml or greater and 1.0 μg/ml or greater after the last dose; study design, prospective controlled trials. Nine primary studies were identified,[54-62] of which six compared PRP and PRP-D.[55,58-62]

Study evaluation and data extraction

We assessed the validity of the prospective studies and the case-control studies using the criteria in Table 2, which are ranked in descending order of their potential impact on study validity.

The validity assessment of each study was reviewed by one of us (D.M.S.). Copies of the papers were given to two other authors (B.G.H. and F.S.S.C.) to independently assess the quality of the studies; they were blinded to the authors, the journal and the results. Disagreements among the reviewers regarding the assessments were resolved by consensus.

Age and demographic characteristics of the study populations, the dose and type of vaccine and the raw data on the incidence of invasive Hib infection were extracted independently from each study by two of us (D.M.S. and A.D.O.). One of us (H.H.F.) extracted the following data from the im-

munogenicity studies that met the inclusion criteria: the number of subjects in each age group for which results were reported, the mode of administration, the amount of PRP in the vaccine, the dose schedule, the geometric mean anti-PRP antibody titre and the proportion of subjects with anti-PRP antibody titres of 0.15 μg/ml or greater and 1.0 μg/ml or greater after the last dose.

Analysis

We calculated the common odds ratios and the 95% confidence intervals using an exact method with a computer program (EGRET Statistical Software, prerelease version, Statistics in Epidemiology Research Corp., Seattle, 1989). Because of the large sample size for the Finnish trials[19,20,28] exact confidence intervals could not be calculated; instead we used the Mantel–Haenszel method[63] and calculated the 95% confidence intervals for the common odds ratio using Cornfield's method.[64] We used the Breslow–Day method[64] to test the homogeneity of the results within groups of clinically similar studies.

The number of children who would need to be vaccinated to prevent one case of invasive Hib disease[65] was calculated as follows.

BI (baseline incidence) = the incidence of invasive Hib disease without vaccination

BO (baseline odds) = BI ÷ (1 − BI)
OV (odds with vaccination) = odds ratio × BO
IV (incidence with vaccination) = OV ÷ (1 + OV)
NNV (number needed to be vaccinated) = 1 ÷ (BI − IV)

For the immunogenicity studies exact confidence intervals based on the binomial were taken from standard tables for proportions, and the exact method in the EGRET program was used to test differences between the proportions.

Results

We identified two prospective trials and one cohort study of conjugated Hib vaccines,[28,47,48,66] two prospective trials of unconjugated Hib vaccines[19,20,46] and five case–control studies of unconjugated Hib vaccines.[49–53] The key characteristics of the prospective and the case–control studies are summarized in Tables 3 and 4 respectively, along with our assessment of the validity of each study. Because of the limitations of retrospective data collection the estimates of vaccine effectiveness derived from the prospective trials were considered to be more persuasive than those derived from the case–control studies;[67,68] the results are presented in two separate categories. None of the prospective trials had major methodologic flaws that would bring the ranking of the evidence into question. The results from the single cohort study were also considered in a sepa-

Table 2: Criteria* used to assess validity of prospective studies and case–control studies

Prospective studies	Case–control studies
Method of allocation? + = Randomized 0 = Quasi-randomized (e.g., alternate allocation) − = Cohort	Explicit and precise case definitions? + = Yes − = No
Baseline comparison of experimental and control groups? + = Documented (data provided) 0 = Mentioned (no data given) − = Not mentioned	Comparability of case and control subjects with respect to age, sex, day-care attendance, race and socioeconomic status demonstrated or controlled for by matching or adjustment in the analysis? + = Yes 0 = Partially or unknown − = No
Explicit diagnostic criteria? + = Yes − = No	Source of vaccination status? + = Medical records − = Parental recollection or unknown
Follow-up? + = ≥ 90% 0 = ≥ 80% to < 90% − = < 80%, passive surveillance or unknown	Blind ascertainment of vaccination status (with respect to whether the child was a case or control subject)? + = Yes 0 = Unknown − = No
Blind outcome assessment? + = Yes − = No	Complete ascertainment of vaccination status? + = ≥ 90% 0 = ≥ 80% to < 90% − = < 80% or unknown
Blind administration of vaccine? + = Yes − = No	

*Listed in order of importance.

rate category; this study was the only one that addressed the effectiveness of PRP-D vaccine when administered as a single dose to children 18 to 60 months of age.

The results of the prospective and case-control studies are summarized in Tables 5 and 6 and in Figs. 1 and 2. In Tables 5, 6 and 7 and Figs. 1 and 2 the studies are in order of methodologic quality, the most rigorous one being listed first, and are ranked in a "nested" manner for each of the validity criteria in Table 2. For example, the prospective studies are first ranked according to the method of allocation, which is the most important criterion. Studies that are of equal quality with respect to the method of allocation are then ranked according to the next most important criterion and so on. The results of the immunogenicity studies are summarized in Tables 8 and 9.

The studies were given equal weight regarding methodologic quality in analyses in which a common magnitude of effect (common odds ratio) was calculated. When there were statistically significant differences between studies (i.e., the difference in reported results was greater than that expected by chance) a common odds ratio was not presented.

Discussion

Clinical effectiveness of PRP-D vaccines

The difference in the odds ratios between the two PRP-D trials was clinically important (0.63 v. 0.17) but not statistically significant. There was much more uncertainty (a greater confidence interval) around the point estimate of the odds ratio in the Alaskan study[47] than in the Finnish study.[28] This

Table 3: Characteristics of prospective studies

Characteristic	Peltola et al[19,20]	Parke et al[42,46]	Eskola et al[28]	Ward et al[47]*	Greenberg et al[48]
Population					
Location	Finland	North Carolina	Finland	Alaska	California
Sample size	100 000	18 000	60 000¶	1 765	98 000
Hib baseline risk per 100 000/yr† (and age range, mo)	13 (3–71)	37 (2–72)	53 (≤ 60)	1 252 (2–12)	27 (18–60)
Intervention					
Vaccine type‡	PRP	PRP	PRP–D	PRP–D**	PRP–D
Dose, μg	12.7	10	25	20	25
Administration	Subcutaneous	Subcutaneous	Intramuscular	Intramuscular	Intramuscular
Schedule, no. of doses	1	1	3	3	1
Age vaccine given, mo	3–60 (booster 3 mo later if < 18 mo)	2–72	3, 4 and 6	2, 4 and 6	18
Outcome					
Duration of follow-up§	4 yr	6 yr	7 mo	About 1 yr	1 yr
Methods‖					
Method of allocation	0	+	0	+	–
Baseline comparison	0	+††	–	0	–
Diagnostic criteria	–	+††	+	+	+
Completeness of follow-up	–	–	–	–	–
Blind outcome assessment	+	+	–	+	–
Blind administration of vaccine	+	+	–	+	–

*Reported in abstract form only.
†For age range in brackets; calculated by dividing the reported proportion of invasive Hib infections in control group by the average length of follow-up.
‡PRP = polyribosyl ribitol phosphate; PRP–D = PRP conjugated with diphtheria toxoid.
§Estimated average length of follow-up for most recent available data (in Table 5).
‖The criteria and scoring system in Table 2 were used to assess the published reports; in addition, the first author was contacted when information was missing.
¶Total number is unknown; number is estimated on the basis of vaccine coverage at a sample of vaccination clinics.
**Developmental vaccine lot.[66]
††Dr. James Parke: personal communication, 1989.

Table 4: Characteristics of case–control studies

Characteristic	Black et al[52]	Harrison et al[49]	Shapiro et al[50]	Osterholm et al[51]	Harrison et al[53]
Population					
Location	California	New Jersey, Los Angeles, Tennessee, Missouri, Oklahoma, Washington	Connecticut, Texas, Pennsylvania	Minnesota	New Jersey, Los Angeles, Tennessee, Missouri, Oklahoma, Washington
No. of cases	35	126	76	68	74
Age distribution, mo	23–72	18–59	24–72	24–71	24–59
Hib baseline incidence per 100 000/yr* (and age range, mo)	19.3 (1–71)	58 (≤ 60)	–	13.6 (24–72)	58 (0–60)
Intervention					
Vaccine type	PRP	PRP	PRP	PRP	PRP
Methods†					
Case definition	+	+	+	+	+
Comparability of case and control subjects	0	0	0	0	0
Source of vaccination status	+	+	+	+	+
Blind ascertainment of vaccination status	0	0	0	0	0
Complete ascertainment of vaccination status	+	+	+	+	+

*For age range in brackets.
†The criteria and scoring system are summarized in Table 2.

Table 5: Results of prospective trials by type of Hib vaccine

Study	No. (and %) of vaccinated subjects		No. (and %) of control subjects		Risk difference	Risk reduction, %	Odds ratio (and 95% confidence interval [CI])
	Total	Cases	Total	Cases			
PRP–D vaccine							
Ward et al[47]	887	7 (0.79)	878	11 (1.25)	−0.0046	+37	0.63 (0.21–1.78)
Eskola et al[28]	30 000	2 (0.01)	30 000	12 (0.04)	−0.0003	+83	0.17 (0.03–0.78)
Common odds ratio							0.38 (0.17–0.87)
Test for homogeneity: p = 0.132.							
Greenberg et al[48]	22 744	0 (0.00)	75 256	18 (0.02)	−0.0002	+100	0.00 (0.00–0.37)
PRP vaccine							
Parke et al[42,46]	9 084	20 (0.22)	8 980	20 (0.22)	−0.0000	+1	0.99 (0.51–1.94)
Peltola et al[19,20]	48 977	12 (0.02)	49 295	25 (0.05)	−0.0003	+52	0.48 (0.23–1.01)*
Common odds ratio							0.71 (0.44–1.14)
Test for homogeneity: p = 0.127.							
Subgroup analysis[19,20]							
Age group							
3–17 mo	11 584	10 (0.09)	10 864	5 (0.05)	+0.0004	−88	1.88 (0.58–6.97)
18–71 mo	37 393	2 (0.01)	38 431	20 (0.05)	−0.0005	+90	0.10 (0.00–0.45)
Test for homogeneity: p = 0.0004.							

*Odds ratio should be interpreted cautiously given the difference in effectiveness between age groups (as shown in results of subgroup analysis below).

Table 6: Results of case–control studies by age group

Study	No. (and %) of case subjects		No. (and %) of control subjects		Odds ratio (and 95% CI)	
	Total	Vaccinated	Total	Vaccinated	Unmatched analysis	Matched analysis*
24–72 mo						
Black et al[52]	35	4 (11)	166	39 (23)	0.42 (0.10–1.30)	0.31 (0.09–1.13)
Harrison et al[49]	84	19 (23)	191	65 (34)	0.57 (0.30–1.06)	0.59 (0.29–1.04)
Shapiro et al[50]						
Connecticut	21	4 (19)	42	21 (50)	0.24 (0.05–0.91)	0.09 (0.01–0.29)
Dallas	27	1 (4)	54	19 (35)	0.07 (0.00–0.52)	0.08 (0.01–0.24)
Pittsburgh	28	4 (14)	56	20 (36)	0.30 (0.07–1.07)	0.19 (0.04–0.55)
Osterholm et al[51]	68	26 (38)	136	42 (31)	1.39 (0.72–2.66)	1.55 (0.71–3.38)
Harrison et al[53]	74	9 (12)	127	28 (22)	0.49 (0.19–1.16)	0.36
Test for homogeneity: p = 0.008.						
18–24 mo						
Harrison et al[49]	42	3 (7)	100	16 (16)	0.40 (0.07–1.54)	0.54 (0.09–3.42)

*The matched results were those reported by the authors;[67, 68] the unmatched analyses were used to test for homogeneity.

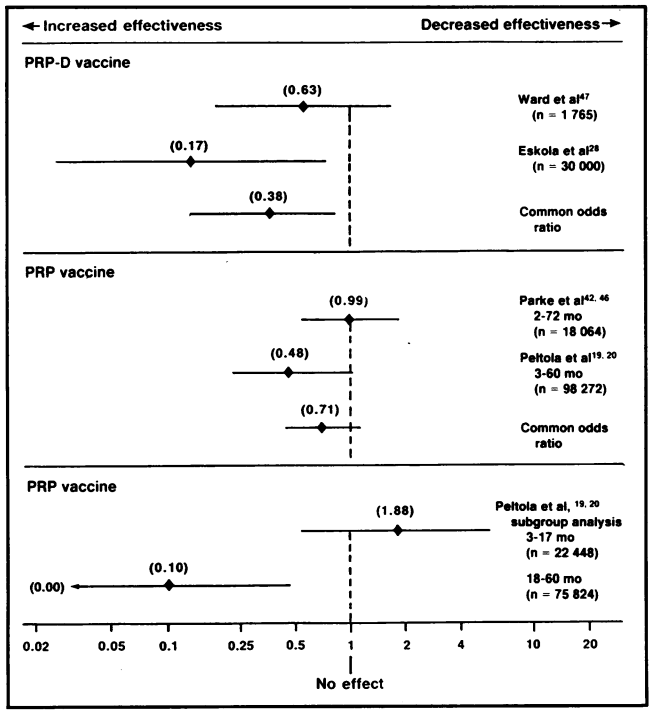

Fig. 1: Effectiveness of *Haemophilus influenzae* type b (Hib) vaccines in prospective trials, as determined by odds ratios and 95% confidence intervals (CIs). PRP = polyribose ribitol phosphate; PRP-D = PRP vaccine conjugated with diphtheria toxoid.

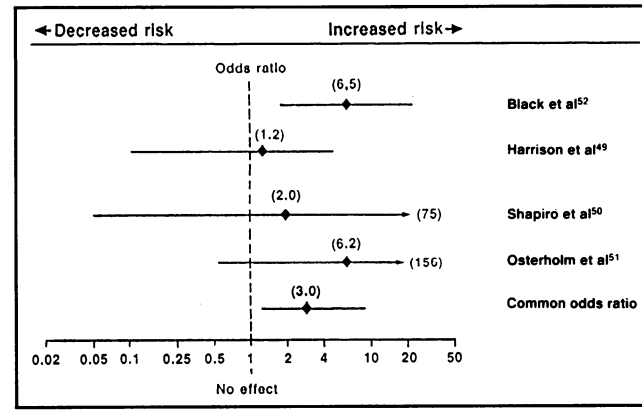

Fig. 2: Risk of Hib disease within 7 days after vaccination, as determined by odds ratios and 95% CIs from case-control studies of PRP vaccines.

uncertainty reflected the smaller sample size and poor statistical power of the Alaskan study (40% to detect a true risk reduction of 50% with a one-sided α of 0.05); that is, there was a relatively high probability of making a type II error (falsely concluding that the vaccine was not effective). The results of the Alaskan study should not be interpreted as evidence that the vaccine is ineffective.

Despite the limited power of the Alaskan study we could pool the Alaskan data with the Finnish data to determine a common odds ratio for the combined population. The common odds ratio 0.38 (95% confidence interval 0.17 to 0.87) indicates that the PRP-D vaccine can be expected to be moderately effective and that the result is statistically significant (95% confidence interval does not overlap 1.0). However, it is unclear to what extent the common odds ratio can be generalized to various populations. Although the difference in the odds ratios between the Alaskan and Finnish studies was not statistically significant the study populations were extremely different with respect to the baseline incidence of invasive Hib disease (Table 3). In addition, the age distribution differs substantially between infants in Finland and the United States.[15] Given these considerations the common odds ratio must be interpreted with caution.

Other authors have considered the difference in results between the Alaskan and Finnish studies to be clinically important.[15,69] Possible explanations for the difference include underlying variations in the immunoresponsiveness of the study populations, the immunogenicity of the vaccines and the study designs.[15,69] Although the Alaskan study was more rigorous in design and had limited statistical power as indicated above, it is unlikely that either study was substantially biased. Both of these sets of data are based on vaccination with three doses of PRP-D vaccine at 2 to 3, 4 and 6 months of age. In the Finnish study 100% effectiveness was achieved after a fourth dose at 14 months of age.[69]

The results of the only study that examined the effectiveness of a single dose of the PRP-D vaccine given between 18 and 60 months of age also appear in Table 5.[48] Although this cohort study had good statistical power because of the large number of subjects, it was undertaken after the licensure of PRP-D primarily to document the safety of the vaccine, and calculation of the incidence of Hib disease was considered a secondary outcome (Dr. David P. Greenberg: personal communication, 1989). No data had been collected to compare the prevaccination risk of Hib disease among vaccinated and nonvaccinated children, the results thus being subject to selection bias. It has been documented in

Table 7: Risk of Hib infection within 7 days after vaccination with PRP vaccine

Study	No. (and %) of case subjects		No. (and %) of control subjects		Odds ratio (and 95% CI)	
	Total	Vaccinated	Total	Vaccinated	Unmatched analysis	Matched analysis
Black et al[52]	31	4 (12.9)	2 844	63 (2.2)	6.54 (1.88–20.44)	6.4 (2.1–19.2)
Harrison et al[49]	104	3 (2.8)	207	5 (2.4)	1.20 (0.22–5.90)	1.8 (0.3–10.2)
Shapiro et al[50]	76	1 (1.3)	152	1 (0.7)	2.01 (0.05–74.80)	–
Osterholm et al[51]	88	3 (3.4)	176	1 (0.6)	6.18 (0.56–156.48)	6.2 (0.6–45.9)
Common odds ratio					2.95 (1.32–8.72)	

Test for homogeneity: p = 0.235.

Table 8: Results of studies of the immunogenicity of PRP and PRP–D vaccines

Study	Age, mo	No. (and schedule) of doses	Geometric mean anti-PRP antibody, μg/ml	% with anti-PRP antibody; titre, μg/ml		
				Total	≥ 0.15	≥ 1.0
PRP–D vaccine						
Eskola et al[54]*	3– 7	3 (3, 5 and 7 mo)	1.56	24	92	50
	7– 9	2 (7 and 9 mo)	1.70	47	87	57
Eskola et al[28]	3– 6	3 (3, 4 and 6 mo)	0.42	99	62	34
Käyhty et al[55]*	3–14‡	4 (3, 5, 7 and 14 mo)	9.01§	12	100	92
	3–18	4 (3, 5, 7 and 18 mo)	24.00	10	100	100
Ward et al[56]	2– 6‖	3 (2, 4 and 6 mo)	–	56	27	16
	2– 6¶	3 (2, 4 and 6 mo)	–	32	50	28
Lepow et al[57]	7–14	2 (2 mo apart)	3.09	217	91	73
Lepow et al[58]	9–15	2 (2 mo apart)	4.77	29	100	88
Berkowitz et al[59]	15–24	1	2.17	178	94	67
Hendley et al[60]	17–22	1	1.76	42	84	65
Musher et al[61]	18–20	1	5.34	14	–	–
Frayha et al[62]	15–17	2 (2 mo apart)	2.17	49	87	77
PRP vaccine†						
Lepow et al[58]	9–15	2 (2 mo apart)	0.09	27	–	–
Käyhty et al[55]	3– 7	3 (3, 5 and 7 mo)	0.26	27	41	15
Berkowitz et al[59]	15–24	1	0.11	147	35	15
Hendley et al[60]	17–22	1	0.23	45	55	14
Musher et al[61]	18–20	1	0.21	–	–	23
Frayha et al[62]	15–17	2 (2 mo apart)	0.43	50	40	22

*Children involved in studies by Eskola et al[54] and Käyhty et al[55] were the same.
†PRP–D studies in which control subjects received PRP vaccine.
‡Serum drawn at 18 mo.
§Serum drawn at 15 mo.
‖Children in Alaska.
¶Children in New York.

the children on whom this study was based that those at greatest risk of disease were the least likely to be vaccinated;[52] this would result in an overestimate of vaccine effectiveness. Thus, the validity of these results is questionable despite the large sample size.

Immunogenicity of PRP-D vaccines

With the exception of one Canadian study,[62] all the studies were conducted either in the United States[56-61] or Finland.[54,55] As can be seen in Table 7 the ages of the subjects, the dosage and the dose schedule varied among the studies.

The differences in immunogenicity among children of similar age may be related to several factors: the potency of the vaccine lot,[57] the antibody assay used to determine the antibody levels[70] and differences in immunoresponsiveness between populations.[71-74]

An anti-PRP antibody titre of 0.15 μg/ml or greater after the last dose is the minimal response thought to confer protection against Hib infection; a titre of 1.0 μg/ml or greater is thought to correlate with immunity for at least 4 years, primarily on the basis of experience with PRP vaccines.[19,20,28,75]

Despite the correlation of total serum anticapsular (PRP) antibody levels with protection from invasive Hib disease, other factors such as the antibody class and the presence of antibodies to noncapsular antigens of Hib may also play a role.[76-79] Because of the PRP-D antigen's T-dependent characteristics — it primes the immune system to mount a secondary antibody response when Hib bacteria or their capsular antigens are encountered — the amount of antibody achieved with PRP-D vaccine may not need to be as high as that with PRP vaccine. This is supported by the findings of the Finnish trial, in which 83% effectiveness of PRP-D vaccine was achieved in the infants, despite only 34% of them having achieved anti-PRP antibody levels of 1 μg/ml or greater.[28]

A statistically significant difference in the immunogenicity of the vaccines was observed in the Alaskan and Finnish studies (Table 9);[28,56] this supports the hypothesis that the observed difference in clinical effectiveness is due to differences in either the immunogenicity of the vaccines used or the immunoresponsiveness of the target populations. Ward and associates[56] observed a difference in immune response between infants in Alaska and New York, even though the same vaccine lot was used in both populations.

Effectiveness of PRP vaccines

The results of the prospective trials of PRP vaccines appear in Table 5 and Fig. 1. When analysed without reference to age at vaccination the difference in the odds ratios between the two studies is clinically important (no effect v. 50% effectiveness) but not statistically significant. However, in the Finnish study[19,20] the results were significantly different between children less than 18 months of age and those 18 months or older (an 88% increase in risk v. a 90% risk reduction, $p = 0.0004$). Thus, the only evidence of the clinical effectiveness of PRP vaccines was from a subgroup analysis of the Finnish data; this is the primary basis for earlier recommendations regarding its use.[16,17]

Subgroup analyses, especially those that are post hoc, must in general be viewed with suspicion.[80] However, in this case there is a strong biologic rationale and consistent indirect evidence from immunogenicity studies that contribute to its plausibility. Although the power of the North Carolina study[46]

Table 9: Results of Alaska and Finland immunogenicity studies

Study	No. (and %) of subjects	95% CI, %*
Anti-PRP antibody titre ≥ 0.15 μg/ml		
Ward et al[56]		
Alaska (n = 56)	15 (27)	16–40
New York (n = 32)	16 (50)	32–68
Eskola et al[28] (n = 99)	61 (62)	51–71
Exact test $p<0.001$.		
Anti-PRP antibody titre ≥ 1.0 μg/ml		
Ward et al[56]		
Alaska (n = 56)	9 (16)	8–28
New York (n = 32)	9 (28)	14–47
Eskola et al[28] (n = 99)	34 (34)	25–45
Exact test $p = 0.051$.		

*Exact 95% CIs based on the binomial.

and the Finnish subgroup analysis[19,20] involving children under 18 months of age is low (50% in both cases to detect a 50% risk reduction with a one-sided α of 0.05), the vaccine was unlikely to be more than 40% to 50% effective in either case, given the 95% confidence limits of the odds ratio.

After the licensure of PRP vaccine in the United States five case-control studies[49-53] were reported that estimated the effectiveness of the vaccine (one study reported results from three sites[50]). Although the studies were homogeneous in design (projects at four of the seven sites were undertaken by one group of investigators)[50,51] the results were still heterogeneous ($p = 0.008$), the estimated odds ratios ranging from 0.08 (highly effective) to 1.55 (an apparent increase in risk with vaccination). Three of the studies revealed a statistically significant benefit,[50] three showed a positive trend,[49,52,53] and one showed a trend toward increased risk with vaccination.[51] Given the confidence interval (0.71 to 3.38) for the Minnesota study it cannot be concluded that the vaccine had a detrimental effect. It has been speculated that the observed differences in clinical effectiveness, which were too great to be expected on the basis of chance alone, could be the result of regional variation in immunoresponsiveness; however, no specific host or bacterial factors have been convincingly demonstrated.[81]

It can be concluded that the observed effectiveness of PRP and PRP-D vaccines has varied substantially in retrospective and prospective studies and in immunogenicity studies. Although this variation might be partly due to differences in study design, it is more likely that there is true variation in vaccine effectiveness because of differences in the immunoresponsiveness of the target populations and the immunogenicity of the different vaccines.

An unresolved question regarding differences in the target populations is whether the PRP vaccine is effective in children 18 to 24 months of age, for whom initial US recommendations for vaccine administration applied if they were at high risk.[17] Reviewers of the Finnish PRP trial questioned whether there were enough subjects in this age range to demonstrate that the vaccine was actually effective or whether a lack of effectiveness in this age range was masked by the effectiveness of the vaccine in those more than 24 months of age.[32] Only one case-control study[49] addressed this question (Table 6), and it did not find a statistically significant effect.

Vaccine safety

PRP and PRP-D vaccines continue to have a good safety record. No serious reactions have been reported since they were introduced in North America.[1,16,17,30] In the Finnish study[28] 20 generalized reactions occurred in 55 000 vaccinees; 2 were considered to be severe and consisted of convulsions 12 hours after vaccination in one case and a hypotonic and hyporesponsive episode 3 hours after vaccination in another. In the two cases the infants had received diphtheria toxoid-pertussis vaccine-tetanus toxoid at the same time as the PRP-D vaccine; thus it was difficult to attribute these reactions solely to the PRP-D vaccine. The infants were subsequently vaccinated with PRP-D vaccine and diphtheria toxoid-tetanus toxoid without further problem. Other systemic reactions that may occur with the polysaccharide vaccines include irritability (in 7.5% to 30% of cases) and fever (in 2% to 5%).[28,55,57-60,62,82] Local reactions, such as redness, swelling and pain, may occur in 3.5% to 27% of cases but usually disappear in 24 hours or less.[28,55,57-60,62,82] Several immunogenicity studies have revealed no statistically significant difference in the rate of adverse reactions between either PRP-D and PRP[55,58-62] or PRP-D and placebo.[57]

Concern has been raised that a possible increased risk of Hib infection within 7 days of vaccination with PRP vaccine[32,34,36-38,43,49-53] could result from transient binding of the vaccine antigen to natural antibody.[51,52] Two follow-up studies have documented transient decreases in anticapsular antibody after vaccination with both PRP and PRP-D vaccines.[83,84] This risk was evaluated in four case-control studies through a comparison of the probability that a case subject received the vaccine within 7 days of diagnosis and the probability that a control subject received the vaccine within 7 days of diagnosis of the matched case subject (Table 7, Fig. 2).

Although a statistically significant risk was observed in only one of the four studies,[52] the results of all four were similar, and the common odds ratio (2.95) was statistically significant (95% confidence interval 1.32 to 8.72). Because the design of the four studies was similar and potentially biased, the results may reflect a consistent bias rather than a true risk. The essential shortcoming of case-control studies is that they are used retrospectively to demonstrate cause-effect relations. For example, in this situation case subjects may have actually been vaccinated because of exposure to Hib disease (although these children were explicitly excluded in one of the studies[52]). Alternatively, Hib infection occurring within 7 days of vaccination may have been more likely to be reported than infection occurring later because of the medical community's concern about this association. These two factors would overestimate the magnitude of the risk of invasive Hib disease within 7 days of vaccination. A postlicensure survey of adverse reactions to the PRP-D vaccine in British Columbia revealed one case of invasive Hib disease within 30 days after vaccination in 5263

vaccinated children; this was not considered to be exceptional given the expected incidence of Hib disease in this group of children.[82] No data from prospective studies have indicated an increased risk during the first week after vaccination.

Mass vaccination

The number of children who would need to be vaccinated to prevent one case of invasive Hib disease, given varying baseline incidence rates and different levels of vaccine effectiveness, are in Table 10, which highlights the effects of variation in disease incidence and vaccine effectiveness on the potential for mass vaccination programs. In a low-risk population such as California children, in whom high vaccine effectiveness has been observed with a single dose of PRP-D at 18 months of age, the potential cost-effectiveness of mass vaccination appears to be relatively poor, as indicated by the relatively large number of children who would need to be vaccinated. This reflects the relatively low incidence of Hib disease in children more than 18 months of age. However, with the one-dose schedule the cost per child vaccinated could also be expected to be relatively low. In a low-risk population in which the vaccine is highly effective after three to four doses, such as Finnish children, the potential cost-effectiveness again appears to be relatively poor. In a high-risk population, in which the vaccine is only moderately effective, such as Alaskan children, the cost-effectiveness is potentially much better (i.e., the number who would have to be vaccinated is relatively small). However, although native children clearly have a higher incidence of Hib disease than other children,[4,5] the actual effectiveness of the PRP-D vaccine in this population is not known with certainty.[47]

In interpreting Table 10 it is important to consider that the estimates of effectiveness (the odds ratios) are based on 1 to 2 years of follow-up. As suggested by the data from the immunogenicity studies summarized in Table 8, the effectiveness of the vaccine may vary not only between populations but also between age groups within the same population. In general the effectiveness of the vaccine can be expected to be higher among older children and after a booster at 14 months of age. On the other hand, the baseline incidence rate can be expected to decrease with age (Table 8). Thus, the number of cases prevented might not be the same in each subsequent year after vaccination. Given the currently available data the number of children who would need to be vaccinated to prevent one case of invasive Hib disease after 5 years of follow-up cannot be estimated accurately.

Cost-effectiveness studies of Hib vaccination have been reported that examined the use of PRP vaccine in the United States.[8,85] However, there are important differences between PRP and PRP-D vaccine with respect to effectiveness, immunogenicity, immunization schedule and cost. There are also differences between the United States and Canada in the cost, the delivery of health care and the availability of social programs; therefore, a Canadian cost-effectiveness analysis of PRP-D vaccine is warranted. Given the wide range of assumptions that might reasonably be made regarding the benefits and the costs of Hib vaccination, careful comparisons of cost-effectiveness between a four-dose schedule (at 2, 4, 6 and 14 months of age) and a one-dose schedule (at 18 months) and between a high-risk strategy and a universal vaccination program are needed.

Conclusions

The number of children who need to be vaccinated to prevent one case of invasive Hib disease is dependent on the baseline risk. With the wide variation in the reported incidence of Hib disease

Table 10: Number of children who would have to be vaccinated to prevent one case of invasive Hib infection

Baseline incidence rate per 100 000	No. of children		
	Eskola et al[28]*	Ward et al[47]†	Greenberg et al[48]‡
1	120 482	270 270	100 000
20	6 024	13 514	5 000§
50	2 410§	5 405	2 000
100	1 205	2 703	1 000
500	241	541	200
1 000	120	270§	100

*Odds ratio of 0.17 corresponding to vaccine efficacy of 83%.
†Odds ratio of 0.63 corresponding to vaccine efficacy of 37%.
‡Odds ratio of 0.00 corresponding to vaccine efficacy of 100%.
§Number needed to be vaccinated (NNV) for approximate baseline incidence of invasive Hib disease in each study for 1 year of follow-up. Observed NNVs were 3 000 after 7 months of follow-up,[28] 216 after about 1 year of follow-up[47] and 4 181 after 1 year of follow-up.[48]

the collection of comprehensive epidemiologic data should be a research priority. Currently the baseline incidence, the age distribution and the geographic variation of invasive Hib disease in Canada are not well documented.

Although the PRP and the PRP-D vaccines are safe the PRP-D vaccine is much more immunogenic and thus is more likely to be effective in younger children, in whom the incidence of invasive Hib infection is highest. However, in two major trials the effectiveness of the PRP-D vaccine varied from moderate in Alaskan infants, who have a high baseline incidence of disease, to high in Finnish infants, who have a relatively low baseline incidence of disease; this difference was probably due largely to differences in the immunoresponsiveness of the two populations and possibly to differences in the immunogenicity of the vaccines. None the less, this difference in vaccine effectiveness and the considerable uncertainty surrounding the actual effectiveness in high-risk populations, although clinically important, are far less important determinants of the potential cost-effectiveness of mass vaccination than is the wide variation in the incidence of Hib disease.

In Canada it is currently recommended that all children receive one dose of the PRP-D vaccine at 18 months of age.[29] However, the available evidence suggests that the cost-effectiveness of an aggressive policy of universal vaccination is likely to be relatively low. A discretionary policy of Hib vaccination focusing on high-risk groups, particularly native children, using a four-dose schedule at 2, 4, 6 and 14 months of age appears likely to be more cost-effective, although a formal economic analysis of various strategies for the prevention of Hib disease in Canada is necessary before such a policy can be recommended. Our analysis has emphasized the importance of considering not only vaccine effectiveness but also disease incidence in formulating recommendations regarding the use of vaccines.

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