Haemophilus influenzae meningitis in Manitoba and the Keewatin District, NWT: potential for mass vaccination

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A community-based surveillance study of all central nervous system infections was carried out in Manitoba and the Keewatin District, NWT, between Apr. 1, 1981, and Mar. 31, 1984. There were 201 cases of bacterial meningitis in Manitoba over the study period, 81 (40%) caused by *Haemophilus influenzae*; all but one isolate tested were type b (Hib). There were nine cases of *H. influenzae* meningitis in the Keewatin District. The overall annual incidence rate of *H. influenzae* meningitis in Manitoba was 2.5/100 000; for children under 5 years the rate was 32.1/100 000. For the Keewatin District the corresponding rates were 69.6/100 000 and 530/100 000. A total of 85% and 100% of the cases of *H. influenzae* meningitis occurred by 24 months of age in Manitoba and the Keewatin District respectively. The age at onset was earlier in native Indian children (22 cases) and Inuit children (9 cases) than in non-native children (59 cases) ($p < 0.005$); thus, vaccine prevention of Hib meningitis will likely be more difficult in native Indian and Métis children. Without evaluating the increased potential of *H. influenzae* vaccines to prevent nonmeningitic forms of disease, we concluded that mass childhood vaccination with polyribosylribitolphosphate (PRP) vaccine is not warranted in Manitoba or the Keewatin District. Immunogenicity studies suggest that administration of conjugated Hib vaccines such as PRP-D in infancy may prevent approximately one-third to two-thirds of cases of *H. influenzae* meningitis; these vaccines warrant consideration for use in mass childhood vaccination programs.

Surveillance sur le terrain des infections du système nerveux central au Manitoba et dans le district de Keewatin (T.N.-O.) du 1 avril 1981 au 31 mars 1984. Sur 201 cas de méningite bactérienne au Manitoba 81 (40%) sont à *Haemophilus influenzae*; sauf une fois il s'agit de souches du type b (Hib) dans les cas où le typage est fait. Au Keewatin on relève neuf cas de méningite à *H. influenzae*. La fréquence annuelle de survenue de la maladie au Manitoba est de 2,5/100 000 (32,1/100 000 chez les enfants moins de 5 ans); au Keewatin les chiffres correspondants sont 69,6/100 000 et 530/100 000. La maladie survient avant l'âge de 2 ans dans 85% des cas au Manitoba et 100% au Keewatin. L'âge au début est plus précoce chez les enfants amérindiens (22 cas) et inuit (9 cas) que chez les non aborigènes (59 cas) ($p < 0,005$), d'où l'on prédit que la prévention de la méningite à Hib sera moins efficace chez les Indiens et les Métis. Sans

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préjuger de la possibilité de prévenir les formes non méningées des infections à Hib, nous concluons que la vaccination de masse par le vaccin polyribosyl-ribitol-phosphaté (PRP) n'est pas indiquée dans les régions en cause. Les travaux portant sur leur pouvoir immunogène permettant de croire que les vaccins combinés, tel le PRP-D, administrés pendant la première année préviendraient environ un tiers à deux tiers des méningites à *H. influenzae*, leur emploi de masse chez les enfants mérite considération.

The leading cause of bacterial meningitis in North America and Europe is *Haemophilus influenzae*.[1] In Canada *H. influenzae* meningitis has been a notifiable disease since 1979, with 222 to 415 cases reported annually and an incidence rate of 0.9 to 1.7/100 000 population.[2] Although the incidence of *H. influenzae* meningitis increased from 1930 to 1950, it has subsequently remained constant.[3] A total of 96% to 100% of cases of invasive *H. influenzae* infection, primarily in children below the age of 5 years, are due to serotype b.[4] The total incidence of other invasive *H. influenzae* type b (Hib) diseases approaches that of Hib meningitis.[4]

In this paper we examine the potential for preventing Hib meningitis in Manitoba and the Keewatin District, NWT.

Methods

An epidemiologic surveillance program for *H. influenzae* meningitis was conducted in Manitoba and the Keewatin District from Apr. 1, 1981, to Mar. 31, 1984, through weekly province-wide laboratory-based surveillance of large hospital laboratories and annual review for any missed cases by means of a computer search of the records of physicians' billings to the Manitoba Health Services Commission (MHSC). *H. influenzae* meningitis was diagnosed if the cerebrospinal fluid (CSF) culture was positive, if the blood culture was positive and there were 10×10^6/L or more leukocytes in the CSF, or if Hib antigen was detected in the CSF.[5] *H. influenzae* isolates were cultured on chocolate agar with CVA (cofactors, vitamins and amino acids) enrichment (Gibco Canada Inc., Burlington, Ont.). They were small, pleomorphic, gram-negative coccobacilli that grew in the presence of X factor (hemin) and V factor (nicotinamide-adenine dinucleotide). The organisms were typed with reference antisera (Wellcome Diagnostics, Guelph, Ont.) by means of counterimmunoelectrophoresis or slide agglutination.

Patients' demographic characteristics, information from the history, clinical and laboratory findings, and follow-up information were recorded. Patients were classified by racial group (white, black, Oriental, native Indian or other) according to their appearance by attending medical or nursing staff. The native Indian group was subdivided on the basis of coded registered identification numbers into those with treaty status and those without treaty status (including both nontreaty Indians and Métis).

The Wilcoxon two-sample rank-sum test,[6] a nonparametric statistical technique, was used to test the equality of the age distribution of two pairs of race categories. We examined a series of two-by-two tables using various age cutoff points for patients classified by race (non-native-Indian/non-Inuit v. native Indian/Inuit). We obtained statistics on the population within Manitoba from the MHSC's annual reports and statistics for the Keewatin District from the 1981 Statistics Canada census.

We evaluated programs using two vaccines against Hib infection, polyribosylribitolphosphate (PRP) and PRP-D vaccines. PRP-D vaccine is a covalently conjugate vaccine (developed by Connaught Laboratories Limited, Willowdale, Ont.) in which PRP is linked to diphtheria toxoid. We estimated the effectiveness of hypothetical vaccination programs using the following equation: Vaccine coverage (%) $\times$ vaccine efficacy (%) $\times$ % of total cases within age of vaccine-induced immunity $\times$ total number of cases of disease per year in population = number of cases prevented per year. We used values from published studies to perform a base-case analysis and a sensitivity analysis at two estimates of vaccine efficacy. In the base-case analysis the most probable values of the variables were used. In the sensitivity analysis we altered one or more variables to estimate how different values of the variables might change the outcome.[4]

Thus, the rate of vaccine coverage was estimated at 90% (on the basis of coverage estimates from the Manitoba Department of Health for diphtheria–pertussis–tetanus–oral poliovirus vaccination at 6, 12 and 18 months). A sensitivity analysis was also performed with the value for vaccine coverage estimated at 75% for PRP vaccine when given at 24 months, because this would require an extra visit for vaccine administration in comparison with current practice. The efficacy of PRP vaccine was assumed to be 90% at 24 months and 75% at 18 months on the basis of an achieved anti-PRP antibody level of at least 1 μg/ml, which has been shown to provide long-term clinical protection.[4,7,8] The estimates of efficacy for PRP-D vaccine were drawn from immunogenicity trials of vaccine given at 3, 5 and 7 months of age.[9,10] The base-case estimate of efficacy was 50%, based on achieved anti-PRP antibody levels of at least 1 μg/ml 1 month after vaccination.[9,10] We assumed, however, that vaccine would be given at 2, 4 and 6 months of age, as with current vaccination programs, and that similar protective antibody levels would be attained 1 month later. A sensitivity analysis was also performed with a vaccine efficacy of 83% on the basis of recent clinical trials of PRP-D vaccine.[11]

Results

Over the 3-year surveillance period there were 201 cases of bacterial meningitis in Manitoba, 81 (40%) caused by *H. influenzae*; all but one isolate tested were type b. The annual incidence rate of *H. influenzae* meningitis was 2.5/100 000 population. Of the 81 cases of *H. influenzae* meningitis 99% occurred in children less than 5 years of age; the annual incidence rate in this age group was 32.1/100 000. The peak incidence was in children aged 6 to 11 months, and only one case occurred beyond 4 years of age. A total of 20%, 51%, 65% and 85% of the 81 cases occurred by 6, 12, 18 and 24 months of age respectively (Fig. 1). The case-fatality rate was 4%.

Of the 81 patients 49 were white, 22 were native Indians (16 nonstatus and 6 status), 2 were black and 2 were other; in 6 cases ethnic origin was not determined. Since reliable denominator data were available for only the status Indian and the remaining non-Indian racial populations of Manitoba, reliable incidence figures could be calculated for only these two populations.

We compared the incidence rates of *H. influenzae* meningitis in native Indian Manitobans and all non-Indian Manitobans. We estimated the nonstatus Indian population in Manitoba to be twice that of the status Indian population (which is approximately 47 000) on the basis of estimates provided by the Northern Medical Unit, University of Manitoba. Therefore, the total native Indian population in Manitoba was estimated at 141 000. We assumed the same age distribution for the nonstatus Indian population as for the status Indian population. The age-specific annual incidence rate of *H. influenzae* meningitis per 100 000 population less than 5 years of age was 34.5 for native Indians, compared with 25.5 for non-Indians. The age-specific annual incidence rate per 100 000 population aged 11 months or less was 126 for native Indians, compared with 70 for non-Indians.

There were nine cases of *H. influenzae* meningitis in the Keewatin District during the study period, all in Inuit. The annual incidence rates were 69.6 per 100 000 total population and 79.8/100 000 for the Inuit (who account for 3760 of the population of 4310). The age-specific annual incidence rates per 100 000 among the Inuit were 530 for those less than 5 years of age, 2333 for those aged 11 months or less, 275 for those aged 12 to 23 months and 265 for those aged 24 to 35 months. Of all the cases 22% occurred by 6 months of age and 89% by 12 months (Fig. 1).

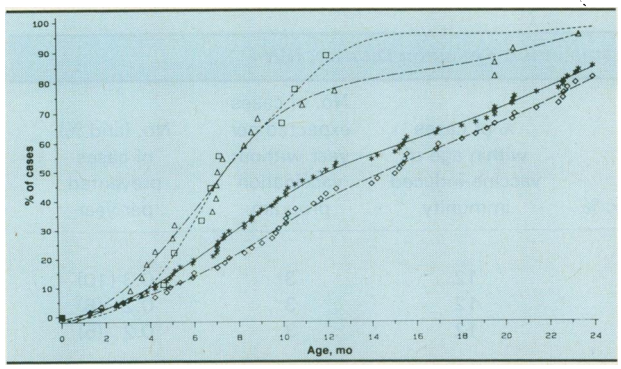

Fig. 1 — Age distribution of infants with *Haemophilus influenzae* meningitis in Manitoba in 1981–84. * = all Manitobans; ◊ = non-native-Indians; △ = native Indians; □ = Inuit.

The differences in age distribution between non-native-Indian/non-Inuit and native Indian/Inuit children and between non-native-Indian/non-Inuit and native Indian children were statistically significant ($p < 0.005$), with an excess of cases among younger children in the native Indian or native Indian/Inuit groups. A chi-squared test for association with Yates' correction for continuity showed significant differences in the incidence of *H. influenzae* meningitis between the non-native-Indian/non-Inuit group and the native Indian/Inuit group at ages 9 months ($p < 0.001$), 12 months ($p < 0.003$) and 15 months ($p < 0.04$). Similar differences were evident between the non-native-Indian/non-Inuit and native Indian groups.

Assuming a vaccine coverage rate of 90% and an efficacy of 90%, administration of PRP vaccine to all children in Manitoba at 24 months of age could prevent 3.3 cases of *H. influenzae* meningitis (12%) per year (Table I). The number of cases prevented per year if the vaccine were administered at 18 months would be 6.4 (24%). Administration of PRP vaccine to all Inuit children in the Keewatin District at 24 months of age could prevent 0.3 cases (10%) per year (Table II). Assuming a base-case efficacy of 50% at 7 months of age, administration of PRP-D vaccine to all children in Manitoba at 2, 4 and 6 months of age could prevent 9.6 cases (36%) per year. The number of cases prevented per year in the Keewatin District would be 0.8 (25%).

Discussion

The annual incidence rates of *H. influenzae* meningitis in Manitoba in 1981–84, 32.1/100 000 population less than 5 years of age and 2.5/100 000 total population, were greater than the corresponding rates reported for Canada, 20/100 000 (1983) and 0.9 to 1.7/100 000 (1979–84).[2] This suggests a rate of underreporting of Hib meningitis of almost 40% in Canada. The annual rate per 100 000 population less than 5 years of age in Manitoba was lower than that found in US studies, 51 to 77.[4,8] However, the rate per 100 000 total population was substantially greater than that found for 1978–81 in the US National Bacterial Meningitis Surveillance Study, 1.4.[1] The trend in age-specific rates in Manitoba was consistent with that in US studies, the peak incidence being in children aged 6 to 12 months. The proportion of cases of *H. influenzae* meningitis among those older than 24 months in Manitoba and in the

Keewatin District, 15% and 12% respectively, were comparable to the combined rate of 13% from two large prospective surveys.[12] The case-fatality rate, 3.7%, was comparable to rates reported in other studies, 5% to 6%.[1,2]

When we included nonstatus Indians in the total native Indian group, we found that the incidence of *H. influenzae* meningitis in children under 5 years of age was 1.4 times higher among native Indians than among non-Indians, and the incidence for those aged 11 months or less was almost twice as high. These findings suggest an increased risk for *H. influenzae* meningitis among the overall Indian population of Manitoba. This is consistent with other studies revealing an increased risk in specific racial groups. US studies show an increased risk among blacks, Hispanics, Navajo Indians and Inuit of southwestern Alaska.[1,3,13] However, the increased risk among Manitoba Indians is not as great as that among Navajo Indians, who show attack rates of 173 per 100 000 population less than 5 years of age, or among Inuit of Alaska or the Northwest Territories.[3]

The markedly increased risk among Inuit in the Keewatin District is similar to that found for Alaskan Inuit in 1971–77.[3] As well, the incidence rates reported for Inuit in the Baffin and Keewatin districts in a retrospective survey[14] and in the Perinatal and Infant Morbidity and Mortality (PIMM) studies in 1973–78 and 1978–83[15,16] were comparable. The annual rate per 100 000 population less than 5 years of age was 530 in our study, 409 in the Alaskan study,[3] 410 in the PIMM study of 1973–78[15] and 470 in the PIMM study of 1978–83.[16]

We found that 89% of the cases of *H. influenzae* meningitis in Inuit occurred before 12 months of age. This age distribution was also seen in the Alaskan study[3] and the second PIMM study,[16] in which 98% and 78% respectively of the children affected were less than 18 months of age. In both these studies the peak incidence was at 4 to 6 months of age. In our study only one case (11%) occurred after 18 months of age and might therefore have been prevented with PRP or PRP-D vaccine given at 18 months, whereas 78% of the cases occurred after 6 months of age and might have been prevented with PRP-D vaccine.

It is currently recommended that Hib PRP vaccine be given to all children at 2 years of age or, for those attending daycare centres, at 18 months.[17,18] This vaccination strategy was shown to be cost-effective in a US model.[4] Vaccination strategies for the prevention of Hib infections have recently been published.[9,19,20] However, the routine use of PRP vaccine in Europe appears unlikely.[20] It

Table I — Estimated effectiveness of mass vaccination programs with polyribosylribitolphosphate (PRP) and PRP-D* vaccines against *Haemophilus influenzae* meningitis in Manitoba

Vaccine; age at vaccination, mo	Type of analysis	Vaccine coverage, %	Efficacy, %	% of cases within age of vaccine-induced immunity	No. of cases expected per year without vaccination program	No. (and %) of cases prevented per year
PRP						
24	Base-case	90	90	15	27	3.3 (12)
	Sensitivity	75	90	15	27	2.7 (10)
18	Base-case	90	75	35	27	6.4 (24)
	Sensitivity	90	50	35	27	4.3 (16)
PRP-D						
2, 4, 6, 18†	Base-case	90	50	79	27	9.6 (36)
	Sensitivity	90	83[11]	79	27	15.9 (59)

*A protein-conjugated form of PRP vaccine.
†Assuming protective levels of anti-PRP antibody of at least 1 μg/ml attained at 7 months of age.

Table II — Estimated effectiveness of mass vaccination programs in the Keewatin District, NWT

Vaccine; age at vaccination, mo	Type of analysis	Vaccine coverage, %	Efficacy, %	% of cases within age of vaccine-induced immunity	No. of cases expected per year without vaccination program	No. (and %) of cases prevented per year
PRP						
24	Base-case	90	90	12	3	0.3 (10)
18	Base-case	90	75	12	3	0.2 (8)
	Sensitivity	90	50	12	3	0.2 (5)
PRP-D						
2, 4, 6, 18*	Base-case	90	50	56	3	0.8 (25)
	Sensitivity	90	83	56	3	1.1 (38)

*As in Table I.

should be noted that the people most at risk for invasive Hib infection may be deficient in their immune response to an Hib vaccine.[20]

An important consideration, though, is that with mass vaccination a higher proportion of cases of nonmeningitic invasive Hib disease would be potentially preventable with *H. influenzae* vaccines[4] because of the higher age distribution of patients with nonmeningitic Hib infections. In the native Indian and Inuit populations, however, epiglottitis is rare with *H. influenzae* infections[3] (Dr. Milton Tenenbein, University of Manitoba: personal communication, 1987).

In conclusion, since mass vaccination with PRP vaccine at 24 months of age would not likely prevent more than 12% of cases of *H. influenzae* meningitis we have not embarked on such a program in Manitoba. Mass vaccination would not be warranted in Manitoba or the Keewatin District owing to its likely low cost-effectiveness and concern about lack of public support for such an ineffective program. Recent vaccine failures in the United States[21] and Canada[22] have necessitated a thorough review of vaccine efficacy in the field. Conjugated vaccines may hold more promise. Protective antibody levels have been demonstrated in young children after administration of Hib polysaccharide/diphtheria toxoid conjugate vaccine,[10,12] and the clinical efficacy of PRP-D vaccine has been shown in a recent Finnish study.[11] We estimate that PRP-D vaccine could prevent 36% to 59% of cases of Hib meningitis in Manitoba and 25% to 38% of cases in the Keewatin District. The earlier age at onset of *H. influenzae* meningitis among native Indians and Inuit may compromise the effectiveness of mass vaccination programs in populations with a greater incidence of this disease.

The initial results with PRP-D vaccine or similar Hib vaccines will be important in planning Hib vaccination policy. In addition, improving surveillance of Hib disease in Canada will help determine the effect of new Hib vaccines.

We thank the physicians throughout Manitoba and the Keewatin District, NWT, who allowed us access to their patients' records. We acknowledge the assistance of Fred Toll, of the Management Information Services of the Manitoba Health Services Commission.

We also thank the National Health Research and Development Program (grant 6607-1206-54) and the Health Sciences Centre Research Foundation, Inc., for their support.

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