RECENT TRENDS IN PEDIATRIC *HAEMOPHILUS INFLUENZAE* TYPE B INFECTIONS IN CANADA

Immunization Monitoring Program, Active (IMPACT) of the Canadian Paediatric Society and the Laboratory Centre for Disease Control

Abstract • Résumé

Objective: To describe changes in the number of cases of *Haemophilus influenzae* type b (Hib) infections among Canadian children before and after the introductory phases of Hib vaccination.

Design: Multicentre case series.

Setting: All 10 pediatric tertiary care centres across Canada participating in the Immunization Monitoring Program, Active (IMPACT) of the Canadian Paediatric Society and the Laboratory Centre for Disease Control.

Patients: Children with a Hib infection admitted to any of the participating hospitals from 1985 to 1994. Annual case totals from 1985 to 1990 were determined from records of hospital laboratories or coded discharge diagnoses, or both. From 1991 to 1994 intensive case surveillance was conducted on the wards in addition to thorough record searches as above.

Outcome measures: Estimated annual case totals for 1985–90. For 1991–94 intensive surveillance for quarterly case totals, yearly age distribution of cases, and proportion of recent cases that represent vaccination failures or missed opportunities to prevent infection.

Results: The total number of Hib cases from 1985 to 1990 was 2095; from 1991 to 1994, there were 326 laboratory-confirmed cases and 15 probable cases supported by Hib antigen detection. The annual number of cases declined from an estimated 485 in 1985 to 24 in 1994, a decrease of 95.1%. The steepest interannual decrease (63.7%) occurred between 1992 and 1993, following the introduction of infant-based vaccination programs across Canada. The number of Hib cases involving children most at risk (those 6 to 18 months old) decreased from 78 in 1991 to 4 in 1994. Of the 24 cases in 1994, 6 were categorized as preventable, 1 was fatal, and 8 were vaccine failures (2 of which involved currently used vaccines).

Conclusion: The prevalence of Hib infections reported by the IMPACT centres has declined greatly since the introduction of vaccination programs. However, deaths and complications continue to occur, attesting to the need to vaccinate all eligible infants and children against this virulent pathogen.

Objectif : Décrire l'évolution du nombre de cas d'infection par le virus *Haemophilus influenzae* de type b (Hib) chez les enfants du Canada avant et après le lancement de la vaccination contre le Hib.

Conception : Étude de cas multicentrique.

Contexte : Les 10 centres de soins pédiatriques tertiaires du Canada qui participent au Programme de surveillance active des effets secondaires associés aux vaccins (IMPACT) de la Société canadienne de pédiatrie et du Laboratoire de lutte contre la maladie.

Patients : Enfants infectés par le Hib admis à n'importe lequel des hôpitaux participants de 1985 à 1994. Les totaux annuels des cas de 1985 à 1990 ont été calculés à partir des dossiers de laboratoires d'hôpitaux ou

Contributors: *Drs. David W. Scheifele (**principal author**), Department of Pediatrics, British Columbia Children's Hospital, Vancouver, BC; Tajdin P. Jadavji, Department of Pediatrics, Alberta Children's Provincial General Hospital, Calgary, Alta; Barbara J. Law, Department of Pediatrics, Health Sciences Centre, Winnipeg, Man.; Ronald Gold, Department of Pediatrics, Hospital for Sick Children, Toronto, Ont.; Noni E. MacDonald, Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, Ont.; Marc H. Lebel, Department of Pediatrics, Hôpital Sainte-Justine, Montreal, Que.; Elaine L. Mills, Department of Pediatrics, Montreal Children's Hospital, Montreal, Que.; Pierre Déry, Department of Pediatrics, Centre hospitalier de l'Université Laval, Ste-Foy, Que.; Scott A. Halperin, Department of Pediatrics, Izaak Walton Killam Hospital for Children, Halifax, NS; Robert F. Morris, Department of Pediatrics, Dr. Charles A. Janeway Child Health Centre, St. John's, Nfld.; Victor Marchessault, executive director, Canadian Paediatric Society, Ottawa, Ont.; Philippe J. Duclos, Childhood Immunization Division, Laboratory Centre for Disease Control, Ottawa, Ont.*

Reprint requests to: *Dr. Victor Marchessault, Canadian Paediatric Society, 401 Smyth Rd., Ottawa ON K1H 8L1*

← For prescribing information see page 1065

de diagnostics codés de libération, ou des deux. De 1991 à 1994, on a assuré une surveillance étroite des cas dans les salles en sus des recherches minutieuses effectuées dans les dossiers comme ci-dessus.

Mesures des résultats : Totaux estimatifs annuels des cas pour la période de 1985 à 1990. Pour celle de 1991 à 1994, surveillance étroite des totaux trimestriels des cas, répartition selon l'âge des cas par année et proportion des cas récents qui représentent des échecs de la vaccination ou des occasions ratées de prévenir l'infection.

Résultats : Le nombre total de cas de Hib de 1985 à 1990 a atteint 2095; de 1991 à 1994, il y a eu 326 cas confirmés par les laboratoires et 15 cas probables appuyés par une détection de l'antigène du Hib. Le nombre annuel de cas est tombé d'un total estimatif de 485 en 1985 à 24 en 1994, ce qui représente une baisse de 95,1 %. La chute la plus marquée d'une année à l'autre (63,7 %) a eu lieu entre 1992 et 1993, à la suite du lancement de programme de vaccination des nouveau-nés au Canada. Le nombre de cas de Hib affectant les enfants les plus à risque (de 6 à 18 mois) est tombé de 78 en 1991 à 4 en 1994. Sur les 24 cas de 1994, 6 étaient évitables, 1 a été fatal et 8 étaient attribuables à un échec de la vaccination (dont 2 cas de vaccins couramment utilisés).

Conclusion : La fréquence des infections par le virus Hib signalées par les centres IMPACT a diminué considérablement depuis le lancement des programmes de vaccination. Toutefois, il y a toujours des décès et des complications, ce qui démontre qu'il faut vacciner tous les nouveau-nés et les enfants admissibles contre cet agent pathogène virulent.

Until recently *Haemophilus influenzae* type b (Hib) was the leading cause of purulent meningitis in children.[1] It was also the principal cause of epiglottitis and an important cause of several additional diseases including septic arthritis, pneumonia and cellulitis.[2,3] About 1 in 200 children had a Hib infection before their fifth birthday,[4] and about 3% to 5% of affected children died.[3,4] Neurologic sequelae and deafness were hazards faced by survivors of Hib meningitis.[5]

Hib vaccines were initially licensed in Canada in 1986,[6] the first one consisting of purified capsular polysaccharide (polyribosylribitol phosphate [PRP]). It was reliably immunogenic only from 24 months of age,[6] by which time about two thirds of Hib cases already occur.[3] In 1988 it was superceded by the first polysaccharide–protein conjugate vaccine (PRP–D [diphtheria protein conjugate]; ProHIBIT, Connaught Laboratories Ltd., North York, Ont.),[7] the greater immunogenicity of which allowed use from 18 months of age. About 40% of cases were potentially preventable using this vaccine.[7] During 1988–89 most provinces implemented universal vaccination programs using PRP–D. Vaccine efficacy in the target age group later proved to be only 74% to 88%.[8,9] Reductions in the incidence of Hib infections were reported among children in the target age group who received the vaccine[10,11] and among those too young to receive it,[11] presumably because of decreased Hib transmission from vaccinated children.[12]

The most recent advance occurred in 1992, when all provinces and territories started programs using more potent PRP–conjugate vaccines given to infants 2 months of age and older.[13] With conjugation of the bacterial polysaccharide to protein carrier molecules such as tetanus or diphtheria toxoid, the immune response to PRP was converted from a T-lymphocyte independent pathway to a T-lymphocyte enhanced pathway, permitting antibody responses to develop in early infancy and establishing immunologic memory, the basis for durable, reinforceable serum antibody responses.[13]

Reports from the United States, where improved conjugate vaccines were licensed a year earlier than in Canada, indicated that infant-based programs rapidly reduced Hib infection rates.[14–16] The Immunization Monitoring Program, Active (IMPACT),[17] operated by the Canadian Paediatric Society with funding from the Laboratory Centre for Disease Control, Ottawa, was well-suited to observe the influence of the new programs. For the 10 pediatric centres involved in this Canada-wide network, there were two questions of interest: How rapidly and extensively would the caseloads decline, and what factors would account for new cases? For the latter question, if missed opportunities to vaccinate were found to be frequent, health authorities would be guided toward developing strategies to improve vaccine coverage. Similarly, if vaccination failures were found to be frequent with a particular product, health authorities would be prompted to consider available alternatives.

Methods

The IMPACT network has been described previously.[17] The 10 participating centres are distributed across Canada and represent about 80% of all tertiary care pediatric beds.

To obtain a more complete picture of temporal changes in the caseload, the centres determined approximate annual rates of hospital admission because of Hib infections from 1985 to 1990. No clinical information was collected. Four centres relied on laboratory reports of Hib isolates identified in blood and cerebrospinal fluid samples, excluding any duplicates; one centre relied on coded discharge diagnoses from its records depart-

ment; and five centres relied on both laboratory reports and coded discharge diagnoses to identify cases.

To determine the caseload from Jan. 1, 1991, to Dec. 31, 1994, a trained nurse monitor at each centre conducted intensive case-finding activities. Cases were identified from hospital microbiology laboratory reports, and the numbers were periodically verified against lists of discharge diagnosis codes (038.41, 041.5, 320.0 and 482.2 of the International Classification of Diseases, 9th revision, clinical modification[18]) supplied by the hospital records departments. The monitors also visited wards, reviewed admission lists and contacted infection-control nurses to find new cases. Prospective case-finding was initiated at five centres in 1991 and at the remaining centres in 1993. Equal effort was exerted to discover all cases, regardless of whether ascertainment was conducted retrospectively or prospectively.

A definite case was one in which Hib was isolated from a sample of normally sterile body fluid (e.g., blood, cerebrospinal fluid or fluid from the pleural or joint space) in a child with an illness indicative of Hib infection. Culture of Hib from the surface of a swollen epiglottis was also considered evidence of definite infection. A probable case was one in which Hib antigen was detected in a sample of cerebrospinal fluid, urine or other normally sterile body fluid in a child with an illness indicative of Hib infection who had not received Hib vaccine within the preceding 14 days (a source of detectable antigen in itself).[19] A probable case was also one in which Hib was recovered from endobronchial secretions of a child with bronchopneumonia, except in the case of long-term airway intubation. Only type b organisms were accepted. Organisms and antigen were identified by hospital microbiology laboratories under routine conditions.

The monitors described cases in detail using a standard report form to abstract information from each child's hospital record. The information collected included age, sex, reporting hospital, admission date, illness manifestations, bacterial culture results (sites, organism), antigen test results, level(s) of care required, duration of admission and patient's condition at discharge. In addition, special efforts were made to document any prior Hib vaccination, including dates and product names. If vaccination details were not found in the hospital record, the monitors contacted the parents, health department or attending physician. The monitors then categorized cases as preventable or not, taking into account the recommended use of the specific product(s) given or available before disease onset. Vaccination failure was defined as the onset of culture-confirmed Hib infection more than 28 days after completion of age-appropriate vaccination.

Case reports were checked for completeness at the IMPACT data centre, Vancouver, and the information was then entered into a database. Dual data entry was performed to minimize transcription errors. All key facts were manually verified before transcribed cases were added to the master database. Descriptive statistical analyses were performed using SAS/STAT software (SAS Institute Inc., Cary, NC).

The centres determined their annual total discharge numbers for 1985 and 1993, using consistent 12-month intervals (fiscal or calendar years), to see whether a decline in the incidence of Hib infections may have reflected fewer hospital admissions in general.

This project was approved by the institutional review board at each of the 10 participating centres.

Results

The participating centres enumerated 2436 admissions because of Hib infections during the study period (Table 1). From 1991–94, the period of intensive case surveillance, cases totalled 341, of which 326 (95.6%) were confirmed by culture. Annual case totals from 1985 to 1994 are shown in Fig. 1. The number decreased steadily from 1988 to 1992, the period during which the PRP–D vaccine was routinely used in most provinces; the average annual rate of decrease during this time was 21%. The steepest decrease (63.7%) occurred from 1992 to 1993, following the introduction of infant-based Hib vaccination programs in all provinces and territories. The overall reduction in annual caseloads between 1985 and 1994 was 95.1%. The annual total number of discharges at the participating centres was 101 806 in 1985 and 91 581 in 1993, the difference representing a decrease of 10.0%.

The age distribution of cases during 1991–94 is shown in Fig. 2. In 1991 the pattern was similar to that during the pre-immunization era,[3,4] children 6 to 18 months accounting for most cases (47.9%). In 1994 fewer cases were seen in all age groups, the fewest occurring among children 6 to 18 months (16.7%). The number of affected children in this age group decreased sharply (by 89.8%) from 1992 to 1993.

Of the 24 cases identified in 1994, 6 were classified as preventable. The parents refused vaccination in two, one of which was fatal, the attending physician inappropriately dissuaded the parents from having their children vaccinated in two cases, and Hib vaccination was not scheduled, for no apparent reason, in two cases, although the children's other vaccinations were up to date.

Among the nonpreventable cases in 1994 were seven children too young to have completed the primary series of Hib vaccination, two 12-year-olds who were too old to have qualified for earlier programs and one 6-year-old child not vaccinated because of HIV-related immu-

nodeficiency who became infected despite intravenous immunoglobulin therapy. The remaining eight children had Hib infection despite having received age-appropriate vaccination.

Vaccine failures were encountered throughout the 1991–94 period (Fig. 3). All were culture-confirmed cases and numbered 36 in total, accounting for 10.6% of the cases seen during 1991–94. Although the eight vaccine failures in 1994 accounted for 33.3% of the cases seen that year, the actual number of vaccine failures did not increase over time (Fig. 3). Most (88.9% [32/36]) of the failures were attributed to vaccines no longer used: PRP accounted for 3, PRP–D for 27 and unnamed early products for 2. Of the four failures attributed to currently used products two occurred in 1993 and two in 1994; PRP–T (tetanus protein conjugate) vaccine accounted for three and oligosaccharide conjugate Hib vaccine (HibTITER, Lederle–Cyanamid Canada Inc., Markham, Ont.) for the other. The latter case was reported previously[20] and involved a child with impaired responsiveness to PRP antigen.

Of the vaccine failures in 1994 five involved children over 5 years old, all of whom had received vaccines no longer used (PRP–D vaccine in three, unspecified product in two). Three involved children 7 months to 5 years old (PRP–D vaccine in one and PRP–T vaccine [ActHIB, Connaught Laboratories] in two). Of the two PRP–T vaccine failures one involved a child who had been given a single dose at 16 months and the other a 15-month-old child who had received three doses appropriately in early infancy; both children were concurrently immunocompromised by extensive burns, from which the second child died.

Some characteristics of Hib infections did not change appreciably from 1991 to 1994. Overall boys outnumbered girls (male:female ratio 1.7:1 [215:125]); this pattern was evident each year except 1994, when the ratio was 1:1.2 (11:13). Meningitis was the most common disease each year, accounting for 172 (50.4%) of the 341 cases during the 4 years. Epiglottitis was the next most common disease, occurring in 65 (19.1%) of the cases during the same period. Immunocompromised children accounted for a small proportion of cases (2.9%). The mean length of hospital stay remained constant (about 10 days). The case-fatality rate in 1994 was 4.2%, similar to that for the previous 3 years (2.5%).

Table 1: Number of cases of *Haemophilus influenzae* type b infection reported from 1985 to 1994 by 10 centres across Canada participating in the Immunization Monitoring Program, Active (IMPACT)

	Year; no. of cases										
Centre	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	Total
Dr. Charles A. Janeway Child Health Centre, St. John's	17	17	14	6	9	6	7	5	3	0	84
Izaak Walton Killam Hospital for Children, Halifax*	76	68	67	36	52	43	7	4	6	1	360
Centre hospitalier de l'Université Laval, Ste-Foy	16	27	15	15	12	6	13	8	3	1	116
Montreal Children's Hospital	63	52	49	40	21	17	10	13	3	3	271
Hôpital Sainte-Justine, Montreal	60	54	67	56	53	44	30	27	6	4	401
Children's Hospital of Eastern Ontario, Ottawa*	43	40	37	19	21	13	10	5	2	1	191
Hospital for Sick Children, Toronto*	64	44	38	37	45	32	27	12	1	2	302
Children's Hospital of Winnipeg*	56	20	27	35	20	21	36	18	9	4	246
Alberta Children's Provincial General Hospital, Calgary	51	57	45	26	20	16	8	6	0	4	233
British Columbia Children's Hospital, Vancouver	39	34	39	30	28	20	15	15	8	4	232
Total	485	413	398	300	281	218	163	113	41	24	2436

*Case-finding for 1985–90 was based on microbiology laboratory records, which possibly resulted in an underestimation of the total numbers.

In 1994 the total number of hospital bed-days for the 24 Hib cases was 222 days, 88 days of which were for intensive care. In 1991 Hib cases required 1723 hospital bed-days, 492 of which were for intensive care. The mean length of stay in 1991 was 10.6 days (95% confidence interval 9.4 to 11.7 days). If one assumes that the mean length of stay in 1985 was similar to that in 1991, Hib cases in 1985 resulted in an estimated 5141 days of hospital care. Thus, from 1985 to 1994 the annual number of hospital bed-days decreased by about 4919 days (95.7%).

Discussion

This multicentre IMPACT study documents a dramatic decrease of 95.1% in the number of invasive Hib infections from 1985 to 1994. Reductions of similar magnitude were seen at all 10 participating centres. The

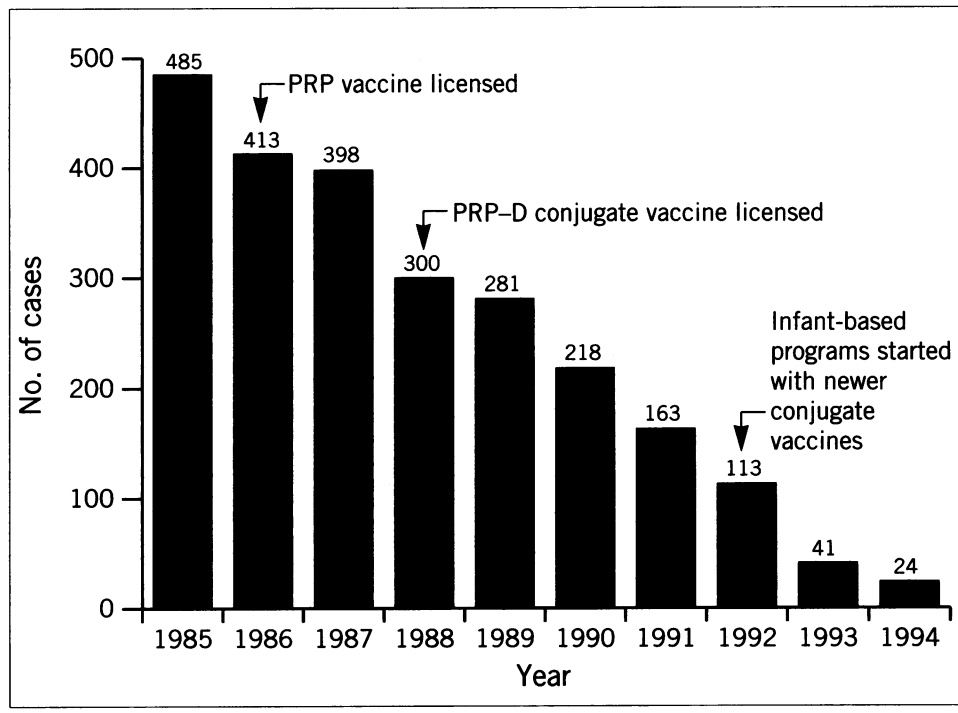

Fig. 1: Number of cases of *Haemophilus influenzae* type b (Hib) enumerated by pediatric tertiary care hospitals participating in the Immunization Monitoring Program, Active (IMPACT). PRP = Hib polysaccharide vaccine, PRP–D = PRP vaccine with diphtheria protein conjugate. Black bars are for years during which intensive case-finding activities were performed.

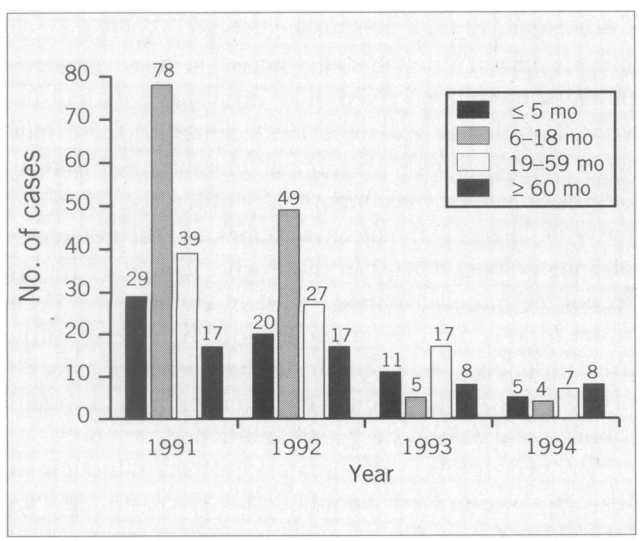

Fig. 2: Age distribution of Hib cases from 1991 to 1994.

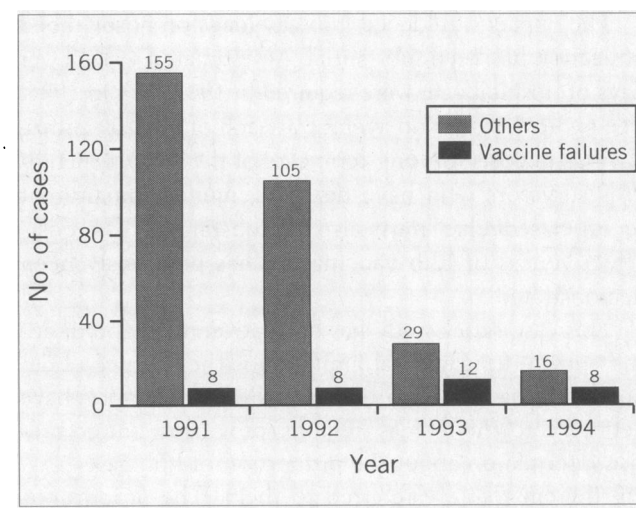

Fig. 3: Proportion of Hib cases categorized as vaccine failures from 1991 to 1994. (See text for definition of vaccine failure.)

decrease may have been even greater because in 1985, the baseline year before Hib vaccination began, four of the centres did not include cases in which Hib was cultured at a referring hospital.

The introduction of vaccination programs appears to be the principal explanation for the decrease in Hib cases. When interpreting annual case totals, one must consider natural variation in Hib prevalence,[3,21] the magnitude of which was not defined at participating centres for a period before the introduction of Hib vaccines. A steady decrease in overall prevalence was evident following the introduction of PRP–D vaccine in 1988, but data for individual centres showed some variability through 1991 (Table 1). The sharpest interannual decline in combined case totals was noted following the introduction in 1992 of the more potent PRP–conjugate vaccines, which can be given from 2 months of age. All provinces and territories implemented infant-based vaccination programs in 1992. All of the IMPACT centres experienced sustained decreases in case totals thereafter. The greatest decrease after 1992 was observed among children 6 to 18 months of age. A similar effect on Hib cases was observed in the United States following the implementation of infant-based programs there in 1991.[14,15]

Other changes may have contributed to reduced Hib caseloads at the participating centres. The total number of hospital admissions decreased by about 10% from 1985 to 1993, reflecting bed closures and possible changes in referral patterns for serious infections. However, the number of admissions because of invasive pneumococcal infections, another target of surveillance at the IMPACT centres, did not decrease from 1990 to 1994 (data not presented). Population-based incidence data are awaited to confirm our observations. Our data provide no evidence that Hib has become less virulent over time: the death rate and syndrome mix in 1994 were unaltered from previous years.

The impact of reduced Hib caseloads on hospital bed utilization has been substantial. An estimated 4919 fewer days of hospital care were required in 1994 than in 1985, freeing up 1.3 beds on average at each of the 10 centres. Savings in costs for long-term care of the 15% of meningitis survivors who have deafness, mental impairment or other sequelae[5] must also be substantial. The cost-effectiveness of Hib vaccination has previously been demonstrated.[22]

This case-series study has both advantages and disadvantages. A fundamental limitation is the absence of denominator data. The participating IMPACT centres have defined catchment areas (regions, provinces) but no precise information about the proportion of Hib cases arising therein that are referred to them. The proportions may differ depending on illness syndrome, severity, local physician availability or parental preferences. Thus, an attempt to estimate the populations served for purposes of calculating disease incidence would be unwise. On the other hand, the data from this case series are likely more complete than the passively reported case data used for most calculations of disease incidence. The superiority of active laboratory-based case surveillance over passive reporting of Hib cases was recently documented in US centers.[23] Only one or two carefully instructed monitors gathered data at each IMPACT centre. The period of intensive surveillance involved varying proportions of retrospective and prospective work at each centre, but complete case ascertainment was attempted in both contexts. The desired case information was readily available from patients' medical records. For both retrospectively and prospectively described cases, nurses obtained information from immunization records directly from parents or health care providers when details were lacking in the hospital records. The ascertainment of cases for 1985 to 1991 was not as uniform or complete as it was for the later years, but the particular case-finding methods used by the centres were applied fully and consistently during this period. We assumed that the microbiology laboratories at the centres could reliably identify Hib organisms. All of the participating laboratories take part in accreditation exercises.

The results of our study indicate a decrease in the number of Hib infections in most areas of Canada. However, Saskatchewan, New Brunswick, Prince Edward Island and the Yukon and Northwest territories were not represented directly. Nevertheless, the IMPACT centres are well distributed across Canada, and all have large catchment areas, some spanning whole provinces or multi-province regions. Together they account for over 80% of the country's tertiary care pediatric beds.[17] We believe that most Hib cases are admitted to tertiary care pediatric centres, at least in the participating areas.

Our data provide reassurance about the efficacy of Hib vaccines. Although some vaccine failures were documented in children given older products, only four involved products used since 1992. Three of these four were associated with host immunocompromise. Similar observations have been reported by others regarding the rarity of failures with current vaccines and the frequency of immunologic defects in those who acquire a Hib infection despite vaccination.[24,25] More children will need to be followed for extended periods before currently used products can be said to be fully assessed. Health care providers who encounter vaccination failures should report case details to their local health department.

Of special note are the data for 1994. Although so few cases of Hib were identified, there were missed vaccination opportunities, some with tragic outcomes. Hib infections remain severe and potentially fatal. Wide-

spread vaccination using conjugate vaccines has reduced Hib colonization rates among young children;[12] however, circulation of the organism continues. Consequently, herd immunity is a poor substitute for personal immunity. All health care professionals who counsel parents regarding childhood vaccination should emphasize the importance of protecting infants against Hib and ensure that the vaccine is administered in a timely fashion to all who need it.

In 1995 the total number of Hib cases at the 10 IMPACT centres was 20.

We are grateful for the excellent service provided by the nurse-monitors of the Immunization Monitoring Program, Active (IMPACT) and the IMPACT coordinators Candice Glover and Nicole Menzies. We also thank the laboratory, medical records and other staff members of the participating hospitals for their generous cooperation.

Financial support was provided by the Laboratory Centre for Disease Control, Health Canada.

References

1. Klein JO, Feigin RD, McCracken GH: Report of the Task Force on Diagnosis and Management of Meningitis. *Pediatrics* 1986; 78 (suppl): 959–982

2. Janai H, Stutman HR, Marks MI: Invasive *Haemophilus influenzae* type b infections: a continuing challenge. *Am J Infect Control* 1990; 18: 160–166

3. *Haemophilus influenzae* infection in Canada, 1969–1985 *Can Dis Wkly Rep* 1986; 12: 37–43

4. Broome CV: Epidemiology of *Haemophilus influenzae* type b infections in the United States. *Pediatr Infect Dis J* 1987; 6: 779–782

5. Jadavji T, Biggar WD, Gold R et al: Sequelae of acute bacterial meningitis in children treated for seven days. *Pediatrics* 1986; 78: 21–25

6. Statement on *Haemophilus* b polysaccharide vaccine. *Can Dis Wkly Rep* 1986; 12: 33–35

7. Statement on *Haemophilus* b conjugate vaccine. *Can Dis Wkly Rep* 1988; 14: 37–40

8. Greenberg DP, Vadheim CM, Bordenave N et al: Protective efficacy of *Haemophilus influenzae* type b polysaccharide and conjugate vaccines in children 18 months of age and older. *JAMA* 1991; 265: 987–992

9. Wenger JD, Pierce R, Deaver KA et al: Efficacy of *Haemophilus influenzae* type b polysaccharide–diphtheria toxoid conjugate vaccine in US children aged 18–59 months. *Lancet* 1991; 338: 395–398

10. Fisk R, Farley J, Angel L: *Haemophilus influenzae* disease trends to 1990, British Columbia. *Dis Surveillance* 1991; 12: 174–177

11. Naus M, Watley R: Impact of Hib vaccine on *Haemophilus influenzae* type b disease in Ontario. *Public Health Epidemiol Rep Ont* (PHERO) 1993; 4: 165–169

12. Barbour M, Mayon-White RT, Coles C et al: The impact of conjugate vaccine on carriage of *Haemophilus influenzae* type b. *J Infect Dis* 1995; 171: 93–98

13. Statement on *Haemophilus influenzae* type b conjugate vaccines for use in infants and children. *Can Commun Dis Rep* 1992; 18: 169–176

14. Murphy TV, White KE, Pastor P et al: Declining incidence of *Haemophilus influenzae* type b disease since introduction of vaccination. *JAMA* 1993; 269: 246–248

15. Adams WG, Deaver JA, Cochi SL et al: Decline of childhood *Haemophilus influenzae* type b (Hib) disease in the Hib vaccine era. *JAMA* 1993; 269: 221–226

16. Schoendorf KC, Adams WG, Kiely JL et al: National trends in *Haemophilus influenzae* meningitis mortality and hospitalization among children, 1980 through 1991. *Pediatrics* 1994; 93: 663–668

17. Morris R, Halperin S, Déry P et al: IMPACT monitoring network: a better mousetrap. *Can J Infect Dis* 1993; 4: 194–195

18. *International Classification of Diseases, 9th Revision (Clinical Modification)*, 4th ed (publ no DHHS [PHS] 91-1260), US Department of Health and Human Services, Washington, 1991

19. Scheifele DW, Bjornson G, Arcand T et al: Antigenuria after receipt of *Haemophilus* b diphtheria toxoid conjugate vaccine. *Pediatr Infect Dis J* 1989; 8: 887–888

20. *Haemophilus* b conjugate vaccine failure. *Can Commun Dis Rep* 1994; 20: 37–39

21. Sherry B, Emanuel I, Kronmal RA et al: Interannual variation in the incidence of *Haemophilus influenzae* type b meningitis. *JAMA* 1989; 261: 1924–1929

22. Hay JW, Daum RS: Cost-benefit analysis of *Haemophilus influenzae* type b prevention: conjugate vaccination at 18 months of age. *Pediatr Infect Dis J* 1990; 9: 246–252

23. Standaert SM, Lefkowitz LB, Horan JM et al: The reporting of communicable diseases: a controlled study of *Neisseria meningitidis* and *Haemophilus influenzae* infections. *Clin Infect Dis* 1995; 20: 30–36

24. Vadheim CM, Greenberg DP, Eriksen E et al: Protection provided by *Haemophilus influenzae* type b conjugate vaccines in Los Angeles County: a case–control study. *Pediatr Infect Dis J* 1994; 13: 274–280

25. Holmes S, Granoff DM: The biology of *Haemophilus influenzae* type b failure. *J Infect Dis* 1992; 165 (suppl): S121–S12